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ENDOCRINE SECRETS

SIXTH EDITION

QUESTIONS YOU WILL BE ASKED

TOP 100 SECRETS ■ KEY POINTS ■ WEB SITES

MICHAEL T. McDERMOTT MD

ENDOCRINE

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Sixth Edition

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This book is dedicated to Libby and Emily, whose courageous battles with conditions they did not want to have are a continuing source of inspiration and strength for all of us.

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PREFACE TO THE SIXTH EDITION

The purpose of this book is to present a comprehensive review of clinical endocrinology in a streamlined, readable text, using a question and answer format similar to that which may be encountered on teaching rounds. I am deeply indebted to the authors who have contributed their time, energy, experience, and wisdom to the chapters in this book. The generosity of such teachers has always been and will continue to be one of the richest sources of instruction and guidance for doctors in training and for those already in practice. The readers of this book and the patients they treat will benefit greatly from the efforts of this very dedicated group of authors. Although information is more easily conveyed in print, I hope that the readers can also appreciate the passion these authors have for their roles as health-care providers and the compassion they feel for their patients. My sincerest hope is that current and subsequent generations of providers will continue to combine a solid grasp of the rapidly growing fund of available medical knowledge with genuine humanism so that we may always show deep respect for the privilege of having patients place the responsibility for their health care in the our hands.

Michael T. McDermott

DIABETES MELLITUS

Marissa Grotzke and Robert E. Jones

1. What is diabetes mellitus?

Diabetes mellitus comprises a group of chronic metabolic disorders characterized by abnormalities in insulin secretion or action (or both) resulting in hyperglycemia. These conditions are associated with disordered carbohydrate, fat, and protein metabolism and can lead to long-term complications involving the nervous, cardiovascular, renal, and sensory organ systems. The types of diabetes are summarized in Table 1-1.

2. What is the prevalence of diabetes?

According to 2011 statistics compiled by the U.S. Centers for Disease Control, 25.8 million children and adults, or 8.3% of the U.S. population, have diabetes. Of those, 18.8 million have been diagnosed, and 7.0 million Americans have diabetes but are unaware of it. Of individuals 20 years or older, 25.6 million (11.3%) have diabetes. In 2010, 1.9 million adults were newly diagnosed with diabetes. Additionally, an estimated 35% of adults were classified as prediabetic.

3. What is monogenic diabetes?

In contrast to type 2 diabetes, which is clearly polygenic, monogenic diabetes is hyperglycemia due to a single gene mutation. Monogenic diabetes is relatively rare, accounting for only 1% to 2% of all cases in Europe. It is loosely divided into neonatal diabetes (diabetes appearing within the first 6 months of life) and maturity-onset diabetes of the young (MODY; diagnosed outside the neonatal period and generally prior to 25 years of age). Mutations involving the beta-cell adenosine triphosphate–sensitive potassium channel (K_{ATP} channel) account for most cases of neonatal diabetes, and the disease in patients with these mutations responds to sulfonylureas, which block the persistently open, mutated K_{ATP} channels, thus allowing insulin secretion. MODY is associated with mutations involving glucokinase or genes coding transcription factors that are important in insulin signaling.

4. Who should be screened for diabetes?

Screening for type 1 diabetes is not feasible. Despite many studies, there is no effective means of preventing diabetes in patients who test positive for autoantibodies associated with type 1 diabetes without an abnormality in glucose tolerance, and there is no consensus as to what should be done about positive results.

The risk for development of type 2 diabetes increases with age, obesity, and sedentary lifestyle. There is an increased risk with a family history of diabetes, in certain ethnic groups, and in women with a history of gestational diabetes. Current recommendations are to screen the general population at 3-year intervals starting at age 45. Earlier or more frequent screening should be performed in adults with a body mass index (BMI) 25 kg/m^2 or greater and additional risk factors (Table 1-2).

5. How is diabetes diagnosed?

There are four different testing options for the diagnosis of diabetes: a fasting plasma glucose (FPG) test, a 75-g oral glucose tolerance test (OGTT), a hemoglobin A_{1C} (HbA_{1C}) measurement, and random plasma glucose measurement. Both the HbA_{1C} measurement and FPG test are more convenient and less expensive and are, therefore, preferred. In a patient with a positive test result, the test should be repeated on a different day to confirm the diagnosis. Table 1-3 describes diagnostic criteria.

TABLE 1-1. TYPES OF DIABETES MELLITUS

Type 1 (T1DM)	Results from an absolute deficiency of insulin secretion due to beta-cell destruction (immune-mediated, 90% [type 1 A], or idiopathic [type 1B]). Patients require insulin and are prone to ketoacidosis.
Type 2 (T2DM)	Results from a combination of insulin resistance and insulin deficiency, which is often preceded by a period of abnormal carbohydrate metabolism (prediabetes). Patients are typically overweight, may not immediately require insulin, and are not usually prone to ketoacidosis.
Gestational (GDM)	Represents diabetes diagnosed during pregnancy and is based on specific screening protocols.
Other specific types	Diabetes caused by other conditions (chronic pancreatitis, pancreatectomy, acromegaly, hemochromatosis, hypercortisolism) or by medications (glucocorticoids, atypical antipsychotics, antiretrovirals), and monogenetic diabetes, also called maturity-onset diabetes of the young [MODY].

TABLE 1-2. ADDITIONAL RISK FACTORS PROMPTING SCREENING FOR TYPE 2 DIABETES MELLITUS IN ADULTS

Physical inactivity
Diabetes in a first-degree relative
High-risk ethnicity: African American, Native American, Latino, Pacific Islander, Asian
History of gestational diabetes or of delivering a baby weighing $>$ 9 lbs
Hypertension: blood pressure $\geq$ 140 mm Hg systolic/90 mm Hg diastolic or current hypertension therapy
Lipid disorders: High-density lipoprotein (HDL) cholesterol $<$ 35 mg/dL or triglycerides $>$ 250 mg/dL
Polycystic ovarian syndrome (PCOS)
History of abnormal glucose metabolism noted in prior testing: fasting glucose $\geq$ 100 mg/dL; hemoglobin $A_{1C} \geq 5.7\%$; 2-hour oral glucose tolerance test (OGTT) result $>$ 140 mg/dL
Clinical evidence of insulin resistance: acanthosis nigricans, pronounced obesity

TABLE 1-3. DIAGNOSTIC CRITERIA FOR ABNORMALITIES OF GLUCOSE METABOLISM

PARAMETER	NORMAL	PREDIABETES	DIABETES	COMMENT
Fasting glucose measurement (mg/dL)	$<$ 100	100-125	$\geq$ 126	Must be repeated on a separate day
Oral glucose tolerance test, 2-hour value (mg/dL)	$<$ 140	140-199	$\geq$ 200	75-g test
Random glucose measurement (mg/dL)	$<$ 140		$\geq$ 200	Rarely diagnostic unless accompanied by symptoms (polyuria, polydipsia)
Hemoglobin A_{1C} measurement (%)	$<$ 5.7	5.7-6.4	$\geq$ 6.5	Must be performed according to Diabetes Control and Complications Trial methodology using an approved standard

6. What are the genetics of type 1 diabetes?

The exact role of genetics versus environment in the development of type 1 diabetes is unknown. Monozygotic twins have a 20% to 50% concordance for type 1 diabetes. The cumulative risk for siblings of diabetic patients is 6% to 10%, versus 0.6% for the general population. Regarding the effect of parental genes, the offspring of women with type 1 diabetes have a lower risk of disease (2.1%) than those of men with type 1 diabetes (6.1%). The reason for this disparity is unknown. The susceptibility for type 1 diabetes is associated with the genetic expression of certain proteins coded by the human leukocyte antigen (HLA) region of the major histocompatibility complex. These proteins are present on the surfaces of lymphocytes and macrophages and are considered essential for triggering the autoimmune destruction of beta cells. Although all of the genetic markers (HLA and others) for type 1 diabetes are not known, future progress in this field will allow population screening for genetic susceptibility. Type 1 diabetes is a major element of autoimmune polyglandular syndrome type 2 (APS-2; see Chapter 52).

7. What are the genetics of type 2 diabetes?

As with type 1 diabetes, the exact interaction of genetics and environment in the development of type 2 diabetes is unclear. However, the familial clustering of type 2 diabetes suggests a strong genetic component. Monozygotic twins have a 60% to 90% concordance for type 2 diabetes. The cumulative risk for type 2 diabetes in siblings of diabetic patients is 10% to 33%, versus 5% for the general population. Offspring of women with type 2 diabetes have a twofold to threefold greater risk of diabetes than offspring of men with the disease. The exact mode of inheritance for type 2 diabetes is not known but is thought to be polygenic. Specific mutations that are associated with risk for type 2 diabetes have been identified, but many of these genes are widely found in the population at large. Because type 2 diabetes is so commonly associated with obesity, many investigators suspect that genes that predispose to obesity are associated with type 2 diabetes as well. There appears to be a strong interplay between genetic and environmental influences in the cause of type 2 diabetes. One illustration is the demonstration of higher fasting insulin levels for every weight category in the offspring of two parents with type 2 diabetes than in control subjects. High insulin levels are a marker for insulin resistance and are predictive of progression to type 2 diabetes.

8. Describe the pathogenesis of type 1 diabetes.

Type 1 diabetes results from host T-cell destruction of beta cells within the pancreas, which causes absolute insulin deficiency. Markers of this autoimmune process include antibodies to islet cells, insulin, and glutamic acid decarboxylase. The autoimmune destruction is believed to be related to genetic predispositions (HLA-DR/DQ alleles) in combination with poorly defined environmental factors. Patients with type 1 diabetes are prone to other autoimmune disorders (Grave's disease and Hashimoto's thyroiditis, celiac sprue, etc.).

9. Describe the pathogenesis of type 2 diabetes.

The pathogenesis of type 2 diabetes is multifactorial, although specific etiologies are unknown. Autoimmune beta-cell destruction does not occur in this form of diabetes, which accounts for 90% to 95% of all cases of diabetes. Instead, type 2 diabetes is characterized by both a defect in insulin action (known as insulin resistance) and a relative insulin deficiency. Years of hyperglycemia often precede the diagnosis, which typically occurs only after non-autoimmune beta-cell failure has begun. Loss of first-phase insulin secretion is the initial defect, with resulting postprandial glucose elevations. Eventually beta-cell death accelerates, and glucose levels rise. It is estimated that by the time of diagnosis of diabetes, patients have lost nearly 50% of their beta-cell mass.

With loss of beta-cell mass, insulin secretion is no longer sufficient to compensate for insulin resistance, defined as a subnormal response to a given insulin concentration. Elevated fasting or postprandial insulin values are the hallmark of insulin resistance, which is often associated with obesity; weight reduction may improve insulin sensitivity.

10. Can diabetes be prevented?

Several studies involving individuals at high risk for development of type 2 diabetes have documented potential beneficial effects of thiazolidinediones (Troglitazone in Prevention of Diabetes [TRIPOD] and Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication [DREAM] studies), metformin (Diabetes Prevention Program [DPP]), alpha-glucosidase inhibitors (Study to Prevent Non–Insulin-Dependent Diabetes Mellitus [STOP-NIDDM] study), intestinal lipase inhibitors (XENical in the Prevention of Diabetes in Obese Subjects [XENDOS] study), and even insulin (Outcome Reduction with Initial Glargine Intervention [ORIGIN] trial) in reducing the rate of progression to overt diabetes. Individuals in the lifestyle modification (7% weight loss and moderate exercise for 150 minutes/week) arm of the DPP showed excellent results, with a 60% lower risk for development of diabetes than those receiving metformin (30%). However, the American Diabetes Association (ADA) recommends pharmacotherapy only in patients who are at high risk for progression to diabetes because of multiple risk factors or an HbA_{1C} level higher than 6% despite lifestyle modifications.

The lower prevalence of type 1 diabetes has made determining who is at risk more difficult. Identifying people in the prediabetic phase of type 1 diabetes requires serial measurements of beta-cell function and close monitoring of immunologic markers, making selection of an appropriate cohort difficult. Two studies, the Diabetes Prevention Trial–Type 1 (DPT-1) and the European Nicotinamide Diabetes Intervention Trial (ENDIT), overcame this issue and examined the use of insulin and nicotinamide, respectively, in high-risk relatives of patients with type 1 diabetes. However, neither study demonstrated effective prevention of progression to type 1 diabetes.

11. What techniques are available to assess insulin resistance?

Lack of standardization of insulin assays prevents use of a specific insulin concentration to define insulin resistance. The gold standards for defining insulin resistance are the intravenous glucose tolerance test, insulin suppression test, and euglycemic insulin clamp. However, these research tools are impractical in a clinical setting. A more clinically applicable tool is the homeostasis model assessment of insulin resistance (HOMA-IR), defined as the product of fasting insulin (in mU/L) and fasting plasma glucose concentrations (in mmol/L) divided by a constant (22.5), as in the following equation:

$$\text{HOMA-IR} = \text{Fasting Insulin (mU/L)} \times \text{Fasting Glucose (mmol/L)}/22.5$$

12. Describe metabolic syndrome.

Metabolic syndrome is defined as the presence of three of the five following criteria:

- Increased waist circumference ($>$ 40 inches in men, $>$ 35 inches in women)
- Plasma triglycerides $\geq$ 150 mg/dL
- Plasma high-density lipoprotein cholesterol $<$ 40 mg/dL in men, $<$ 50 mg/dL in women
- Blood pressure $\geq$ 130 mm Hg systolic/85 mm Hg diastolic
- Fasting plasma glucose $\geq$ 100 mg/dL

In 2004, the American Heart Association modified this definition to include the use of medications for hypertension or to the criteria for blood pressure and hyperglycemia to the fasting plasma glucose levels.

13. What causes beta-cell failure in type 2 diabetes?

It is estimated that at the time of diagnosis, patients with type 2 diabetes have lost nearly 50% of their insulin-producing cells. The system of programmed beta-cell death (apoptosis) occurs progressively over the course of type 2 diabetes and has many potential triggers, although two specific possibilities have been characterized. Elevations of glucose and free fatty acids, collectively called *glucolipotoxicity*, and chronic increases in certain cytokines, notably tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β), have been documented to activate "death" genes (caspases) in beta cells. Both of these conditions have been amply described in subjects with either prediabetes or overt diabetes and clearly contribute to the genesis of type 2 diabetes by reducing the number of functioning beta cells.

14. What are the standards of care for the management of diabetes mellitus?

Both the ADA and the American Association of Clinical Endocrinologists (AACE) have published evidence-based minimum standards of diabetes care. Both recommend that patients have a complete history and physical examination at the initial visit. Laboratory testing should include a fasting lipid profile and measurement of HbA_{1C}. Surveillance for complications should include an annual physical examination, ophthalmologic examination, and a screen for microalbuminuria. Overall glycemic control (HbA_{1C}) should be assessed at least semiannually in all patients and quarterly in insulin-treated patients and in patients with poorly controlled type 2 diabetes. Published targets include an HbA_{1C} value under 7.0% (ADA) or 6.5% (AACE), low-density lipoprotein (LDL) cholesterol less than 100 mg/dL ($<$ 70 mg/dL in high-risk patients), and blood pressure lower than 130/80 mm Hg.

15. Describe the current management approach to type 1 diabetes and the role of intensive therapy modeled by the Diabetes Control and Complications Trial (DCCT).

Diabetes is a self-management illness and requires that the patient be educated in glucose self-monitoring, nutrition therapy, exercise, and the proper use of medications. Similarly, the patient must be taught how to recognize and treat hypoglycemia. Because patients with type 1 diabetes are completely insulin deficient, the medical regimen is straightforward and centered on insulin replacement. The most physiologic replacement regimen, known as the basal-bolus technique, can be accomplished either with the use of a long-acting (basal) insulin in combination with a rapid-acting (bolus) insulin or a continuous subcutaneous infusion using an insulin pump.

The DCCT showed a 34% to 76% reduction in clinically significant diabetic microvascular complications (retinopathy, neuropathy, and nephropathy) in type 1 diabetes subjects randomly assigned to intensive insulin therapy in comparison with subjects assigned to standard diabetes management. After an average 17 years of follow-up, the intensively treated cohort also enjoyed an approximate 50% reduction in cardiovascular risk. The only major adverse effect of intensified control was a threefold higher risk of severe hypoglycemia. An intensive therapy regimen requires blood glucose monitoring four to eight times daily with multiple daily insulin injections or an insulin pump and is best managed by a team comprising a physician, certified diabetes educator, nurse, and dietitian.

16. Is intensive diabetes therapy cost-effective?

The potential reduction in cost for treating diabetic complications (laser photocoagulation, dialysis, kidney transplants, hospitalizations, and rehabilitation following amputations) has been shown to justify the cost of personnel and supplies for intensive therapy. The risk-to-benefit ratio for intensive therapy may be less favorable for prepubertal children, patients with advanced complications, and patients with coronary or cerebrovascular disease.

17. What is the United Kingdom Prospective Diabetes Study (UKPDS)?

The UKPDS is the largest and longest prospective study on type 2 diabetes ever conducted. Investigators recruited 5102 patients with newly diagnosed type 2 diabetes in 23 centers within the United Kingdom between 1977 and 1991. Patients were followed up for an average of 10 years to determine the impact of intensive therapy using pharmacologic agents in comparison with dietary therapy alone. The study also tested the relative efficacy of intensive (tight) blood pressure control and "less tight blood pressure control." The results of the study showed a significant reduction in microvascular complications in patients randomly assigned to the intensive therapy arm. Tight blood pressure control was associated with a reduction in both microvascular and macrovascular events. When the entire cohort of patients was studied together, the mean HbA_{1C} level for the duration of the study was a strong positive predictor of all diabetes-related end points, including death, amputation, myocardial infarction, and stroke. The benefits of early glucose and blood pressure control in reducing the both the microvascular and macrovascular complications and all-cause mortality persisted 10 years after the end of the original trial.

18. What is the current management approach to type 2 diabetes?

Because type 2 diabetes is a heterogeneous disorder and patients may have other comorbid illnesses, treatment and therapeutic targets must be individualized. A patient-centered approach has been advocated. The foundation of therapy is diet, exercise, and patient education; unless there are contraindications to its use, metformin should be started at the time of diagnosis. The next steps may involve additional oral agents or injectable medications, and all further treatment decisions must consider the individual characteristics of the patient as well as comorbidities. Ultimately, the majority of patients requires supplemental insulin. Emphasis should be placed on addressing cardiovascular risk reduction (blood pressure, lipids) at each encounter with the patient.

19. What are the clinical implications of the ACCORD trial?

The Action to Control Cardiovascular Risk in Type 2 Diabetes (ACCORD) trial was undertaken to address whether intensive versus standard glucose control (HbA_{1C} target $<$ 6% vs. 7.0%-7.9%), intensive versus standard blood pressure control (systolic blood pressure $<$ 120 mm Hg vs. $<$ 140 mm Hg), and fenofibrate versus placebo (both treatment arms were allowed statins) further reduced cardiovascular outcomes in patients with long-standing type 2 diabetes. In all study arms there was no reduction in the primary outcome, which was a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. Unexpectedly, both total mortality (hazard ratio 1.22) and cardiovascular death (hazard ratio 1.35) were increased in the intensive glucose control arm. Benefits were seen, however, in some secondary cardiovascular and microvascular outcomes. The clinical translation of the ACCORD study is somewhat murky, but it is apparent that intensive glucose management with the intention of normalizing HbA_{1C} (HbA_{1C} $<$ 6%) is likely not warranted. Another lesson learned from ACCORD is that the management of people with type 2 diabetes must be individualized.

20. What are insulin analogs?

Insulin analogs are recombinant proteins that are based on the structure of human insulin but that have undergone selected amino acid substitutions, deletions, or additions. These amino acid alterations are designed to either enhance or protract the subcutaneous absorption of the molecule without altering its biologic properties. Native human insulin (regular) exists as a molecular hexamer that must be progressively broken down into dimers and then monomers before absorption. Amino acid substitutions in the carboxy-terminal region of the beta chain of insulin tend to destabilize hexamer formation and speed the rate of absorption. Examples of these analogs are the insulins lispro (Humalog), aspart (NovoLog), and glulisine (Apidra). These insulins are excellent for premeal use, and because they also have a shorter duration of action than native human insulin (regular), they provide better mealtime coverage with a lower risk of postmeal hypoglycemia.

Conversely, basal insulin should have both a peakless action profile and a prolonged duration of action. In the case of insulin glargine (Lantus), these features are achieved by amino acid additions that shift the isoelectric point to promote hexamer formation. After injection, glargine is buffered to a physiologic pH and forms a microprecipitate that is then slowly absorbed. The protraction of insulin detemir (Levemir) is due to fatty acylation of the insulin molecule, which results in albumin binding. Degludec, a fatty acylated insulin, is currently undergoing review by the U.S. Food and Drug Administration (FDA).

21. What is amylin?

Amylin is a beta-cell hormone that is co-secreted with but structurally distinct from insulin. Under normal circumstances, amylin acts to reduce postprandial glucose excursions by reducing the gastric emptying rate and suppressing glucagon production, thereby reducing postprandial hepatic glucose production. It is also believed to inhibit the stomach hormone ghrelin, resulting in appetite suppression. In addition to an absolute insulin deficiency, patients with type 1 diabetes also have a complete deficiency of amylin, and patients with type 2 diabetes taking insulin have clearly reduced amylin responses to meals. Mealtime replacement of amylin in subjects who required insulin was shown to reduce HbA_{1C} levels modestly while promoting weight loss. Currently available as the synthetic analog pramlintide, amylin is approved for use in type 1 and type 2 diabetics as an injection before meals.

22. What are incretins?

The *incretin effect* refers to the enhanced insulin secretory response observed after an oral glucose load in comparison with an intravenous or parenteral glucose load. After eating, the cells of the distal small intestine release incretins such as glucagon-like peptide-1 (GLP-1) into the blood. GLP-1 secretion is under neurogenic control. It acts to increase glucose-dependent insulin secretion, suppress glucagon release, delay gastric emptying, enhance satiety through a direct effect on the central nervous system, reduce beta-cell apoptosis, and possibly stimulate beta-cell neogenesis. GLP-1 is quickly inactivated by an enzyme, dipeptidyl peptidase IV (DPP-IV); as a result, the therapeutic potential for GLP-1 is limited by its extremely short half-life.

23. How are incretins used to treat type 2 diabetes?

There are currently two types of incretin-based therapies available, GLP-1 analogs, which are not substrates for DPP-IV, and DPP-IV inhibitors, which protract the half-life of endogenous GLP-1. The two GLP-1 analogs available are exenatide and liraglutide. Both are given by injection and are associated with moderate weight loss in addition to modest HbA_{1C} lowering (0.6%-1.2%). The three DPP-IV inhibitors are available in the United States, sitagliptin, saxagliptin, and linagliptin. In comparison with the GLP-1 analogs, DPP-IV inhibitors are associated with lower weight loss and less HbA_{1C} lowering is; however, they are administered orally. Both types of incretins can be used as monotherapy or in combination with other available antihyperglycemia agents.

24. What are the classes of oral diabetes medications? How do they work?

In addition to the DPP-IV inhibitors mentioned earlier, several classes of diabetes medications are available for optimizing glycemic control in people with type 2 diabetes (Table 1-4). Sulfonylureas (glyburide, glipizide, and glimepiride) and meglitinides (repaglinide and nateglinide) enhance the secretion of endogenous insulin through membrane-associated receptors. Metformin, the only biguanide available, reduces hepatic gluconeogenesis, thereby indirectly increasing peripheral insulin sensitivity. The alpha-glucosidase inhibitors (miglitol and acarbose) slow the absorption of dietary carbohydrates by inhibiting the intestinal brush-border enzymes (Table 1-4) that break down polysaccharides into absorbable monosaccharides. The thiazolidinediones (pioglitazone and rosiglitazone) act by binding nuclear peroxisome proliferator–activated receptor-gamma (PPAR-γ) to increase insulin sensitivity and directly enhance insulin action in muscle and fat cells. Rosiglitazone has been linked to nonfatal myocardial infarction, and observational studies have associated pioglitazone with a risk of bladder cancer.

TABLE 1-4. ORAL DIABETIC MEDICATIONS

CLASS	MEDICATION(S)	MECHANISM	ACTION	MONOTHERAPY EFFICACY (HEMOGLOBIN A_{1C} LOWERING) (%)	COMMENTS
Sulfonylureas	Glyburide Glipizide Glimepiride	Closes beta-cell K_{ATP} channels	↑ Insulin secretion	1.5	Hypoglycemia; weight gain
Meglitinides	Repaglinide Nateglinide	Closes beta-cell K_{ATP} channels	↑ Insulin secretion	1.0-1.5	Expensive
Biguanides	Metformin	Activates adenosine monophosphate kinase	↓ Hepatic glucose production	1.5	Weight neutral; may reduce insulin requirements
Thiazolidinediones	Pioglitazone Rosiglitazone	Activates peroxisome proliferator-activated receptor-gamma	↑ Insulin sensitivity	0.8-1.0	Congestive heart failure; edema; may be associated with nonfatal myocardial infarction and bladder carcinoma
α-Glucosidase inhibitors	Acarbose Miglitol	↓ Intestinal absorption of carbohydrates	↓ Prandial glucose excursion	0.5-0.8	Gastrointestinal side effects: flatulence, diarrhea
Dipeptidyl peptidase-4 inhibitors	Sitagliptin Saxagliptin Linagliptin	Inhibit degradation of glucagon-like peptide-1	↓ Prandial glucose excursion	0.5-0.9	Expensive
Bile salt binders	Colesevelam	↓ Bile acid reabsorption	Unknown	~0.5	Expensive; lowers low-density cholesterol and glucose
Dopaminergic agonists	Bromocriptine (quick release)	Activates dopamine-2 receptors	Central effect and ↑ insulin sensitivity	~0.5	Expensive; dizziness; nausea; fatigue

BIBLIOGRAPHY

American Diabetes Association: Standards of medical care in diabetes–2012, *Diabetes Care* 35 (Suppl 1): S11–S63, 2012.
Ashcroft FM, Rorsman P: Diabetes mellitus and the β cell: the last ten years, *Cell* 148:1160–1171, 2012.
Bolen S, Feldman L, Vassy J, et al: Systematic review: comparative effectiveness and safety of oral medications for type 2 diabetes mellitus, *Ann Int Med* 147:386–399, 2007.
Davidson JA: Incorporating incretin-based therapies into clinical practice: differences between glucagon-like peptide receptor 1 agonists and dipeptyl peptidase 4 inhibitors, *Mayo Clin Proc* 85 (Suppl):S27–S47, 2010.
Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus, *N Engl J Med* 329:977–986, 1993.
Diabetes Prevention Trial—Type 1 Diabetes Study group: Effects of insulin in relatives of patients with type 1 diabetes mellitus, *N Engl J Med* 346:1685–1691, 2002.
Edelman SV, Weyer C: Unresolved challenges with insulin therapy in type 1 diabetes: potential benefit of replacing amylin, a second β-cell hormone, *Diabetes Technol Therapeut* 4:175–189, 2002.
Egan JM, Bulotta A, Hui H, Perfetti R: GLP-1 receptor agonists are growth and differentiation factors for pancreatic islet beta cells, *Diabetes Metab Res Rev* 19:114–123, 2003.
Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the expert committee on the diagnosis and classification of diabetes mellitus, *Diabetes Care* 20:1183–1196, 1997.
Gale EA: European Nicotinamide Diabetes Intervention Trial (ENDIT): a randomized controlled trial of intervention before the onset of type 1 diabetes, *Lancet* 363:925–931, 2004.
Genuth S, Ismail-Beigi F: Clinical implications of the ACCORD trial, *J Clin Endocrinol Metab* 97:41–48, 2012.
Gerstein HC, Miller ME, Byington RP, et al: Action to control cardiovascular risk in diabetes study group. Effects of intensive glucose lowering in type 2 diabetes, *N Engl J Med* 358:2545–2559, 2008.
Holman RR, Farmer AJ, Davies MJ, et al: 4-T study group. Three year efficacy of complex insulin regimens in type 2 diabetes, *N Engl J Med* 361:1736–1747, 2009.
Holman RR, Paul SK, Bethal MA, et al: 10-year follow-up of intensive glucose control in type 2 diabetes, *N Engl J Med* 359:1577–1589, 2008.
Inzucchi SE, Bergenstal RM, Buse JB, et al: Management of hyperglycemia in type 2 diabetes: a patient centered approach, *Diabetes Care* 35:1364–1379, 2012.
Knowler WC, Barrett-Conner E, Fowler SE, et al: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin, *N Engl J Med* 346:393–403, 2002.
Owens DR, Luzio SD, Sert-Langeron C, Riddle MC: Effects of initiation and titration of a single pre-prandial dose of insulin glulisine in type 2 diabetes: a 6-month "proof-of-concept" study, *Diabetes Obes Metab* 13:1020–1027, 2011.
The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group: Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes, *N Engl J Med* 353:2643–2653, 2005.
UK Prospective Diabetes Study (UKPDS) Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33), *Lancet* 352: 857–858, 1998.
Vajo Z, Fawcett J, Duckworth WC: Recombinant DNA technology in the treatment of diabetes: insulin analogs, *Endocr Rev* 22:706–717, 2001.

CHAPTER 2

ACUTE AND CHRONIC COMPLICATIONS OF DIABETES

Marissa Grotzke and Robert E. Jones

1. What are the acute complications of diabetes?

Hyperglycemia and hypoglycemia; both are the result of an imbalance between medications (insulin or oral diabetic agents) and the patient's food intake and exercise.

2. Describe the symptoms of hyperglycemia.

Initial symptoms are increased thirst (polydipsia), increased urination (polyuria), fatigue, and blurry vision. If uncorrected, hyperglycemia may eventually lead to diabetic ketoacidosis (DKA) or hyperosmolar hyperglycemic syndrome (HHS). Rather than distinct entities, DKA and HHS represent a spectrum of a disease process characterized by varying degrees of insulin deficiency, overproduction of counterregulatory hormones, and dehydration. In some situations, features of both DKA and HHS may occur concurrently.

3. What is DKA?

DKA is a state of uncontrolled catabolism triggered by a relative or absolute deficiency in circulating insulin. The DKA triad is hyperglycemia (blood glucose [BG] usually $>$ 250 mg/dL), metabolic acidosis (pH $<$ 7.35), and ketonuria. Insulin deficiency is accompanied by a reciprocal elevation in counterregulatory hormones (glucagon, epinephrine, growth hormone, and cortisol), which causes increased glucose production by the liver (gluconeogenesis) and catabolism of fat (lipolysis). Lipolysis provides the substrate (free fatty acids) for the uncontrolled production of ketones by the liver. The production of ketones then leads to metabolic acidosis.

4. What causes DKA?

Any disorder that alters the balance between insulin and counterregulatory hormones can precipitate DKA. A minority of cases occurs in people not previously diagnosed with diabetes, but most cases (up to 80%) occur in people with previous diagnoses. DKA is most often associated with type 1 diabetes; however, it may also occur in older patients with type 2 diabetes, particularly when associated with a major intercurrent illness.

5. What illnesses may trigger DKA?

Infection and myocardial infarction are the illnesses most commonly known to trigger DKA. Even localized infections, such as urinary tract infections and prostatitis, have precipitated DKA. Other triggers are severe emotional stress, trauma, medications (i.e., corticosteroids), and hormonal changes (i.e., preovulation) in women. Nonadherence and improper insulin self-management during an intercurrent illness are other common causes of DKA. Both represent a lack of knowledge and may be remediated through appropriate education (sick day rules to frequently measure glucose/ketones) or psychological intervention.

6. What are the signs and symptoms of DKA?

Nausea and vomiting, generalized abdominal pain, dehydration, rapid (Kussmaul) respirations, and a sweet (acetone) odor on the breath represent the classic clinical picture. In addition, patients may have an altered mental status and symptoms due to their possible precipitating illness.

7. How is DKA diagnosed?

DKA should be suspected if the patient presents with marked hyperglycemia (BG $>$ 250 mg/dL) and metabolic acidosis (pH $<$ 7.35). An elevated anion gap ($>$ 13 mEq/L) is usually, but not always, present. The finding of elevated ketones in the blood or urine confirms the diagnosis.

8. Is the ketone test result always positive with DKA?

No. If blood or urine ketone results are negative and DKA is strongly suspected, treatment with fluids and insulin should still be initiated. During the course of treatment, the blood and urine ketones test results will become positive. This "delay" in positivity for measured ketones is due to a limitation of the laboratory test for ketones, which detects only acetoacetate. The predominant ketone in untreated DKA is beta-hydroxybutyrate. As DKA is treated, acetoacetate becomes the predominant ketone, causing the test for ketones to turn positive.

9. What lab tests are recommended in the first hour of treatment for DKA?

- Baseline electrolytes, blood urea nitrogen (BUN), creatinine, and glucose measurements, anion gap calculation, urinalysis, urine and blood ketone measurements, and electrocardiogram (ECG) should be performed.
- An arterial blood gas (ABG) analysis should be obtained if the patient appears ill or tachypneic or if the serum bicarbonate is very low ($<$ 10 mEq/L).
- Fluid intake, urine output, and progression of laboratory changes should be recorded.
- Further lab testing should be based on findings of suspected triggers (i.e., infection, myocardial infarction).

10. Summarize the strategy for fluid and potassium administration in the first hour.

- Fluids: Normal saline given at 15 mL/kg/h (approximately 1 L/h for a 70-kg individual).
- Potassium: If T waves on the ECG are peaked or normal, no potassium replacement is initially necessary. If T waves are low or U waves are seen, 40 mEq potassium chloride (KCl) should be added to each liter of intravenous (IV) fluids.

11. How should insulin treatment be started with DKA?

An initial IV bolus of 10 to 20 units of regular insulin should be followed by a continuous infusion of 0.5 units/mL of regular insulin mixed in normal saline at a rate of 5 to 10 units per hour (0.1 unit/kg/h).

12. Summarize the strategy for clinical assessment, and fluid and potassium administration in the second hour of treatment.

- Fluids: Continue normal saline at approximately 1 L/h.
- Potassium: Adjust or add KCl to IV fluids to maintain serum potassium at 4 to 5 mEq/L.
- Monitor vital signs (including respiratory rate), level of consciousness, hydration status, and urine output.
- Repeat measurements of electrolytes, BG, and urine and blood ketones. Calculate anion gap.

13. How should insulin be adjusted during treatment?

If the serum glucose drops to less than 250 mg/dL, fluids should be changed to a 5% to 10% dextrose–containing solution. The insulin infusion rate may be doubled if the serum glucose does not decline after the first hour. The optimal rate of glucose decline is 100 mg/dL/h. The glucose level should not be allowed to fall to less than 250 mg/dL during the first 4 to 5 hours of treatment.

14. Summarize the basic strategy after the second hour of treatment.

- Assess the patient and repeat previously discussed lab tests hourly.
- Fluids: Adjust the rate of infusion according to the level of hydration. Consider changing to 0.45% normal saline if the patient is euvolemic and hypernatremic.
- Potassium: Continue to adjust to a goal serum value of 4 to 5 mEq/L.
- Insulin: Continue IV infusion as long as acidosis is present; supplement with dextrose as necessary.

15. When can the insulin infusion be discontinued?

When the anion gap corrects to normal, the pH is 7.3 or greater, or the serum bicarbonate is 18 mEq/L or greater, the patient can be given a subcutaneous dose of regular insulin or a short-acting insulin analog (lispro, aspart, glulisine) to cover a meal. The infusion should be stopped 30 minutes after the subcutaneous insulin is given. If the patient is unable to eat, give 5 units of regular or a short-acting insulin analog, continue the IV dextrose solution, and give supplemental short-acting insulin every 4 hours on the basis of the glucose level.

16. What other interventions may be necessary in the treatment of DKA?

If the initial serum phosphorus is less than 1.0 mg/dL, consider giving 10 to 20 mEq/h potassium phosphate in the IV fluids.

Bicarbonate (in the form of sodium bicarbonate) replacement is not recommended unless other causes of severe acidosis are present (e.g., sepsis, lactic acidosis) or the arterial pH is less than 6.9. If used, sodium bicarbonate should be diluted in the IV fluids and given over 1 hour.

17. What is hyperosmolar hyperglycemic syndrome?

Formerly known as hyperosmolar hyperglycemic nonketotic syndrome or coma, and described first in 1957 by Sament and Schwartz, hyperosmolar hyperglycemic syndrome (HHS) is a constellation of hyperglycemia, hyperosmolarity, and altered level of consciousness, most typically in the absence of acidosis.

18. Who is at risk for HHS and why?

Elderly patients, with or without a history of type 2 diabetes, are at particular risk for HHS because of a higher rate of impaired thirst perception and increased prevalence of impaired renal function. Precipitating factors, such as infection, myocardial infarction, cerebrovascular events, pancreatitis, gastrointestinal hemorrhage, and use of exogenous medications, may also be present.

19. What are the signs of HHS?

- Marked hyperglycemia (BG $>$ 600 mg/dL)
- Hyperosmolarity (serum Osm $>$ 320 mOsm/L)
- Arterial pH greater than 7.3

Hyperglycemia, once triggered, leads to glycosuria, osmotic diuresis, hyperosmolarity, cellular dehydration, hypovolemia, shock, coma, and, if untreated, death.

20. Why is ketoacidosis typically not seen in HHS?

Although glucose levels are generally higher in HHS than in DKA, the residual insulin secretory capacity of type 2 diabetics likely prevents severe acidosis and ketosis in HHS. The presence of circulating insulin or lower levels of counterregulatory hormones (or both) prevents lipolysis and significant ketone production. Lactic acidosis may be seen, however.

21. What are the symptoms of HHS?

Polyuria and polydipsia often occur days to weeks before manifestation of HHS. Patients are unable to drink enough to match a brisk osmotic diuresis, exacerbating the hyperglycemia. The imbalance of fluid intake and output eventually results in impairment of renal function, decrease in glucose excretion, and further worsening of hyperglycemia. Profound dehydration is typical. Fever is not part of the syndrome and, if present, suggests an infectious component. Focal neurologic defects may be seen in patients, including bilateral or unilateral hyporeflexia or hyperreflexia, seizures, hemiparesis, aphasia, presence of Babinski sign, hemianopsia, nystagmus, visual hallucinations, acute quadriplegia, and dysphagia.

22. What is the most common presenting symptom of HHS?

Altered mental status occurs in approximately 90% of cases and is the most common reason that patients are brought to the hospital. An effective osmolarity higher than 340 mOsm/L is required for

coma to be attributed to HHS and is present in 10% of patients upon presentation. *Effective osmolarity* refers to the true osmolarity seen by the cells and is calculated by means of the following equation:

$$\text{Effective osmolarity (mOsm/L)} = 2[\text{measured Na (mEq/L)}] + [\text{glucose (mg/dL)}/18]$$

23. What is the hallmark laboratory finding in patients with HHS?

Marked hyperglycemia (BG $>$ 600 mg/dL and often $>$ 1000 mg/dL) is characteristic: The serum sodium concentration is often factitiously low. To correct for the hyperglycemia, the following formula is used:

$$\text{Corrected Na} = \text{serum Na} + [1.6(\text{serum glucose} - 100)]/100$$

Other laboratory abnormalities include elevated BUN and creatinine, hypertriglyceridemia, and leukocytosis.

24. What is the first step in treating HHS?

Aggressive volume resuscitation is imperative and should be addressed before insulin administration to avoid intracellular fluid shifts (from falling glucose levels) that may worsen systemic perfusion. The fluid deficit is typically severe—on the order of 9 to 12 L. In patients with renal insufficiency or cardiac disease, central venous access may be necessary to monitor the response to therapy, and patients with altered mental status may require an indwelling urinary catheter.

25. Should isotonic or hypotonic fluids be used?

There is controversy regarding this issue; however, isotonic (0.9%) saline at a rate of approximately 1 to 2 L over the first hour is generally recommended. After the first hour, fluids may be changed on the basis of the serum sodium concentration: If serum Na is between 145 and 165 mEq/L, a change to half-normal saline (0.45%) may be considered; if serum Na is lower than 145 mEq/L, isotonic saline should be continued. Replacement of one half of the calculated fluid deficit over the initial 5 to 12 hours is recommended, with the balance of the deficit replaced over the subsequent 12 hours.

26. What role does insulin play in the treatment of HHS?

Continuous IV insulin infusion, as previously described for DKA, is helpful to reduce glucose levels at a predictable rate. Patients may be transitioned directly from IV to subcutaneous insulin as described for DKA. Because the presence of HHS suggests a significant insulin deficiency, most patients require discharge after being started on an insulin regimen, with the appropriateness of oral agents determined in the outpatient setting.

27. Describe the signs and symptoms of hypoglycemia.

To be defined as hypoglycemia-induced, Whipple's triad (low blood glucose, symptoms consistent with hypoglycemia, and resolution of symptoms by raising blood glucose) must be present. Symptoms can be divided into adrenergic and neuroglycopenic symptoms (Table 2-1), with different symptoms manifesting at progressively lower blood glucose levels. Adrenergic symptoms originate with the autonomic nervous system and include norepinephrine-mediated palpitations, tremor, anxiety and acetylcholine-mediated sweating, hunger, and paresthesias. Neuroglycopenic symptoms can include weakness, visual changes, behavior changes, confusion, seizure, loss of consciousness, and, if untreated, death; these symptoms represent the effects of low glucose levels on the central nervous system. Typical signs are pallor, diaphoresis, and tremor.

28. Discuss therapy-related causes of hypoglycemia in diabetes.

It is impossible to mimic the peaks and troughs of a normal insulin secretory pattern with subcutaneous insulin injections, and even a perfectly designed insulin regimen can lead to hypoglycemia when the patient decreases food intake, delays a meal, or exercises even slightly more than usual. Menstruating women can experience hypoglycemia at the time of menses because of a rapid fall in estrogen and progesterone. Elderly patients given a sulfonylurea for the first time may respond with severe hypoglycemia.

TABLE 2-1. CLINICAL MANIFESTATIONS OF HYPOGLYCEMIA

Adrenergic	Diaphoresis
	Palpitations
	Tremor
	Arousal/anxiety
	Pallor
	Hypertension
Neuroglycopenic	Cognitive impairment
	Fatigue
	Dizziness/faintness
	Visual changes
	Paresthesias
	Hunger
	Inappropriate behavior
	Focal neurologic deficits
	Seizures
	Loss of consciousness
	Death

Adapted from Cryer PE, Gerich JE: Hypoglycemia in insulin-dependent diabetes mellitus: insulin excess and defective glucose counterregulation. In Rifkin H, Porte E, editors: *Ellenberg and Rifkin's diabetes mellitus: theory and practice,* ed 4, New York, 1990, Elsevier, pp 526–546.

29. What other conditions may contribute to the development of hypoglycemia?

In addition to therapy-related factors, disorders such as those listed in Table 2-2 may precipitate hypoglycemia.

30. What is "hypoglycemia unawareness"?

Defective counterregulation is often associated with hypoglycemia unawareness, in which the patient reports an absence of the normal adrenergic warning symptoms of hypoglycemia. In contrast, the predominant signs and symptoms are due to decreased delivery of glucose to the brain (neuroglycopenic symptoms). The cognitive impairment associated with neuroglycopenia may prevent the patient from responding appropriately to self-treat the hypoglycemia. The result may be a traumatic automobile accident, seizure, coma, or death.

TABLE 2-2. CAUSES OF FASTING (POSTABSORPTIVE) HYPOGLYCEMIA

1. Drugs: insulin, sulfonylureas, alcohol
2. Critical organ failure: renal, hepatic, cardiac failure; sepsis; inanition
3. Hormonal deficiencies: cortisol and/or growth hormone; glucagon + epinephrine
4. Non–beta-cell tumor
5. Endogenous hyperinsulinism: beta-cell tumor (insulinoma); functional beta-cell hypersecretion; autoimmune hypoglycemia; ? ectopic insulin secretion
6. Hypoglycemias of infancy and childhood

From Cryer PE, Gerich JE: Hypoglycemia in insulin-dependent diabetes mellitus: insulin excess and defective glucose counterregulation. In Rifkin H, Porte E, editors: *Ellenberg and Rifkin's diabetes mellitus: theory and practice,* ed 4, New York, 1990, Elsevier, pp 526-546.

31. Can hypoglycemia unawareness be prevented?

Studies suggest that hypoglycemia unawareness may be the body's maladaptation to previous episodes of hypoglycemia. A single episode of hypoglycemia has been shown to reduce autonomic and symptomatic responses to hypoglycemia on the following day in normal subjects and in patients with type 1 diabetes. In contrast, meticulous prevention of hypoglycemia has been shown to reverse the defective counterregulation and reestablish the adrenergic symptoms after 3 months. Thus, meticulous attention to prevent hypoglycemia in patients without established autonomic neuropathy may be beneficial in reversing hypoglycemic unawareness.

32. How is hypoglycemia treated?

Mild hypoglycemia (BG 50-60 mg/dL) should be treated with 15 g of simple carbohydrate, such as 4 oz of unsweetened fruit juice or nondietetic soft drink. For more profound hypoglycemia, 15 to 20 g of simple carbohydrate should be ingested quickly, followed by 15 to 20 g of a complex carbohydrate, such as crackers or bread. All diabetic patients should be taught how to treat their hypoglycemia appropriately.

33. What should be done if the patient is unconscious?

Patients who are unconscious should not be given oral liquids. More viscous sources of sugar (e.g., honey, glucose gels, cake icing in a tube) can be carefully placed inside the cheek or under the tongue. Alternatively, 1 mg of glucagon may be injected intramuscularly. Glucagon indirectly raises the blood glucose level by increasing hepatic glucose production (glycogenolysis). In the hospital setting, IV dextrose (50% dextrose injection [D50]) is usually more accessible than glucagon and results in a prompt return of consciousness.

34. Discuss the role of education in treating hypoglycemia.

Instruction in the use of glucose gels and glucagon should be an essential part of training for all individuals living with insulin-treated diabetic patients. Patients and family members should be instructed not to overtreat hypoglycemia, particularly if it is mild. Overtreatment leads to subsequent hyperglycemia. Patients should also be instructed to test the blood glucose level when symptoms occur to confirm hypoglycemia whenever feasible. If testing is not possible, it is best to treat first. Patients taking diabetes medication should be instructed to test their glucose level before driving a vehicle. If the glucose level is lower than a preset level (e.g., < 125 mg/dL), the patient should be instructed to ingest a small source of carbohydrate before driving.

35. Summarize the common long-term complications of diabetes mellitus.

The chronic complications of diabetes can be divided into two broad categories: microvascular complications and macrovascular complications. Microvascular complications are considered relatively specific to diabetes; they are associated with pathologic endothelial changes, such as basement membrane thickening and increased vascular permeability, and can cause damage to the eyes (retinopathy), kidneys (nephropathy), and peripheral nerves (neuropathy). Macrovascular complications encompass an increased susceptibility to large blood vessel damage (atherosclerosis) and its ensuing complications.

36. What basic mechanism underlies the development of long-term diabetic complications?

Hyperglycemia is the major force underlying the microvascular complications of diabetes and has been implicated in the excessive risk for atherosclerosis seen in patients with insulin resistance. However, it is difficult to ascribe all of these observations to glucotoxicity alone.

37. How does chronic hyperglycemia affect cellular function?

- Nonenzymatic mass-action glycation of proteins: These proteins ultimately form advanced glycosylation end products (AGEs), which are associated with altered protein function. AGEs have been found in the connective tissue of blood vessels and in the renal glomerular matrix and have been shown to modify low-density lipoprotein (LDL) composition.

- Enzymatic conversion of glucose to sorbitol by aldose reductase in the eyes and peripheral nerves: Because the cellular clearance of sorbitol is extremely slow, it accumulates as an osmotically active molecule. This accumulation is also associated with neuronal myoinositol depletion.
- Excess intracellular glucosamine: Another product of glucose, intracellular glucosamine has been linked to endothelial dysfunction and to impaired insulin action.
- Activation of protein kinase C (PKC) by glucose: Thought to be due to depressed nitric oxide production and increased endothelin-1 activity, activation of PKC has been shown to mediate retinal and renal blood flow abnormalities and to increase endothelial cell permeability.
- Hyperglycemia-driven oxidative stress: The resulting activation of poly(ADP-ribose) polymerase (PARP) has been tied to glycemic injury and may serve, in part, to increase substrate flux into AGE, polyol, and glucosamine formation and to promote PKC activation.

38. Describe the characteristics of diabetic retinopathy.

Significant diabetic retinopathy may progress without symptoms. The initial visible lesions are microaneurysms that form on the terminal capillaries of the retina. Increased capillary permeability is manifested by the leaking of proteinaceous fluid, causing hard exudates. Dot-and-blot hemorrhages result from leaking of red blood cells. These findings by themselves do not lead to visual loss and are categorized as nonproliferative retinopathy (Table 2-3).

Proliferative retinopathy (see Table 2-3) develops when the retinal vessels are further damaged, causing retinal ischemia. The ischemia triggers new, fragile vessels to develop, a process termed *neovascularization*. These vessels may grow into the vitreous cavity and may bleed into preretinal areas or vitreous, causing significant vision loss. Loss of vision also may result from retinal detachment secondary to the contraction of fibrous tissue, which often accompanies neovascularization. Diabetic macular edema occurs when fluid from abnormal vessels leaks into the macula. It is

TABLE 2-3. CLINICAL MANIFESTATIONS OF DIABETIC EYE DISEASE

Nonproliferative diabetic retinopathy	Retinal microaneurysms
	Occasional blot hemorrhages
	Hard exudates
	One or two soft exudates
Preproliferative diabetic retinopathy	Presence of venous beading
	Significant areas of large retinal blot hemorrhages
	Multiple cotton-wool spots (nerve fiber infarcts)
	Multiple intraretinal microvascular abnormalities
Proliferative diabetic retinopathy	New vessels on the optic disc (NVD)
	New vessels elsewhere on the retina (NVE)
	Preretinal or vitreous hemorrhage
	Fibrous tissue proliferation
High-risk proliferative diabetic retinopathy	NVD with or without preretinal or vitreous hemorrhage
	NVE with preretinal or vitreous hemorrhage
Diabetic macular edema	Any thickening of retina $<$ 2 disc diameters from center of macula
	Any hard exudates $<$ 2 disc diameters from center of macula with associated thickening of the retina
	Any nonperfused retina inside the temporal vessel arcades
	Any combination of the above

From Centers for Disease Control: *The prevention and treatment of complications of diabetes mellitus*, Atlanta, 1991, Division of Diabetes Translation, Department of Health and Human Services.

detected with indirect funduscopy as the finding of a thickened retina near the macula and is commonly associated with the presence of hard exudates.

39. How common is diabetic retinopathy and how is it managed?

If glucose levels are not controlled, up to 70% of type 1 diabetics may experience proliferative retinopathy over their lifetime. Among type 2 diabetics, 21% may have significant nonproliferative and even proliferative retinopathy or macular edema at the time of diagnosis. This may be due to the long undiagnosed period of hyperglycemia that often occurs in people with type 2 diabetes.

Vision-threatening retinopathy can be managed with retinal photocoagulation, surgery (principally vitrectomy), and intraocular injections of anti-VEGF (vascular endothelial growth factor) compounds or steroids. Fenofibrate may also help.

40. What are the risk factors for development of diabetic retinopathy?

- Duration of diabetes
- Level of glycemic control
- Presence of hypertension
- Diabetic nephropathy is strongly associated with proliferative retinopathy in type 1 diabetes and insulin-treated type 2 diabetes.

41. How serious a problem is diabetic nephropathy, and how can its progression be slowed?

Diabetic nephropathy is the leading cause of end-stage renal disease in the United States. Its progression follows a predictable pattern characterized into stages I through V (Table 2-4).

Improved blood pressure and glucose control, the use of either an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) or the reduction of dietary protein intake can slow the rate of progression of renal failure in patients with nephropathy.

42. What is the risk that nephropathy will develop in a diabetic person?

Older epidemiologic studies suggest that patients with poorly controlled type 1 diabetes are at highest risk for nephropathy, which affects 30% of these patients. The risk of nephropathy is about 10 times less for patients with type 2 diabetes, but because of the higher prevalence of type 2 diabetes, this group currently outnumbers type 1 patients with end-stage renal disease. One explanation for the difference in risk for nephropathy between type 1 and type 2 diabetes is that the development of proteinuria in people with type 2 diabetes is associated with increased mortality.

TABLE 2-4. STAGING OF CHRONIC KIDNEY DISEASE

STAGE	ESTIMATED GFR (ML/MIN)	FINDINGS
1	90	Asymptomatic, ± HTN, renal hypertrophy, possible increase in GFR (GFR > 125 mL/min confers high risk of progression)
2	60-89	± Edema, ± HTN, glomerular histologic changes
3	30-59	Edema, HTN, anemia, microalbuminuria (urinary albumin excretion 30-300 mg/day)
4	15-29	Edema, fatigue, dyspnea, HTN, electrolyte abnormalities, proteinuria (urinary albumin excretion > 300 mg/day or total protein excretion > 500 mg/day)
5	< 15	Anorexia, dyspnea, HTN, encephalopathy, end-stage renal disease

GFR, glomerular filtration rate; HTN, hypertension.

43. What factors affect the development of diabetic nephropathy?

In addition to glycemic control, genetic factors play a key role in determining risk for diabetic nephropathy. Genes coding for essential hypertension appear to increase the risk. Known risk factors for diabetic nephropathy are as follows:

- Family history of hypertension (relative risk [RR] $\geq$ 3.7)
- Sibling with diabetic nephropathy (RR $>$ 4.0)
- Black race (RR $\geq$ 2.6 vs. white race)
- Smoking history (RR $\geq$ 2.0)
- History of poor glycemic control (RR $\geq$ 1.3-2.0)

44. Name the types of diabetic neuropathies.

There are four principal types: distal symmetric polyneuropathy, diabetic amyotrophy, diabetic mononeuropathy, and autonomic neuropathy. Distal symmetric polyneuropathy is the most common form and is slowly progressive. Amyotrophy manifests as pain and weakness in the thighs and may spontaneously improve. Mononeuropathy may affect both cranial and spinal nerves. Forms of autonomic neuropathy include gastroparesis and orthostatic hypotension.

45. Summarize the symptoms of distal symmetric polyneuropathy.

The disorder is usually discovered on physical examination by finding loss of vibratory sense in the toes and loss of ankle reflexes. Light touch and pinprick sensations are subsequently lost. Common associated symptoms are paresthesias and numbness of the feet, especially at night. The paresthesias may evolve to severe knifelike or burning pain, which can be disabling.

46. Explain the basic pathophysiology of distal symmetric polyneuropathy.

Pathologically, the nerves show axonal degeneration. Sensory loss or pain in the hands may also occur, but more commonly it is a manifestation of an entrapment neuropathy, such as carpal tunnel syndrome. Entrapment neuropathies are common in patients with diabetes and may result from increased susceptibility of these nerves to external pressure.

47. What causes the foot problems in patients with diabetes?

Loss of proprioceptive nerve fibers can result in an abnormal gait, leading to "pressure spots" on the foot that are signaled by the presence of thick calluses. If untreated, the calluses may ulcerate and become infected. Neuropathy, vascular disease, and predisposition to infection are the primary pathogenic components in the increased incidence of foot injury and amputation in diabetic patients.

48. How common is diabetic autonomic neuropathy? How does it affect survival rates?

Depending on the sophistication of testing used, up to 90% of people with diabetes have some degree of autonomic dysfunction. However, less than 50% of affected people are symptomatic. Patients with clinically significant autonomic neuropathy have a 10-year survival rate less than 50%. Both the sympathetic and parasympathetic nervous systems may be affected by diabetic neuropathy, and because these neuropathies initially damage nerves with the longest axons, patients with diabetic autonomic neuropathy also have readily apparent peripheral neuropathy.

49. Describe the classic signs of diabetic autonomic neuropathy.

Unexplained resting tachycardia and postural hypotension (with absence of fever, hypoglycemia, hyperthyroidism, etc.) are characteristic. Gastrointestinal symptoms are due to lack of peristalsis in the stomach (gastroparesis) or intestine and include early satiety, bloating, nausea, belching, abdominal distension, constipation, and diarrhea. Urinary retention or overflow incontinence may indicate autonomic neuropathy involving the urinary bladder. Erectile dysfunction is also a common symptom of autonomic neuropathy in diabetic men.

50. How is diabetic autonomic neuropathy diagnosed?

Lack of R-R variation on an electrocardiogram during deep breathing or the Valsalva maneuver can be used to confirm the diagnosis. Postural hypotension can be diagnosed by documenting a fall in upright blood pressure without a concurrent increase in pulse rate. Gastroparesis is diagnosed by the demonstration of prolonged gastric emptying using standardized radiolabeled meals; however, even mild hyperglycemia (BG $>$ 150 mg/dL) at the time of the test may functionally slow gastric emptying. Urinary and erectile problems are diagnosed by careful history taking.

51. How is painful diabetic neuropathy treated?

Multiple medications have been tried, with mixed success. These include nonsteroidal anti-inflammatory drugs, tricyclic antidepressants, anticonvulsants, opioids, and the serotonin-noradrenaline reuptake inhibitors (SNRIs). The most effective medications among those currently available appear to be pregabalin (Lyrica; starting dose 50 mg three times daily [TID] with titration to 100 mg TID, if tolerated), gabapentin (Neurontin; starting dose 300 mg twice daily with titration to 600 mg TID, as necessary), and the SNRI duloxetine (Cymbalta; dose 60 mg daily).

52. What are the risks associated with macrovascular disease in diabetes?

Patients with diabetes are at a twofold to fourfold higher risk for both cardiovascular disease (CVD) and peripheral vascular disease than the nondiabetic population. Women with diabetes have as high a risk for CVD as men. The commonly identified risk factors for CVD—smoking, hypercholesterolemia, and hypertension—also adversely affect CVD risk in people with diabetes. As a consequence, three out of four people with diabetes will die from CVD.

53. How can macrovascular disease be prevented in the diabetic population?

Cardiovascular risk factor reduction should be initiated at the first visit and pursued as aggressively in diabetic patients as in patients with known coronary artery disease. Aggressive blood pressure control is strongly supported by later randomized controlled trials, with a target blood pressure less than 130 (systolic)/80 (diastolic) mm Hg. Some studies have suggested that ACE inhibitors may be more effective than other antihypertensive agents in preventing CVD events and are currently the antihypertensive agents of choice. Control of hyperlipidemia should be pursued just as aggressively; the recommended goal for LDL cholesterol is less than 100 mg/dL ($<$ 70 mg/dL in high-risk patients). Improving glycemic control typically causes a significant reduction in triglyceride levels and modest reduction in LDL cholesterol. If goals for lipids are not achieved through glycemic control, diet, and exercise, then antihyperlipidemic drug therapy should be considered. The hydroxyl methyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are the drug class of choice. Smoking cessation should be strongly encouraged, as should exercise and weight loss (if the patient is overweight). Low-dose aspirin therapy is also recommended in high-risk individuals, but there is considerable controversy about the effectiveness of this intervention.

54. Does aggressive lipid-lowering therapy improve cardiac outcomes in diabetic patients?

Yes. A bevy of studies have proved the benefit of HMG-CoA reductase inhibitors in reducing the cardiovascular burden associated with diabetes by approximately 50%. On the basis of these studies, aggressive lipid-lowering therapy should be advocated in all diabetic patients, particularly those with known coronary artery disease.

55. How important is glycemic control in preventing the chronic complications of diabetes mellitus?

As discussed in Chapter 1, the Diabetes Control and Complications Trial (DCCT) involving people with type 1 diabetes and the United Kingdom Prospective Diabetes Study (UKPDS) using subjects with newly diagnosed type 2 diabetes have established that improving glycemic control effectively reduces the risk of development of microvascular complications (retinopathy, nephropathy, and neuropathy) in patients with type 1 and type 2 diabetes. Cardiovascular outcomes were also

significantly reduced in the long-term follow-up of subjects in both studies. However, several later trials involving people with long-standing type 2 diabetes (ACCORD [Action to Control Cardiovascular Risk in Type 2 Diabetes], ADVANCE [Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation], and VADT [VA Diabetes Trial]) have suggested a limited role for tight glucose control in preventing the cardiovascular complications associated with diabetes. It must be kept in mind that both the DCCT and the UKPDS were conducted prior to the introduction of statins as well as ACE inhibitors and ARBs and the current standards of percutaneous coronary interventions. In addition, there was a significant reduction in microvascular complications. Indeed, the diminution in microvascular complications in the ADVANCE trial and VADT was clearly related to both the duration of diabetes prior to study entry and the degree of hyperglycemia as represented by the initial hemoglobin A_{1C} value. Without question, management of diabetes must be focused early in the disease.

56. Does improved glycemic control in hospitalized patients affect outcome?

Adults with diabetes are six times more likely to be hospitalized than those without diabetes, and once hospitalized, they have a higher risk of mortality and a 30% longer length of stay. Under any circumstances, poorly controlled diabetes is a catabolic condition, and in hospitalized patients with diabetes who are under physiologic stress, catabolism is certainly detrimental. In addition, leukocytes and immune function are impaired by hyperglycemia. An early single-center study comparing very tight glucose management (BG range 80-110 mg/dL) with usual care (BG range 180-200 mg/dL) in patients in surgical intensive care units (ICUs) reported reductions in in-hospital mortality by 34%, sepsis by 46%, hemodialysis rate by 44%, transfusions by 50%, and critical illness–related polyneuropathy by 44%. Subsequently, several prospective and observational trials documented mixed results, and this issue was compounded by several meta-analyses that offered mixed conclusions about very tight glucose control in the ICU setting. A multicenter trial, Normoglycemia in Intensive Care Evaluation—Survival Using Glucose Algorithm Regulation (NICE-SUGAR), compared tight glucose control (BG target 81-108 mg/dL) with usual therapy (BG target $<$ 180 mg/dL) with the primary end point being mortality at 90 days from study entry. Mortality was unexpectedly increased by 14% in the intensively managed group. Also, there was no difference in secondary end points, including length of stay, rate of organ failure, and mechanical ventilation. As a result, the current consensus is to view blood glucose no greater than 180 mg/dL as the threshold for starting intravenous insulin in the ICU setting and establishing a blood glucose target between 140 and 180 mg/dL.

The data are less robust in patients hospitalized in non–critical care settings, but a meta-analysis has suggested that improved glycemic control significantly reduces the risk of infection and likely lowers the risk of hypoglycemia. Consensus statements have established treatment targets for non–critical care patients: preprandial BG less than 140 mg/dL and random BG level less than 180 mg/dL.

BIBLIOGRAPHY

The ACCORD Study Group: Long-term effects of intensive glucose lowering on cardiovascular outcomes, *N Engl J Med* 364:818–828, 2011.

The ADVANCE Collaborative Group: Intensive blood glucose control and vascular outcomes in type 2 diabetes, *N Engl J Med* 358:2560–2572, 2008.

American Diabetes Association: Standards of medical care in diabetes—-2012, Diabetes Care 35 (Suppl 1):S11–S63, 2012.

Antionetti DA, Klein R: Diabetic retinopathy, *N Engl J Med* 366:1227–1239, 2012.

Chong MS, Hester J: Diabetic painful neuropathy: current and future treatment options, *Drugs* 67:569–585, 2007.

Chrysant SG: The ALLHAT study: results and clinical implications, *Q J Med* 96:771–772, 2003.

Collins R, Armitage J, Parish S, et al: MRC/BHF heart protection study of cholesterol-lowering with simvastatin in 5963. people with diabetes: a randomized placebo-controlled trial, *Lancet* 361:2005–2016, 2003.

DCCT/EDIC Research Group: Intensive diabetes therapy and glomerular filtration rate in type 1 diabetes, *N Engl J Med* 365:2366–2376, 2011.

The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group: Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes, *N Engl J Med* 353:2643–2653, 2005.

Duckworth W, Abrira C, Moritz T, et al: Glucose control and vascular outcomes in veterans with type diabetes, *N Engl J Med* 360:129–139, 2009.
Folwaczny C, Wawarta R, Otto B, et al: Gastric emptying of solid and liquid meals in healthy controls compared with long-term type-1 diabetes mellitus under optimal glucose control, *Exp Clin Endocrinol Diabetes* 111:223–229, 2003.
Fritsche A, Stefan N, Häring H, et al: Avoidance of hypoglycemia restores hypoglycemia awareness by increasing β-adrenergic sensitivity in type 1 diabetes, *Ann Intern Med* 134:729–736, 2001.
Haffner SM, Lehto S, Ronnemaa T, et al: Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 339:229–234, 1998.
Hasler WL: Gastroparesis: symptoms, evaluation, and treatment, *Gastroenterol Clin North Am* 36:619–647, 2007.
Hollenberg NK: Treatment of the patient with diabetes mellitus and risk of nephropathy, *Arch Intern Med* 164:125–130, 2004.
Kitabchi A, Wall BW: Management of diabetic ketoacidosis: diabetic ketoacidosis and hyperglycemic hyperosmolar syndrome, *Crit Care Clin* 17:75–106, 2001.
Murad MH, Coburn J, Coto-Yglesias F, et al: Glycemic control in non-critically ill hospitalized patients: a systematic review and meta-analysis, *J Clin Endocrinol Metab* 97:49–58, 2012.
The NICE-SUGAR Study Investigators: Intensive versus conventional glucose control in critically ill patients, *N Engl J Med* 360:1283–1297, 2009.
Pyörälå K, Pederson TR, Kjekshus J, et al: Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease: a subgroup analysis of the Scandinavian Simvastatin Survival Study (4S), *Diabetes Care* 20:614–620, 1997.
Reusch JEB: Diabetes, microvascular complications, and cardiovascular complications: what is it about glucose? *J Clin Invest* 112:986–988, 2003.
Ritz E, Orth SR: Nephropathy in patients with type 2 diabetes mellitus, *N Engl J Med* 341:1127–1133, 1999.
Russell M, Silverman A, Fleg JL, et al: Achieving lipid targets in adults with type 2 diabetes—the SANDS Study, *J Clin Lipidol* 4:435–443, 2010.
Sarafidis PA: Antihypertensive therapy in the presence of proteinuri, *Am J Kidney Dis* 49:12–26, 2007.
Simó R, Hernández C: Advances in the medical treatment of diabetic retinopathy, *Diabetes Care* 32:1556–1562, 2009.
Umpierrez GE, Hellman R, Korytowski MT, et al: Management of hyperglycemia in hospitalized patients in non-critical care setting: an Endocrine Society Clinical Practice Guideline, *J Clin Endocrinol Metab* 97:16–38, 2012.
Van den Berghe G, Wouters P, Weekers F, et al: Intensive insulin therapy in the surgical intensive care unit, *N Engl J Med* 342:1301–1308, 2000.
Vinik AI, Mehrabyan A: Diagnosis and management of diabetic autonomic neuropathy, *Compr Ther* 29:130–145, 2003.

CHAPTER 3

INTENSIVE INSULIN THERAPY

Jennifer M. Trujillo

1. What is intensive insulin therapy?

Intensive insulin therapy (IIT) is the use of multiple daily injections (MDIs) of insulin (both long-acting and rapid-acting formulations) or an insulin pump in an effort to mimic the normal secretion of insulin by the pancreas. IIT may also be referred to as physiologic, multiple-component, or basal-bolus insulin therapy. IIT is only one aspect of comprehensive, intensive diabetes therapy to achieve tight glycemic control. IIT is complex because it requires multiple injections or pump boluses per day in addition to routine monitoring and collaborative decision making.

2. List critical components of intensive therapy.

- Frequent self-monitored blood glucose (SMBG) measurements
- Defined and individualized target blood glucose (BG) levels
- Use of SMBG data and glucose patterns to meet treatment goals
- Dose modifications according to the individual's response to therapy
- Understanding of diet composition, specifically carbohydrate content
- Careful balance of food intake, activity, and insulin dosage
- Use of carbohydrate-to-insulin ratios according to food intake
- Use of correction factors (CFs) for the adjustment of insulin according to glucose levels
- Patient education and motivation, and ongoing interaction between patient and health care team

3. Summarize studies evaluating optimal glycemic control to decrease chronic diabetes complications.

The Diabetes Control and Complications Trial (DCCT), evaluating patients with recent-onset type 1 diabetes, showed that improved glycemic control (hemoglobin A_{1C} [HbA_{1C}] $< 7\%$) significantly reduced rates of microvascular complications, including progression of retinopathy, nephropathy, and neuropathy, but increased rates of hypoglycemia. Intensive insulin therapy was a key part of achieving glycemic control in the DCCT. The Kumamoto Study and the United Kingdom Prospective Diabetes Study (UKPDS) confirmed that improved glycemic control ($HbA_{1C} < 7\%$) was associated with significantly reduced rates of microvascular complications in patients with recent-onset type 2 diabetes. The long-term extensions of the DCCT and the UKPDS showed significant reductions in cardiovascular complications with good glycemic control and demonstrated that the microvascular benefits of good glycemic control persisted for decades. Later studies in patients with more advanced type 2 diabetes (Action to Control Cardiovascular Risk in Diabetes [ACCORD] trial, Action in Diabetes and Vascular Disease [ADVANCE] trial, and VA Diabetes Trial [VADT]) failed to show that more aggressive glycemic targets ($HbA_{1C} < 6.0\%$-6.5%) reduced cardiovascular complications, and one study showed an increase in mortality. Rates of hypoglycemia with more aggressive glucose control were significant in all three trials.

4. Which patients are candidates for IIT?

All people with diabetes should be considered potential candidates for IIT. However, the degree of therapy intensification must be based on each patient's personal situation and abilities. Patient characteristics that predict greater success with IIT include motivation, willingness to perform frequent SMBG (up to 6-10 times/day) measurements and record results, time to spend with a

diabetes educator, the ability to recognize and treat hypoglycemia, sick day planning, and a supportive network of family or friends. In addition, implementation of IIT requires a cohesive diabetes team that is available for frequent interaction and discussion about results of monitoring, insulin adjustments, and other issues.

5. What are the risks of intensive insulin therapy?

Hypoglycemia and weight gain are the most common adverse effects of insulin therapy. IIT in the DCCT resulted in a three-fold increased risk of severe hypoglycemia in comparison with conventional treatment (62 episodes per 100 patient-years of therapy). Since the completion of the DCCT, newer rapid-acting and long-acting insulin analogs have been developed that are associated with less hypoglycemia than the short-acting and intermediate-acting human insulin products used in the trial. Frequent episodes of hypoglycemia can lead to loss of clinical warning symptoms (e.g., palpitations, sweating, hunger) with hypoglycemia (known as *hypoglycemia unawareness).* A unique risk of pump therapy is diabetic ketoacidosis because pump malfunctions or infusion site problems can interrupt insulin delivery. Finally, IIT requires time and commitment from the patient and may have negative psychosocial and economic implications.

6. Explain the difference between basal and bolus insulin coverage.

Intensive insulin therapy attempts to mimic normal insulin secretion, which includes continuous basal coverage in addition to bursts of insulin to regulate the rise in glucose after food intake (Fig. 3-1). Basal insulin secretion suppresses hepatic glucose production to control blood glucose levels in the fasting state and premeal periods. Normal basal insulin secretion from the pancreas varies slightly throughout the day, responding to changes in activity, blood glucose levels, and regulatory hormones. Basal coverage is usually accomplished with injections of long-acting insulin preparations or with the basal infusion function on the insulin pump. Bolus insulin doses consist of two components, the nutritional dose (the amount of insulin required to manage glucose excursions following meals) and the correction dose (the amount of insulin required to reduce a high glucose level detected before a meal). Bolus coverage is accomplished by injections of rapid-acting or short-acting insulin preparations or with use of the bolus function on the insulin pump. Physiologic insulin secretion requirements are approximately 50% basal and 50% bolus.

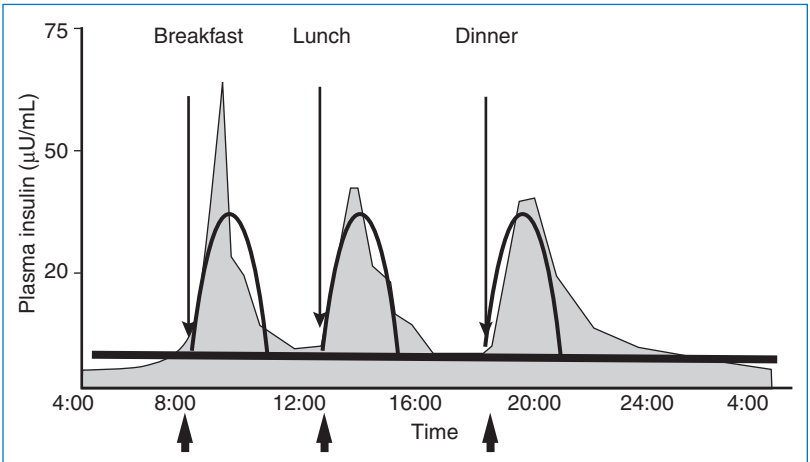

Figure 3-1. Schematic representation of insulin therapy pattern provided by once daily long-acting basal insulin and rapid-acting bolus insulin before each meal to mimic normal physiologic insulin secretion. *Source: White RD. Insulin Pump Therapy (Continuous Subcutaneous Insulin Infusion).* Primary Care: Clinics in Office Practice *2007;34:845-71.*

7. How are basal and bolus insulins used with an MDI regimen?

A long-acting insulin is injected either once or twice daily to provide the basal insulin portion of an MDI regimen, which is approximately 50% of a patient's total daily dose. Ideally, basal insulin should cover background insulin needs only, independent of food intake. A rapid-acting or short-acting insulin is injected before meals to provide the bolus insulin portion of an MDI regimen (see Fig. 3-1). Rapid-acting insulin is preferred because of the rapid onset and short duration of action. A patient can adjust each bolus dose to match the carbohydrate intake and to correct for high glucose levels before the meal, whereas the basal dose remains constant from day to day. Premixed "biphasic" insulin preparations combine either a rapid-acting insulin analog or regular human insulin with a crystalline protaminated form of the analog or NPH (neutral protamine Hagedorn) human insulin in an attempt to imitate basal and bolus therapies with fewer injections.

8. What are the currently available insulin preparations?

See Table 3-1.

9. Describe the pharmacodynamics of insulin preparations.

See Table 3-1.

10. When should bolus insulin be taken?

- Five to 10 minutes before meals and snacks when BG is in the normal range (70-130 mg/dL)
- Fifteen to 30 minutes before meals if the premeal BG is higher than 130 mg/dL (Correctional bolus insulin [CF] is added to meal insulin when the BG is elevated.)
- Immediately after eating, if gastroparesis or an intercurrent illness is present
- Upon arrival of food, if the patient is unfamiliar with meal size, content, or timing (i.e., in a restaurant or hospital)

TABLE 3-1. THE PHARMACODYNAMICS OF INSULIN PREPARATIONS

	ONSET	PEAK*	DURATION*
Bolus Insulin Products			
Rapid-acting analog: Insulin aspart (NovoLog) Insulin lispro (Humalog) Insulin glulisine (Apidra)	5-30 min	1-2 hr	4-6 hr
Short-acting: Regular (Humulin R, Novolin R)	30-60 min	2-3 hr	4-8 hr
Basal Insulin Products			
Intermediate-acting: NPH (Humulin N, Novolin N)	2-4 hr	4-10 hr	8-18 hr
Long-acting analog: Insulin detemir (Levemir) Insulin glargine (Lantus)	2-4 hr	6-16 hr†	16-24 hr
Combinations			
70% NPH, 30% regular (Humulin 70/30, Novolin 70/30)	30-60 min	Dual	10-16 hr
75% NPL, 25% lispro (Humalog 75/25)	5-15 min	Dual	10-16 hr
50% NPL, 50% lispro (Humalog 50/50)	5-15 min	Dual	10-16 hr
70% insulin aspart protamine, 30% insulin aspart (NovoLog 70/30)	5-15 min	Dual	15-18 hr

NPH, neutral protamine Hagedorn; NPL, neutral protamine lispro suspension.
*The peak and duration of insulin action are variable, depending on injection site, duration of diabetes, renal function, smoking status, and other factors.
†Insulin glargine is considered "peakless" although it has exhibited peak effects during comparative testing.

11. When should basal insulin be taken?

- Insulin glargine or detemir should be taken at bedtime if a dawn phenomenon is present or at any consistent time, approximately every 24 hours. (Insulin glargine or detemir cannot be mixed with other insulins.)
- If nocturnal hypoglycemia results from taking a full dose of glargine or detemir at bedtime, an option would be to split the dose so that 50% is taken in the morning and the other 50% is taken in the evening, approximately 12 hours apart.
- NPH insulin is given in the morning and at bedtime to avoid nocturnal hypoglycemia.

12. What is an insulin pump?

An insulin pump is a small, lightweight, portable, battery-operated device that is either attached directly to the body (patch pump) or worn on clothing or a belt like a pager (traditional pump). A traditional pump is composed of a pump reservoir (which holds a 2- to 3-day supply of rapid-acting or short-acting insulin) connected to an infusion set, which ends in a cannula that is inserted into the skin and changed every 2 to 3 days. A patch pump is tubing free and consists of a disposal reservoir that attaches directly to the body with self-adhesive backing and a built-in infusion set in the device for insertion into the subcutaneous tissue. The patch pump is controlled by a handheld personal digital assistant. Insulin is delivered through either system in microliter amounts continuously over 24 hours. The user is responsible for setting basal rates and determining bolus doses, depending on the meal ingested and the SMBG results. Currently, six companies offer insulin pumps in the United States; several other pumps are in development. Each pump has special features and functions that are unique and help with the flexibility of pump use. To learn more about each of these pumps, contact the companies listed in Table 3-2.

13. What are the patient's responsibilities before insulin pump therapy can be initiated?

- Commit at least 2 to 3 months to pump initiation, including multiple meetings with the diabetes team before, during, and after the pump is initiated.
- Demonstrate the ability to monitor BG values at least 4 to 10 times per day; keep logs of BG readings, insulin doses, and food consumed; and communicate information to the team.
- Review pump training materials and practice pump functions at least 2 or 3 times before wearing the pump.
- Be willing to test basal rates or agree to wear a continuous glucose monitoring (CGM) system or device to ensure that basal rates are set appropriately.

14. Describe the benefits of insulin pump therapy.

Currently, insulin pump therapy is the dosing strategy that most closely mimics physiologic insulin secretion. Benefits include better, more precise glucose control with less glycemic variability, a reduction in frequency and severity of hypoglycemia, ability to adjust basal rates throughout the day (Fig. 3-2), ability to extend bolus dose durations to better cover high-fat meals (see Fig. 3-2),

TABLE 3-2. CURRENTLY AVAILABLE INSULIN PUMPS

COMPANY	INSULIN PUMP	WEBSITE
Roche Insulin Delivery Systems	ACCU-CHEK Spirit	Accu-chekinsulinpumps.com
Sooil Development	Dana Diabecare IIS	Sooilusa.com
Medtronic Diabetes	MiniMed Paradigm Real-Time Revel	Minimed.com
Insulet Corporation	OmniPod	MyOmniPod.com
Animas Corporation	OneTouch Ping	Animas.com
Tandem Diabetes Care	t:slim	Tandemdiabetes.com

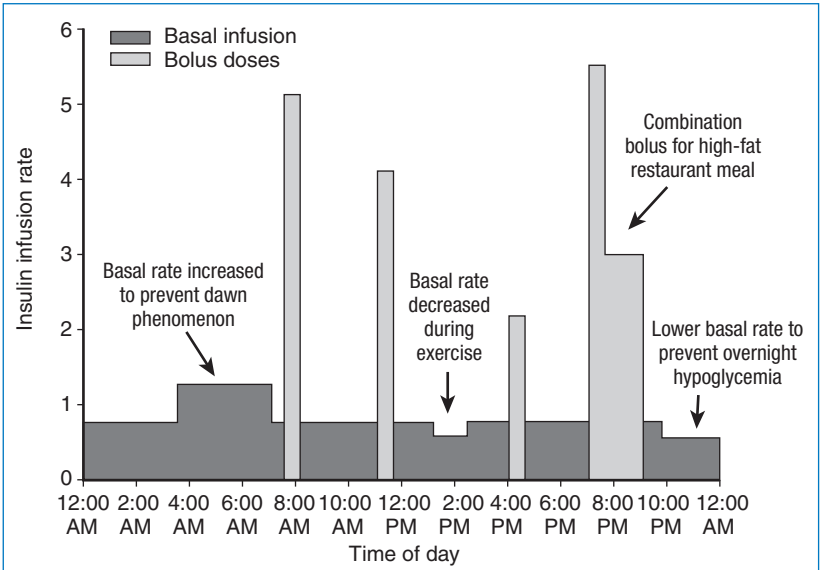

Figure 3-2. Insulin delivery pattern with pump therapy.

improved flexibility of lifestyle, ability to administer small amounts of insulin (as little as 0.025 units), protection from overcorrection by tracking of active insulin, and ability to integrate with continuous glucose monitor technology.

15. Describe the limitations of insulin pump therapy.

The cost of an insulin pump and supplies is higher than that of an MDI regimen. The device must be worn 24 hours a day, and optimal use requires a highly motivated, competent patient and a higher level of training. A strong support system from a diabetes team is beneficial. Other limitations include infusion-site infections and risks of diabetic ketoacidosis (DKA) if insulin delivery is interrupted.

16. What is a glucose sensor?

Currently, there are three glucose-sensing, or continuous glucose monitoring (CGM), devices available for purchase—the Guardian Real-Time by Medtronic Diabetes (Northridge, CA), the MiniMed Paradigm Real-Time Revel by Medtronic Diabetes, and the SEVEN PLUS by DexCom (San Diego, CA). The sensing system consists of a monitor that collects the data and a sensor that is placed temporarily under the skin, generating an electrical signal that is proportional to the amount of glucose present in the interstitial fluid. The interstitial values are calibrated with finger-stick readings that must be entered into the system at least three times per day. These devices provide values every 5 minutes within a range of 40 to 400 mg/dL that are available to the wearer and feature alarms that sound if the values fall out of the target ranges programmed. Because the systems measure interstitial fluid glucose versus blood glucose (from the finger-stick readings) and lag behind changing glucose values by approximately 20 minutes, the sensor values cannot be used to determine bolus amounts. However, sensor information can be helpful for following blood glucose trends and patterns as well as for picking up on unexpected hypoglycemia, especially nocturnal episodes. Currently insurance coverage for these devices is limited.

17. Define carbohydrate counting. How is it used with IIT?

Currently, carbohydrate counting is considered the “gold standard” for estimation of mealtime insulin doses. Carbohydrate counting is a tool used to match bolus insulin doses to food intake because

carbohydrates have the greatest effect on BG levels. The peak of bolus insulin analogs should match the peak of BG following carbohydrate digestion and absorption (≈1-3 hours, depending on the fat and fiber content of the meal).

18. List common foods that contain dietary carbohydrates.

- Starch: cereals, grains, beans, bread, rice, pasta, and starchy vegetables
- Sugar: lactose (milk and yogurt), fructose (fruit, juice, and honey), and sucrose (table sugar and desserts)
- Fiber: cellulose and hemicellulose, lignins, gums, or pectins found in fruits, vegetables, legumes, and whole grains

19. How are carbohydrates counted?

Calculating the number of carbohydrates may initially require measuring and weighing commonly eaten foods. Nutrition labels on food packages state the number of grams of carbohydrates based on the serving size. Carbohydrate reference books are available at bookstores or through the American Dietetic Association (http://www.eatright.org) or the American Diabetes Association (ADA; http://www.diabetes.org). Software programs are available for personal digital assistants (PDAs) or online. Many restaurant chains provide nutrition brochures.

20. Explain the carbohydrate-to-insulin (C:I) ratio.

The C:I ratio is used to estimate how many grams of carbohydrate each unit of rapid-acting insulin will cover (e.g., 20:1 = 20 g of carbohydrate consumed requires 1 unit of meal insulin).

21. How do you determine an initial C:I ratio?

Ratios are based on a patient's total daily dose (TDD) of insulin, which usually indicates his or her sensitivity to insulin. An MDI regimen of basal insulin and premeal injections of rapid-acting insulin must be previously (or concurrently) implemented before a C:I ratio is established. A person must be taught to count carbohydrates before using a C:I ratio safely. Determine the C:I ratio as follows:

1. Add up the patient's TDD of insulin with current therapy.
2. Consider the patient's HbA_{1c} value (ADA target is $< 7\%$), frequency of hypoglycemia, and comorbidities.
3. The initial C:I is estimated by dividing 550 by the TDD. Example: 550 ÷30 units = 18. The C:I ratio is 18:1.

In clinical practice, the constant in the C:I formula may range from 350 to 550. The initial calculated C:I must then be adjusted on the basis of each patient's records and is therefore only a starting point.

22. Give an example of an initial C:I ratio when changing to basal and bolus insulins.

- 40 units of Humulin 70/30 premixed insulin in the morning
- 17 units of Humulin 70/30 premixed insulin before the evening meal
- TDD = 57 units (HbA_{1c} 8.5% with 2-3 nocturnal hypoglycemic episodes per week)
- 550 ÷ 57 = 9.6
- Begin with a C:I of 10:1.

In this example, 1 unit of rapid-acting insulin will be given for every 10 g of carbohydrate eaten.

23. How do you adjust the C:I ratio once the initial ratio has been established?

Fine-tuning of a C:I ratio is based on BG records before meals and 2 hours after meals. The desired premeal BG is 70 to 130 mg/dL for most patients using IIT. A C:I ratio is correct if the BG increases by approximately 30 to 50 mg/dL over the premeal value at the 2-hour postprandial reading and returns to the range of 70 to 130 mg/dL by about 5 hours after the bolus insulin is given (Fig. 3-3). If 2-hour postprandial BG increases exceed 50 mg/dL, the C:I ratio should be adjusted and testing repeated, with further adjustments until the desired excursion is consistently achieved.

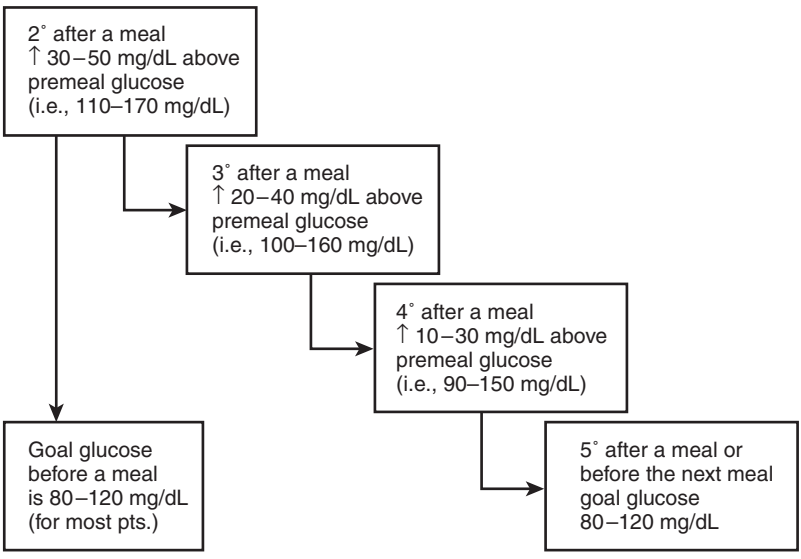

Figure 3-3. Expected postprandial blood glucose (BG) range with rapid-acting bolus insulin.

24. What are common causes of high BG?

- Missing an injection or bolus dose of insulin
- Underestimating carbohydrates
- Decreased physical activity
- Stress, illness, or infection
- Menstrual cycle
- Steroids or other medications

25. What are other factors to consider in troubleshooting high BG readings?

- Dawn phenomenon: A rise in BG occurs in predawn hours because of increased growth hormone and cortisol production.
- Bad insulin: High BG occurs when insulin denatures, which can be the result of (1) exposure to moderate to extreme temperatures or agitation, (2) use beyond the expiration date, or (3) use of a vial for more than 1 month.
- Insulin pump or infusion set technical problems: settings programmed incorrectly; battery depleted; pump malfunction; tubing incorrectly primed; air bubbles in the tubing; dislodged, bent, or kinked cannula; occlusion at infusion site; infusion set in place for longer than 72 hours.

26. What causes high postprandial BG readings that are difficult to explain?

- Coffee (caffeine): A rise in BG after drinking coffee (including drinking it black, without cream or sugar) is seen in many patients' records and is likely due to increases in epinephrine or free fatty acid mobilization and subsequent worsening insulin resistance.
- Cereal: A rise in BG is seen by patients consuming cereal, which requires a lower C:I (more insulin) and may be related to the glycemic index of most cereals combined with greater insulin resistance in the morning.
- Food on the fingers: High BG readings occur from residual food or dextrose on fingers during testing (patient must wash hands or wipe off the first drop of blood).

- Restaurant meals: Chinese food, Mexican food, pizza, and fried foods are high in fat and may require more insulin because of insulin resistance. A delay in digestion following a high-fat meal may require a split or extended bolus dose.

27. How is correctional insulin added for high BG before meals?

Correctional or supplemental insulin (high-BG CF) is used to reduce a high BG detected before meals. A high-BG CF is the expected amount by which one unit of insulin will decrease the BG under normal circumstances. It is determined using a formula based on the person's insulin sensitivity. The initial CF is estimated by dividing 1650 by the patient's TDD. In clinical practice, the constant in the CF formula may range from 1500 to 1800. The initial calculated CF must then be adjusted on the basis of each patient's records and is therefore only a starting point.

28. Give an example of determining an initial CF.

- The patient uses 17 units of insulin glargine at noon and 5 units insulin lispro before each meal.
- TDD = 32 units (HbA_{1C} of 7.2% with 1-2 hypoglycemic episodes per week)
- 1650 ÷ 32 = 52
- Begin with a CF of 50:1.

In this example, 1 unit of rapid-acting insulin will lower the BG about 50 mg/dL. Therefore, 1 extra unit will be taken (in addition to the meal insulin dose) for each 50 mg/dL by which the premeal BG exceeds the premeal goal of 100 mg/dL.

29. Give an example of C:I and CF usage.

To determine the amount of insulin needed before a meal, start by calculating the amount of bolus insulin needed to cover the meal:

- C:I is 20:1.
- Meal consists of 80 grams of carbohydrates.
- Calculation: 80 ÷ 20 = 4 units of insulin

Next, determine the amount of correctional insulin needed. If the BG is out of the target range before a meal, subtract the goal BG (100 mg/dL) from the actual BG, and divide by the CF.

- CF is 60:1.
- Preprandial BG is 220 mg/dL.
- Calculation: 220 − 100 mg/dL = 120 mg/dL above target
- Calculation: 120 (mg/dL) ÷ 60 = 2 units of insulin

In this example, the patient should take 6 units of bolus insulin before the meal, 4 units to cover the carbohydrates in the meal and 2 units to return the premeal high BG to the target range.

30. When is a CF used?

- It is recommended that correction boluses for high BG be taken before meals or at least 5 hours after the last bolus because of the duration of action of the bolus insulin analogs.
- Hypoglycemia may occur from the accumulation of active insulin if BG corrections are performed too frequently.
- A CF bolus is more effective if it is taken 15 to 30 minutes before eating. This time frame allows the insulin to begin working before the BG rises further because of the meal.

31. What can be done for a high postprandial BG reading?

- If a postprandial BG is dangerously high (i.e., > 300 mg/dL) or a patient insists on making high BG corrections less than 5 hours since the last bolus or during the night, he or she should be instructed in how to take a partial correction for safety.
- A target level of 150 mg/dL (expected BG level 2 hours postprandial) rather than a target BG of 100 mg/dL is used in the correction calculation between meals.
- Using half of the usual premeal CF to calculate the bolus needed to lower the BG to the target level is safest between meals because of the active insulin still present from the prior bolus.

32. Provide an example to calculate a half-CF bolus.

- BG before dinner = 100 mg/dL
- BG 2 hours after dinner = 300 mg/dL
- "Expected" BG 2 hours after dinner = ≈130 to 150 mg/dL
- Calculation: 300 −150 mg/dL = 150 mg/dL above target
- CF is 60:1.
- Calculation: 150 ÷ 60 = 2.5 units (full CF bolus)
- The premeal insulin is still active for about 3 more hours; therefore, use half the CF bolus.
- Calculation of half CF bolus: 2.5 (units) ÷ 2 = 1.3 units

In this example, 1.3 units with an insulin pump or 1 unit with a syringe or insulin pen should be given 2 hours after the meal to bring the postprandial BG into the target range. BG should be rechecked within 2 hours to avoid a severely low glucose reading.

KEY POINTS 1: INTENSIVE INSULIN THERAPY

1. Studies have clearly demonstrated that optimal diabetes management decreases chronic complications.
2. Intensive insulin therapy, or basal-bolus therapy, is required to mimic normal pancreatic insulin secretion.
3. *Basal insulin* is physiologic insulin required to manage blood glucose (BG) fluctuations due to hepatic glucose production.
4. *Bolus insulin* is matched to carbohydrates using a carbohydrate-to-insulin ratio.
5. Correctional bolus insulin reduces the BG to within normal limits when a high glucose correction factor is used.

33. Calculate an initial basal rate for insulin pump therapy.

- An established C:I ratio and CF with MDI therapy are critical for a smooth transition to pump therapy because the same C:I and CF will be used with the pump.
- To calculate an initial basal rate, reduce the patient's current TDD of insulin with MDI therapy by 25% (or other appropriate reduction, depending on current hemoglobin A_{1C} level and number of hypoglycemic episodes) to estimate the new TDD to be used with the pump.
- Use 50% of the reduced TDD as the total basal dose to be given over 24 hours.
- Start with one basal rate for 24 hours (divide the total basal dose by 24). [Initial basal rate per hour = (TDD × 0.75) ÷ (2 × 24).]
- The remaining 50% will be used as bolus doses for meals on the basis of carbohydrate counting, using the established C:I ratio and CF.

34. Calculate an example of an initial basal rate for insulin pump therapy.

1. Current TDD of insulin is 50 units. 25% reduction of TDD = 37.5 units.
2. 50% of reduced TDD = 37.5 ÷ 2 = 18.75 units as total basal insulin.
3. Total basal insulin = 18.75 ÷ 24 = 0.78 U/hr

In this example, the initial basal rate is 0.8 U/hr. Basal rate adjustments will then be made on the basis of testing and recording BG of profiles throughout the day.

35. When are nighttime basal rate adjustments made?

Nighttime basal rates should be adjusted before the daytime basal rates are verified. Testing is typically performed during the first week of insulin pump therapy. Be aware that patients transitioning from glargine (Lantus) or detemir (Lavema) insulin may have overlapping insulin coverage, causing hypoglycemia during the first week. Testing is then repeated if a significant weight change occurs, if an exercise routine is begun or altered, after hormonal changes (i.e., puberty, menopause), or as needed.

36. List recommendations to follow during the nighttime basal rate verification process.

- Assess basal rate accuracy on three nights.
- Eat evening meal early, preferably before 5 PM (or begin the test period ≈5 hours after eating). Take the usual bolus for dinner and the correction if needed.
- Patients who typically eat high-fat meals or are unsure of their carbohydrate counting skills should choose a meal that they frequently eat or one for which they are confident about the carbohydrate amount.
- Avoid meals with more than 15 to 20 g of fat, 10 g of fiber, and alcohol on testing nights.
- Avoid any food or insulin boluses after the evening meal.
- Avoid exercise other than typical activity on test evenings.
- Monitor BG before and 2 hours after the evening meal, at 9 PM, 12 midnight, 3 AM, and 6 AM, and before breakfast.
- Stop the test if BG is less than 70 mg/dL or greater than 250 mg/dL during the basal test, and treat the abnormal BG.

37. How are nighttime basal rate adjustments made?

- If BG levels change by more than 20 to 30 mg/dL during overnight monitoring, adjust the basal rate for the next night by 0.1 U/hr, starting 1 to 3 hours before the BG change was seen.
- Changes are made until the fasting BG in the morning is within the target range (70-130 mg/dL) and within 30 mg/dL of the bedtime BG.
- Daytime basal rates are verified next, usually 1 to 2 weeks after pump initiation or as necessary.

38. Describe the procedure for making daytime basal rate adjustments.

- Have patients skip breakfast and check their BG levels every hour from 7 AM to 12 noon to verify the morning basal rate.
- If BG levels change by more than 20 to 30 mg/dL during this time, adjust the basal rate for the next day by 0.1 U/hr, starting 1 to 3 hours before the glucose change was seen.
- After the morning basal rate is set, have patients skip their other meals (on separate days) and follow the same monitoring and adjustment procedures to confirm the afternoon and evening basal rate(s).

39. What is the recommended treatment of hypoglycemia?

Dextrose should be taken for a BG less than 70 mg/dL. The patient should take 15 g of a quick-acting carbohydrate: glucose tablets or gel or dextrose-based candy (SweetTARTS, Smarties, Spree). The patient should wait 15 minutes and test BG again. If the second BG is less than 70 mg/dL, additional dextrose should be taken.

40. Why does rebound hyperglycemia occur after hypoglycemia?

- Overtreatment with an inappropriate amount of carbohydrate may occur.
- No treatment (i.e., sleeping through a low glucose episode) may result in counterregulatory hormone release and increased hepatic glycogenolysis.
- Treatment with a food that contains fat delays digestion and absorption, thereby prolonging hypoglycemia and causing counterregulatory hormone release with subsequent hepatic glycogenolysis.

41. Discuss the use of glucagon to treat severe hypoglycemia.

All patients using MDI or pump therapy should be given a glucagon emergency kit prescription and a demonstration. Glucagon is used to raise BG in a person who is unable to swallow. This inability may occur as a result of either a seizure or unconsciousness. Family members should receive instruction on administering the glucagon, and the patient should be able to demonstrate the procedure to a third party (coworker or neighbor).

BIBLIOGRAPHY

American Diabetes Association: Standards of medical care in diabetes–2012, *Diabetes Care* 35(Suppl 1):S11–S63, 2012.

Aschner P, Horton E, Leiter A, et al: Practical steps to improving the management of type 1 diabetes: recommendations from the Global Partnership for Effective Diabetes Management, *Int J Clin Pract* 64:305–315, 2010.

Davidson PC, Hebblewhite HR, Steed RD, Bode BW: Analysis of guidelines for basal-bolus insulin dosing: basal insulin, correction factor, and carbohydrate-to-insulin ratio. *Endocr Pract* 14:1095–1101, 2008.

DeWitt DE, Hirsch IB: Outpatient insulin therapy in type 1 and type 2 diabetes mellitus, *JAMA* 289:2254–2264, 2003.

Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus, *N Engl J Med* 329:977–986, 1993.

Duckworth W, Abraira C, Moritz T, et al: VADT Investigators: Glucose control and vascular complications in veterans with type 2 diabetes, *N Engl J Med* 360:129–139, 2009.

Heinemann L: Insulin pump therapy: what is the evidence for using different types of boluses for coverage of prandial insulin requirements? *J Diabetes Sci Technol* 3:1490–1500, 2009.

Nathan DM, Cleary PA, Backlund JY, et al: Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group: intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes, *N Engl J Med* 353:2643–2653, 2005.

Ohkubo Y, Kishikawa H, Araki E, et al: Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study, *Diabetes Res Clin Pract* 28:103–117, 1995.

Patel A, MacMahon S, Chalmers J, et al: ADVANCE Collaborative Group: Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes, *N Engl J Med* 358:2560–2572, 2008.

Pickup JC: Insulin-pump therapy for type 1 diabetes mellitus, *N Engl J Med* 366:1616–1624, 2012.

Skyler JS, Bergenstal R, Bonow RO, et al: Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA Diabetes Trials, *Diabetes Care* 32:187–192, 2009.

The Action to Control Cardiovascular Risk in Diabetes Study Group: Effects of intensive glucose lowering in type 2 diabetes, *N Engl J Med* 358:2545–2559, 2008.

UK Prospective Diabetes Study (UKPDS) Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33), *Lancet* 352: 837–853, 1998.

UK Prospective Diabetes Study (UKPDS) Group: Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34), *Lancet* 352:854–865, 1998.

White RD: Insulin pump therapy (continuous subcutaneous insulin infusion), *Primary Care: Clinics in Office Practice* 34:845–71, 2007.

Wolfsdorf JI, editor: Intensive Diabetes Management, ed 5, Alexandria, American Diabetes Association, Inc., 2012.

INPATIENT MANAGEMENT OF DIABETES AND HYPERGLYCEMIA

CHAPTER 4

Stacey A. Seggelke and Boris Draznin

1. Does evidence support intensive management of blood glucose in the hospital setting?

Although it is well established that hyperglycemia can lead to adverse patient outcomes, there is controversy over what degree of glycemic control is most appropriate. The largest randomized controlled trial (RCT), the Normoglycemia in Intensive Care Evaluation—Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study, demonstrated a higher risk of mortality in patients with tight glycemic control (blood glucose [BG] target 81-108 mg/dL) than in those with standard glycemic control (BG target 144-180 mg/dL). The increase in mortality is thought to be partially due to the increase in hypoglycemia ($\leq$ 40 mg/dL) seen in the intensively treated group. Although this study corroborated previous suggestions that glycemic control is important, it did underscore the risks of hypoglycemia and relaxing of glycemic targets.

2. What are the glycemic targets for the critically ill patient population?

The American Diabetes Association (ADA) recommendations are to initiate insulin therapy for treatment of hyperglycemia at a threshold of no greater than 180 mg/dL. Insulin therapy should then be titrated to maintain glycemic levels between 140 and 180 mg/dL. The glycemic goal can be further lowered to 110 to 140 mg/dL in select patients as long as it can be attained without hypoglycemia. It is further recommended that all patients entering the hospital undergo glucose testing to detect previously undiagnosed hyperglycemia that will require treatment.

3. What are the glycemic targets for non–critically ill patients?

There is only one RCT that examines the effect of glycemic control in non–intensive care unit (ICU) settings. The Randomized Study of Basal-Bolus Insulin Therapy in the Inpatient Management of Patients with Type 2 Diabetes Undergoing General Surgery (RABBIT 2 Surgery trial) showed that a basal-bolus insulin regimen was associated with fewer hospital complications than sliding-scale insulin therapy in the general surgery population. In addition, a number of observational trials have shown an association between hyperglycemia and adverse events such as prolonged hospital stays, infection, and mortality. The ADA's current recommendations are to maintain premeal blood glucose targets at less than 140 mg/dL and random BG values at less than 180 mg/dL. In patients with a history of tighter outpatient glycemic control, the target can be lowered with the avoidance of hypoglycemia.

4. What are the inpatient glycemic targets for pregnant patients?

Blood glucose goals for pregnancy are tighter than those for the general population. Hyperglycemia during pregnancy is associated with many adverse outcomes, including macrosomia, congenital abnormalities, fetal hyperinsulinemia, and fetal mortality. For patients with gestational diabetes, the recommendations are a fasting blood glucose level lower than 95 mg/dL, a 1-hour postmeal blood glucose of 140 mg/dL or less, and a 2-hour postmeal blood glucose level of 120 mg/dL or less. For patients with preexisting diabetes, the ADA recommends that premeal, bedtime, and nocturnal glucose levels remain between 60 and 99 mg/dL and that peak postmeal glucose levels remain between 100 and 129 mg/dL.

KEY POINTS 1: TARGET GLUCOSE LEVELS FOR HOSPITALIZED PATIENTS

1. Critically ill: 140-180 mg/dL
2. Non–critically ill: premeal $<$ 140 mg/dL; random $<$ 180 mg/dL
3. Pregnant: fasting $<$ 95 mg/dL; 1 hr postprandial $\leq$ 140 mg/dL; 2 hr postprandial $\leq$ 120 mg/dL

5. Which patients are at high risk for hyperglycemia during their hospital stay?

Numerous factors can lead to hyperglycemia in patients with and without a preexisting diagnosis of diabetes. These situations include initiation of glucocorticoid therapy, enteral or parenteral nutrition, immunosuppressive agents, and periods of increased metabolic stress. It is recommended that all patients undergo glucose monitoring if they are receiving therapy that may cause hyperglycemia. If hyperglycemia occurs, appropriate treatment should be given using glycemic goals consistent with those for someone with known diabetes. The ADA recommends that a hemoglobin A_{1C} (HbA_{1C}) level be measured in all patients with diabetes admitted to the hospital if the results of testing in the previous 2 to 3 months are not available.

6. What is the best treatment for inpatient management of diabetes?

Insulin therapy, given as an intravenous (IV) infusion or subcutaneous injections, is the safest and most effective way to treat hyperglycemia in the hospital setting. Insulin is effective and can be rapidly adjusted to adapt to changes in glucose levels or food intake. It is also recommended that standardized insulin protocols be used whenever available.

7. What is an intravenous insulin infusion and why is it used in critically ill patients?

An intravenous insulin infusion is composed of 1 unit of regular human insulin per 1 mL of 0.9% NaCl (normal saline). When given intravenously, regular insulin has a rapid onset and short half-life, allowing for quick adjustment of insulin doses to achieve appropriate glycemic control.

8. At what rate should an insulin infusion be started?

An insulin infusion is usually initiated at 0.1 unit per kg body weight. Alternately, the starting dose can be based on the current blood glucose level, with rates varying from 1 to 7 units per hour depending on the severity of hyperglycemia. An initial bolus of regular insulin is also generally given if blood glucose levels are higher than 150 mg/dL at the start of the insulin infusion.

9. How should the IV insulin infusion rate be adjusted?

Insulin infusions should be adjusted on an hourly basis. Dosage adjustments should be made on the basis of the current glucose level and the rate of change from the previous glucose level. If the blood glucose levels do not change by 30 to 50 mg/dL within an hour, the insulin drip rate should be increased. Conversely, if glucose levels drop more than 30 to 50 mg/dL in an hour, the insulin drip rate should be reduced. Many insulin infusion protocols have been published and are available for use.

10. How do you transition a patient off an insulin infusion?

Because of the short duration of action of IV regular insulin, it is imperative to give subcutaneous basal insulin, long-acting or intermediate-acting, at least 2 hours or rapid-acting insulin 1 to 2 hours before discontinuation of the insulin infusion. To calculate the total daily dose (TDD) of subcutaneous insulin needed, add the amount of insulin given during the past 6 hours of the IV insulin infusion; multiply by 4 for an estimate of the 24-hour requirement; and then reduce that amount by 20% for a new TDD. This TDD should then be split as 50% to 80% basal insulin (higher amount if patient is fasting) and 20% to 50% bolus insulin.

11. How should you select a basal insulin dose?

Basal coverage can be achieved through the use of intermediate-acting insulin (NPH [neutral protamine Hagedorn] insulin) dosed twice daily or, preferably, long-acting insulin (glargine, detemir) dosed once or twice a day. Long-acting insulins generally provide more consistent coverage with minimal insulin peaks, whereas NPH insulin is more likely to cause hypoglycemia because of variable insulin action and peaks. Regardless of the type of insulin used, the basal insulin dose usually accounts for approximately 50% of the TDD of insulin.

12. How should you select a prandial dose for patients on insulin?

Prandial insulin should include both nutritional (meal coverage) and correctional (treatment of hyperglycemia) components. Rapid-acting insulin analogs (lispro, aspart, glulisine) should be given 0 to 15 minutes prior to meals, whereas short-acting insulin (regular) should be given 30 minutes prior to meals. Rapid-acting analogs provide greater flexibility in dosing and have a shorter duration of action, making them the preferred method of treatment. In general, the total bolus insulin doses each day should be about 50% of the TDD of insulin delivery. However, in the hospital setting a reduced prandial dose may be needed because of decreased appetite or variance in oral intake. Correction insulin dosing can be calculated on the basis of the patient's insulin sensitivity. This insulin is either added to the nutritional dose or given alone if the patient is not receiving calories. For patients who have type 1 diabetes or who are insulin sensitive, a good starting point for correction dosing is 1 unit of insulin for every 50-mg/dL increase in BG above a goal of 100 mg/dL. For patients with type 2 diabetes or insulin resistance, 1 unit of insulin should be given for every 25-mg/dL increase above 100 to 150 mg/dL. (See Table 4-1 for example). To prevent hypoglycemia due to "stacking" of insulin, correction insulin doses should, in general, not be given more often than every 4 hours.

13. How should you adjust insulin dosages?

Glucose levels should be assessed on a daily basis. Basal insulin dosages are assessed mainly by review of fasting glucose levels. Blood glucose levels should remain relatively steady through the night. A significant rise or drop in glucose during the night would necessitate a change in basal insulin dosing. Prandial insulin is assessed by pre-lunch, pre-dinner, and bedtime values. For more precise prandial dosing, a 2-hour postprandial glucose check can be performed. It is expected that this postprandial value will be about 30 to 50 mg/dL higher than the preprandial reading.

14. Is "sliding-scale" insulin therapy still used?

Sliding-scale insulin therapy is not an effective treatment for hyperglycemia and therefore should not be used. The sliding scale in this approach was a set amount of bolus insulin, usually regular insulin, that was given to treat high blood glucose levels, generally more than 200 mg/dL. The insulin was given without thought as to meal times, previous dosages, carbohydrate content of meals, or the patient's insulin sensitivity. This approach often resulted in a wide fluctuation of glucose levels because hyperglycemia was not treated preemptively but instead was treated after the fact.

KEY POINTS 2: TREATMENT OF HYPERGLYCEMIA INPATIENT

1. Insulin is the most appropriate treatment agent for hyperglycemia in the hospital.
2. Intravenous insulin infusion is the best therapy for critically ill patients.
3. Basal/bolus (prandial and correction) insulin therapy is the best treatment for non–critically ill patients.
4. Blood glucose levels should be evaluated daily, and insulin adjusted as needed.

15. What is hypoglycemia and how should it be treated?

Hypoglycemia is defined as a blood glucose level lower than 70 mg/dL, which is considered the initial threshold for counterregulatory hormone release. Patients at high risk for hypoglycemia include those

TABLE 4-1. EXAMPLE OF NUTRITIONAL AND CORRECTIONAL INSULIN DOSING CHART

	☐ PATIENT SENSITIVE TO INSULIN:		☐ PATIENT RESISTANT TO INSULIN:		☐ PATIENT EXTRA-RESISTANT TO INSULIN:		☐ CUSTOMIZED PLAN	
	Type 1 DM Stress hyperglycemia Normal body weight		Type 2 DM Steroids Overweight/obese		Blood glucose uncontrolled by "Resistant to Insulin" column			
Blood glucose ≤ 70 mg/dL	Implement hypoglycemia orders		Implement hypoglycemia orders		Implement hypoglycemia orders		Implement hypoglycemia orders	
Blood Glucose (mg/dL)	***Receiving Calories***	***Not Receiving Calories***	***Receiving Calories***	***Not Receiving Calories***	***Receiving Calories***	***Not Receiving Calories***	***Receiving Calories***	***Not Receiving Calories***
71-124	3 units	No insulin	6 units	No insulin	10 units	No insulin	_____units	_____units
125-149	3 units	No insulin	7 units	1 unit	11 units	1 unit	_____units	_____units
150-199	4 units	1 unit	8 units	2 units	12 units	2 units	_____units	_____units
200-249	5 units	2 units	10 units	4 units	14 units	4 units	_____units	_____units
250-299	6 units	3 units	12 units	6 units	16 units	6 units	_____units	_____units
300-349	7 units	4 units	14 units	8 units	18 units	8 units	_____units	_____units
350-399	8 units	5 units	16 units	10 units	20 units	10 units	_____units	_____units
≥ 400	Call MD		Call MD		Call MD		Call MD	

DM, diabetes mellitus; MD, medical doctor.

with renal or liver failure, altered nutrition, and a history of severe hypoglycemia. Treatment of hypoglycemia is based on the patient situation. For a patient who is able to take oral treatment, 15 to 20 g of a quick-acting carbohydrate such as juice, regular soda, or glucose tablets is the preferred treatment. If unconscious or unable to take oral treatment, the patient can be given 25 g (½ ampule) of dextrose 50% intravenously or 1 mg of glucagon intramuscularly. The glucose level should be rechecked within 15 minutes of treatment to assess its efficacy. If the blood glucose level is still lower than 70 mg/dL, treatment should be repeated.

16. Are oral agents or noninsulin injectables appropriate to use in hospitalized patients?

There are limited data on the safety and efficacy of using oral agents or noninsulin injectables (glucagon-like peptide-1 [GLP-1] analogs, pramlintide) in hospital settings. In most cases of hyperglycemia, noninsulin treatment options can be effective in lowering blood glucose to goal levels, especially in acute illness. In general their use should be limited to patients who are eating regularly. Additionally, oral agents may be initiated or resumed in clinically stable patients in anticipation of discharge.

17. What is the best treatment for steroid-induced hyperglycemia?

Steroids impair insulin action, resulting in insulin resistance and diminished insulin secretion, which manifests largely as elevated postprandial blood glucose excursions. The extent of blood glucose elevation depends on the amount and duration of steroid therapy. Individuals who are on low doses of steroids and who are insulin naive may be treated with bolus insulin at mealtimes. If the patient is receiving higher doses of steroids or has a history of insulin-treated diabetes, a good treatment option is an intermediate-acting basal insulin, NPH insulin, dosed at the same time as administration of the steroid. Insulin needs should be assessed and adjusted with tapering or discontinuation of steroid therapy.

18. What is the best treatment for hyperglycemia with enteral or parenteral nutrition?

There are several approaches to insulin treatment for hyperglycemia with nutritional support. For total parenteral nutrition (TPN), the addition of regular insulin to the TPN bag is the safest approach to glycemic control. The initial dosing recommendation is 1 unit for every 10 to 12 g of dextrose in the TPN solution. The amount of insulin can be adjusted daily or an additional rapid-acting correction scale can also be used for immediate correction of hyperglycemia. Another approach to treatment is the use of a basal/bolus regimen. The latter poses an increased risk of hypoglycemia if TPN is unexpectedly discontinued or the TPN dextrose concentration is changed without adjustment of insulin dosing.

There are many approaches to treatment for enteral nutrition (EN). Basal insulin can be administered once or twice daily in combination with a rapid-acting insulin according to a correction scale every 4 to 6 hours. Alternatively, intermediate-acting 70/30 human insulin given every 8 hours with rapid-acting insulin according to the correctional scale every 4 hours is an approach that the authors use. Hypoglycemia is of immense concern in these patients, as feeding can be interrupted unexpectedly with dislodging of the feeding tube or discontinuation of the EN due to nausea or diagnostic testing. It is important to remember that these patients are in a consistent postprandial state and to adjust glucose goals accordingly.

19. Can a continuous subcutaneous insulin infusion be used in the inpatient setting?

Continuous subcutaneous insulin infusion (CSII), also known as an insulin pump, can be safely used in the inpatient setting. It is imperative that the patient is mentally and physically able to operate his or her own insulin pump. It is also recommended that personnel with CSII experience help manage the patient. Current pump settings, including basal rates, bolus settings, and bolus dosages, should be documented on a daily basis.

20. How do you adjust diabetes medications prior to surgery?

Hypoglycemia is a considerable risk for patients undergoing surgery because of their NPO (nothing by mouth) status. Oral agents should be held the morning of the procedure. It is recommended that patients on long-acting insulin (glargine/detemir) therapy take about 80% of their normal dose the

night before surgery. Patients on intermediate-acting insulin (NPH), therapy should take 50% of their typical dose the morning of the procedure. Correctional doses of rapid-acting analogs can be given in the perioperative periods every 4 hours to maintain glycemic levels below 180 mg/dL. If the procedure is prolonged or if prolonged NPO status is expected, the use of an insulin infusion is recommended.

21. How do you decide what home regimen to order at discharge?

If the patient has had good glycemic control as an outpatient, it is recommended that the patient be sent home on the regimen he/she was on previously. For the patient with a new diagnosis of diabetes or requiring a change in previous therapy due to poor glycemic control, recommendations should be based on the patient's preference/ability as well as the cost of and contraindications to medications. It is also recommended that medication administration instructions, especially for insulin, be given in both oral and written formats and that details of discharge medications and instructions be communicated promptly and clearly also to the patient's primary care provider.

WEBSITES

1. American Association of Clinical Endocrinologist Inpatient Glycemic Control Resource Center: http://resources.aace.com.
2. Society of Hospital Medicine Glycemic Control Resource Room: http://www.hospitalmedicine.org/ResourceRoomRedesign/RR_LandingPage.cfm.

BIBLIOGRAPHY

American Diabetes Association: Standards of medical care in diabetes 2012, *Diabetes Care* 35:S36–S40, 2012.

Fowler MJ: Inpatient diabetes management, *Clinical Diabetes* 27:119–122, 2009.

Magaji V, Johnston JM: Inpatient management of hyperglycemia and diabetes, *Clinical Diabetes* 29:3–9, 2011.

Moghissi ES, Korytkowski MT, DiNardo M, et al: American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control, *Diabetes Care* 33:1119–1131, 2009.

Van den Berghe G, Wilmer A, Hermans G, et al: Intensive insulin therapy in the medical ICU, *N Engl J Med* 354:449–446, 2006.

Umpierrez GE, Hellman R, Korytkowski MT, et al: Management of hyperglycemia in hospitalized patients in non-critical care setting: an Endocrine Society clinic practice guideline, *J Clin Endocrinol Metab* 97:16–38, 2012.

Umpierrez GE, Smiley D, Jacobs S, et al: Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes undergoing surgery, *Diabetes Care* 34:256–261, 2011.

DIABETES IN PREGNANCY

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CHAPTER 5

1. How does normal pregnancy affect fuel metabolism?

Pregnancy is a complex metabolic state that involves dramatic alterations in the hormonal milieu (increases in estrogen, progesterone, prolactin, cortisol, human chorionic gonadotropin, placental growth hormone, and human placental lactogen), inflammatory cytokines (tumor necrosis factor-alpha [TNF-α], C-reactive protein), and adipokines (leptin and adiponectin) to alter maternal insulin resistance so that the mother can provide the necessary nutrients for the growing fetal-placental unit.

2. Summarize the changes in the first trimester of pregnancy.

Pregnancy is characterized by profound metabolic changes that promote adipose tissue accretion in early gestation; many women show increased insulin sensitivity between 10 and 20 weeks of pregnancy. Interestingly, a few studies have reported transient increases in insulin resistance prior to 10 weeks, although others describe more frequent episodes of hypoglycemia. Fasting insulin levels and glucose values are lower, and women are prone to nocturnal hypoglycemia and ketogenesis, especially if they suffer from nausea and vomiting during pregnancy. In addition to increased insulin sensitivity and fat storage, the first and early second trimesters are usually characterized by an earlier transition from carbohydrate to fat utilization in the fasting state. Pregnant women deplete their glycogen stores quickly and switch from carbohydrate to fat metabolism within 12 hours, often becoming ketonemic.

3. Summarize the changes in the second and third trimesters and immediate postpartum period.

The late second and third trimesters, in contrast, are consistently characterized by insulin resistance, with a nearly 50% decrease in insulin-mediated glucose disposal (assessed by the hyperinsulinemic euglycemic clamp technique) and a 200% to 300% increase in insulin secretion in late pregnancy. These changes shunt necessary fuels to meet the metabolic demands of the placenta and growing fetus, which requires 80% of its energy as glucose, while maintaining euglycemia in the mother. Women usually have lower fasting plasma glucose levels and fasting hypoinsulinemia because of continued shunting of carbohydrate to the fetal-placental unit in the unfed state, often resulting in the presence of urinary ketones. Because of the increasing placental-fetal glucose demands, glycogen stores are depleted rapidly, and pregnant women must transition from carbohydrate to fat metabolism earlier in the fasting state, a phenomenon called “accelerated starvation.” There is a dramatic insulin resistance in skeletal muscle and in the liver, resulting in increased hepatic gluconeogenesis to ensure adequate substrate delivery to the fetus. The ability of insulin to suppress whole-body lipolysis is also reduced during late pregnancy, causing free fatty acid (FFA) levels to increase. However, owing to the placental hormone–mediated increase in insulin resistance with maternal hyperinsulinemia in the fed state, pregnant women demonstrate minimally elevated postprandial glucose excursions. In an extensive review of glycemia patterns in normal pregnancy, mean fasting blood glucose (FBG) levels were 72 mg/dL, 1-hour postprandial values were 109 mg/dL, and 2-hour values were 99 mg/dL, with a 24-hour mean glucose level of 88 mg/dL, all much lower than current therapeutic targets. Immediately after delivery, insulin sensitivity returns, and the early postpartum period is often one of extreme insulin sensitivity, especially if mothers are breastfeeding; a subgroup of postpartum diabetic women requires almost no insulin for several days.

4. Do normal-weight women have different glycemic patterns from those of obese women in pregnancy?

In a study that examined continuous glucose profiles in women in both early (~16 weeks) and late (~28 weeks) gestation and used a controlled eucaloric diet with the same macronutrient composition in both groups, obese pregnant women demonstrated 24-hour glycemic profiles that were higher than normal-weight women both early and late in gestation. At 28 weeks of gestation, nearly all fasting and postprandial glycemic values were higher in obese women, as were fasting insulin, triglyceride, and FFA values. Mean 1-hour and 2-hour postprandial glucose levels were 102 and 96 mg/dL, compared with 115 and 107 mg/dL in the normal-weight and obese women, respectively. In late pregnancy, 95% of all glucose values were lower than 116 mg/dL, compared with 133 mg/dL in obese women. Interestingly, although pre-pregnancy body mass index (BMI), late gestation average daytime glucose level, and late gestation fasting insulin correlated with infant percentage body fat, maternal triglyceride and FFA values were stronger predictors of excess newborn fat.

5. Is glucose the only fuel altered in normal pregnancy?

No. Amino acids, triglycerides, cholesterol, and FFAs are also increased; the increase in FFAs may further accentuate the insulin resistance of pregnancy. A growing number of studies support that elevations of maternal triglycerides and FFAs are an important source of excess fuel to the fetus and are predictive of LGA (large-for-gestational-age; $>$ 90th percentile for gestational age) status and increased newborn adiposity. At this time, there are no formal recommendations to target maternal triglycerides in pregnancy as a potential intervention to decrease the risk for newborn adiposity or macrosomia (birth weight $>$ 4000 gm), but trials using high doses of fish oils are ongoing.

6. Explain the effect of the metabolic changes in pregnancy on diabetes management in the first trimester.

Optimally diabetes should be under tight control before conception. During the first trimester, nausea, increased insulin sensitivity, and accelerated starvation may put the mother at risk for severe hypoglycemia, and thus, insulin requirements are the least stable at this time. This risk is especially high at night because of prolonged fasting and continuous fetal-placental glucose utilization. Women with type 1 diabetes must have a bedtime snack and usually need to have the basal insulin decreased or the evening dose of neutral protamine Hagedorn (NPH) insulin lowered and moved from supper to bedtime administration to avoid early-morning hypoglycemia. Severe hypoglycemia occurs in 30% to 40% of pregnant women with type 1 diabetes in the first 20 weeks of pregnancy, most often between midnight and 8:00 AM. Diabetic women who have gastroparesis or hyperemesis gravidarum are at the greatest risk for daytime hypoglycemia. During the first trimester, glycemic control just above the normal range (hemoglobin A_{1C} [HbA_{1C}] $<$ 7.0%) may thus be safer than "normal" and may decrease the risk of both maternal and fetal hypoglycemia.

7. How do metabolic changes in pregnancy affect the management of diabetes in the second and third trimesters?

After 20 weeks, peripheral insulin resistance increases insulin requirements. It is not unusual for a pregnant woman to require two to three times as much insulin as she did before pregnancy. Fasting hyperglycemia and postprandial hyperglycemia are risk factors for LGA status or macrosomia. Therefore, tight glucose control in women with preexisting diabetes usually requires both basal insulin and rapid-acting insulin at each meal with frequent monitoring to allow appropriate insulin dosage adjustments.

8. What are the key preconception recommendations in counseling a diabetic woman who wants to become pregnant?

The most important recommendation in preconception counseling is the need for optimal glucose control before conception. Unplanned pregnancies occur in about two thirds of women with diabetes, making it critical that the primary care physician, endocrinologist, or obstetrician-gynecologist address preconception care in women of childbearing age. Providing effective contraception until

optimal glycemic control is achieved is the most common error of omission by all health professionals who care for women with diabetes. In a retrospective study, only 25% of women of childbearing age with preexisting diabetes had preconception counseling of any kind. Four times as many fetal and neonatal deaths and congenital abnormalities occurred in a group of women who did not receive prenatal counseling than in those who did. In all series, preconception counseling significantly improved glycemic control, lowered rates of major malformations, and reduced rates of major adverse pregnancy outcomes, including very premature delivery, stillbirth, and neonatal death.

Women should begin folic acid supplementation with 0.8 to 1 mg daily before trying to conceive because the neural tube is formed by 4 weeks after conception. Maternal screening for abnormal thyroid function, retinopathy, and nephropathy should be carried out. Women with cardiovascular symptoms or additional risk factors should also be evaluated for underlying coronary artery disease with a stress study. Women with diabetes are at high risk for depression, anxiety, and eating disorders, all of which can affect glycemic control and fetal outcomes, and therefore, psychosocial screening is recommended. The risk of fetal exposure to untreated major depression is considered a greater cause of concern than the risk of fetal exposure to antidepressant medications of the selective serotonin reuptake inhibitor (SSRI) class. In addition, women with type 1 diabetes are at risk for B12 deficiency, celiac sprue, and vitamin D deficiency and should be screened if they have any suggestive symptoms or signs.

9. Why is maintenance of glucose control essential for the well-being of the fetus and pregnancy outcomes?

The maintenance of normal glucose control is the key to preventing complications, such as fetal malformations in the first trimester, macrosomia in the second and third trimesters, and neonatal metabolic abnormalities. Hyperglycemia modulates the expression of an apoptosis regulatory gene as early as the preimplantation blastocyst stage in the mouse, resulting in fetal wastage that can be prevented by treating with insulin. This finding may account for the high risk of first-trimester loss in pregnant women with poor glycemic control. In later pregnancy, there is a fourfold to fivefold higher rate of stillbirths and perinatal deaths in diabetic women than in the general population. Glycemic control as indicated by HbA_{1C} was assessed in the Diabetes and Preeclampsia Intervention Trial; women in whom preeclampsia developed had significantly higher HbA_{1C} values before and during pregnancy. In comparison with optimal control, an HbA_{1C} of 8.0% or higher in early pregnancy was associated with an odds ratio of 3.7 for preeclampsia.

10. Describe the relationship among A_{1C}, the teratogenic effects of hyperglycemia, and abnormal fetal growth.

Epidemiologic and prospective studies have shown that the HbA_{1C} level in the 6 months before conception and during the first trimester correlates with the incidence of major malformations, such as neural tube and cardiac defects. The neural tube is completely formed by 4 weeks and the heart by 6 weeks after conception. This fact underscores the need for preconception counseling to achieve these goals because many women do not even know that they are pregnant this early. Overall, the risk of an adverse outcome is halved with each percentage reduction in HbA_{1C} level achieved before pregnancy. It has been demonstrated that women with a normal HbA_{1C} value at conception and during the first trimester have no increased risk, whereas women with an HbA_{1C} value greater than 12% have up to a 25% risk of major fetal malformations. The International Diabetes Federation recommends a goal pre-pregnancy HbA_{1C} of less than 7.0%, and other guideline committees recommend less than 6.5% if it can be safely achieved. Excess fetal growth has been associated with an abnormal HbA_{1C} in the first trimester as well as in the second and third trimesters. Both fasting hyperglycemia and postprandial hyperglycemia are contributors to excess fetal growth and metabolic complications.

11. How has the incidence of congenital abnormalities and macrosomia in the offspring of diabetic mothers changed over the past decade?

The incidence of congenital abnormalities in the offspring of diabetic mothers in the early era of insulin use was 33%. Since the mid-1990s, with the advent of home glucose monitoring and more

rigid objectives, this percentage has fallen to less than 10%. The randomized prospective Diabetes Control and Complications Trial (DCCT) has shown that timely institution of intensive therapy for blood glucose prior to conception is associated with rates of spontaneous abortion and congenital malformations that are similar to those in the nondiabetic population. Although the rate of LGA infants has been recognized to be high in women with type 2 diabetes, this rate has also significantly increased in women with type 1 diabetes, likely owing to the growing number of women who are also overweight and insulin resistant.

12. What are the risks of severe hypoglycemic episodes in the mother and fetus?

The fetus has minimal ability for hepatic gluconeogenesis until close to delivery, so profound and sustained maternal hypoglycemia is likely to cause the same in the fetus. Further, the best predictors of severe hypoglycemia during pregnancy are hypoglycemic unawareness and the presence of at least one episode of severe hypoglycemia the year before pregnancy. Severe hypoglycemia is five times more common in pregnancy if present in the year prior to pregnancy and most often occurs in the first trimester, especially between 8 and 16 weeks. The risk is highest during fasting and sleep because the fetal-placental unit continues to extract glucose during these times. Whether severe and prolonged hypoglycemia could have long-term adverse neurologic effects in the offspring has not yet been well studied.

13. What are the risks if a woman conceives while taking an oral hypoglycemic agent?

Oral hypoglycemic agents, such as sulfonylureas and metformin, do not appear to be teratogenic. There are very few data on meglitinide use in pregnancy. A retrospective series of 332 women with type 2 diabetes treated with diet, insulin, or oral sulfonylureas during the first 8 weeks of gestation found no significant adverse effects. There are few data on the risk of thiazolidinediones in the first trimester; these agents should definitely be stopped before a woman actively tries to become pregnant. Alpha-glucosidase inhibitors, such as acarbose, have not been associated with any abnormal outcomes. Therapy with an incretin, such as an amylinomimetic, GLP-1-mimetic, or DPP-IV inhibitor, has not been well studied in pregnancy and therefore is not recommended, but it is unlikely that these agents would increase the risk of major malformations if conception occurred during their use. Women who are actively trying to become pregnant should be switched to insulin during the preconception period because it may take some time to determine the ideal insulin dose before the critical time of embryogenesis.

14. How is glyburide different from the other sulfonylureas?

Glyburide crosses the placenta less than all other sulfonylureas and appears to affect fetal insulin levels minimally. In the only large randomized prospective trial, however, it was not given until after 24 weeks of gestation to women with gestational diabetes mellitus (GDM). Since that time, many more studies have utilized glyburide in pregnancy, primarily after 24 weeks of gestation in women with GDM. The International Association of Diabetes in Pregnancy Study Group (IADPSG) approved the use of glyburide as an alternative treatment in a subset of women with GDM.

15. Can glyburide or metformin be continued in pregnancy?

It is recommended that oral hypoglycemic agents be avoided during pregnancy, with the possible exception of glyburide and metformin, which have been used to treat GDM in the late second and third trimesters. Although metformin does cross the placenta, there are a fair amount of data using metformin throughout the first trimester of pregnancy in women with polycystic ovarian syndrome (PCOS) without any apparent risk, and a few small studies suggest that it decreases the risk for development of GDM. There are no known adverse effects of glyburide use in the first trimester although the vast experience with glyburide, like that with metformin, is in women with GDM after 24 weeks of gestation. However, a woman taking a sulfonylurea or metformin who is discovered to be pregnant should not stop these agents until she can be effectively switched to insulin, because the risk of teratogenicity from hyperglycemia is much higher than any risk from these agents. Both

metformin and glyburide are much less likely than insulin to be effective in pregnancy, especially for women with preexisting diabetes, because of the profound insulin resistance in the second and third trimesters of pregnancy.

16. How should hypertensive women who take angiotensin-converting enzyme inhibitors or angiotensin receptor blockers be counseled in the preconception period?

Women should be counseled that angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are contraindicated in the second and third trimesters of pregnancy because of the risk of fetal anuria. A report in 2006 from a Tennessee Medicaid population described increased cardiac and central nervous system malformations in fetuses exposed in the first trimester. However, a subsequent report of pregnant women in the Kaiser Permanente Northern California region from 1995 to 2008 did not confirm this association, instead showing ACE inhibitors in the first trimester to confer a risk similar to that from other antihypertensives. It is now recommended that women who are actively trying to conceive and who have no history of infertility should probably be switched to a safer agent before pregnancy (calcium channel blocker, methyldopa, or hydralazine). A woman who receives treatment with an ACE inhibitor or ARB for significant diabetic nephropathy and who is not actively trying to conceive should be told to perform home pregnancy tests if she misses a period and to immediately stop her ACE inhibitor or ARB if there is any suspicion of pregnancy. At that time, she can be switched safely to an alternative agent.

17. How does pregnancy affect the morbidity and mortality of coronary artery disease in diabetic women?

The morbidity and mortality rates of coronary artery disease are high in pregnant women with diabetes. Cardiac status should be assessed with functional testing before conception in women older than 35 years who have any additional cardiac risk factors, such as hyperlipidemia, hypertension, smoking, cardiac autonomic neuropathy, or a strong family history and in women with any suggestive symptoms. A resting electrocardiogram (ECG) should be considered for asymptomatic women age 35 or older. Pregnancy causes a 25% increase in cardiac output, a significant decrease in systemic vascular resistance (which can shunt blood away from the coronary arteries), and an increase in oxygen consumption, all of which reduce the ability of maternal coronary blood flow to meet the demands of the myocardium. Myocardial demands are even higher at labor and delivery, and activation of catecholamines can further promote myocardial ischemia.

18. How should women with diabetes be screened and treated for thyroid disease prior to pregnancy?

Women with type 1 diabetes have an increased risk of hypothyroidism due to Hashimoto's thyroiditis, and it is recommended by both the Endocrine Society and the American Thyroid Association that they be screened. It is less clear that women with type 2 diabetes have an increased risk, but some consensus panels recommend screening for them as well. It is recommended that women with a thyroid-stimulating hormone (TSH) level higher than 2.5 to 3.0 mU/L in the first trimester and higher than 3.0 to 3.5 mU/L in the second and third trimesters be treated, especially if they are shown to have thyroid peroxidase (TPO) antibodies, although the long-term neurologic benefit to the offspring of such treatment has not yet been demonstrated. The American College of Obstetricians and Gynecologists (ACOG) has not made any formal recommendations to screen and treat subclinical hypothyroidism in pregnancy until results of the ongoing Maternal Fetal Medicine Units (MFMU) network trial are available. Screening for TPO antibodies is not recommended in euthyroid women with or without a history of pregnancy loss because of insufficient data that treatment with thyroid hormone is effective.

19. Should statins or fibrates be discontinued before conception?

Data about the safety of statins during human pregnancy are inadequate, but animal data on these agents are concerning. Although statins have been given a classification of "X" by the U.S. Food and

Drug Administration (FDA), there are no data in human pregnancy to support their being a major teratogen in a woman who is taking them and does not realize she is pregnant. However, statins should be discontinued in women who are actively trying to conceive and should not be continued during pregnancy. There does not appear to be an increased risk of malformations in women who conceive while taking fibrates. In fact, if a woman has severe hypertriglyceridemia, which puts her at high risk for pancreatitis, it may be necessary to use a fibrate in the second or third trimester of pregnancy if a low-fat diet and use of fish oils are not effective or tolerated. Serum triglyceride levels double to triple in pregnancy and therefore treatment may be indicated, especially if they approach 1000 mg/dL after meals.

20. Summarize the effects of smoking during pregnancy.

Smoking continues to be the leading cause of low-birth-weight infants in patients with and without diabetes and puts the infant at increased risk for respiratory infections, reactive airway disease, and sudden infant death syndrome. Smoking cessation efforts must be intensified before conception. The nicotine patch is believed to be safer than continuing smoking in pregnancy and should be offered to women addicted to nicotine who are already pregnant and unable to quit without its use.

21. How does pregnancy affect diabetic nephropathy?

Proteinuria increases in pregnancy, and women with proteinuria often become nephrotic owing to the increased glomerular filtration of protein during pregnancy. In some patients, proteinuria can become massive and result in significant hypoalbuminemia, edema, and a hypercoagulable state, and ultimately, in fetal growth restriction. Although women with mild renal insufficiency are not at an appreciable risk for irreversible progression of nephropathy, those with more severe renal insufficiency (serum creatinine $>$ 2.5 mg/dL or estimated glomerular filtration rate [GFR] $<$ 30 mL/min) have a 30% to 50% risk of a permanent pregnancy-related decline in GFR and may require dialysis in pregnancy.

22. Does nephropathy increase the risk of preeclampsia?

Preeclampsia complicates approximately 20% of pregnancies in women with preexisting diabetes, and the risk is much higher in women with hypertension or renal disease. The risk for development of preeclampsia in women with nephropathy is greater than 50%. The preeclampsia may be severe, especially in women who are hypertensive and have decreased renal function, particularly those with a serum creatinine level higher than 1.4 mg/dL. Women with significant nephropathy are also at higher risk of having preterm and low-birth-weight infants. Therefore a woman with diabetic nephropathy should be counseled to have children when her diabetes is optimally controlled and preferably early in the course of the nephropathy. Some experts recommend a target blood pressure of less than 135/85 mm Hg in women with diabetic renal disease to reduce the risk of further end-organ damage and, possibly, preeclampsia. However, reducing the blood pressure too aggressively may worsen perfusion pressure in the woman whose placental bed has a high vascular resistance due to preeclampsia, and it may worsen instead of improve fetal growth.

23. How does renal transplantation affect the outcome in pregnant women?

Women who have undergone successful renal transplantation at least 1 to 2 years before pregnancy and who have good renal function, adequate blood pressure control, and a low requirement for antirejection medications have a much more favorable outcome than women with severe renal disease who have not received a transplant. Women with severe renal insufficiency who require dialysis in pregnancy have the highest risk of adverse pregnancy outcomes, including severe growth restriction, prematurity, preeclampsia, and stillbirth.

24. Summarize the effects of pregnancy on diabetic retinopathy.

Retinopathy may progress during pregnancy either from the institution of tight glycemic control or from the increases in growth factors, blood volume, cardiac output, anemia, and the hypercoagulable state of pregnancy. Women with proliferative retinopathy are at the highest risk of progression;

in one series, retinopathy worsened in more than 50% of the women. It is therefore imperative that retinopathy be optimally treated with laser therapy before pregnancy, although laser therapy can be instituted during pregnancy. It is less likely that only background retinopathy will progress significantly during pregnancy, but there are reports that as many as 20% of cases do progress. Baseline and follow-up retinal examinations are recommended for all diabetic pregnant women at risk for retinopathy.

25. What is the White classification of diabetes in pregnancy?

Priscilla White at the Joslin Diabetes Center observed that the patient's age at onset of diabetes, duration of diabetes, and severity of complications, including vascular disease, nephropathy, and retinopathy, significantly influenced maternal and perinatal outcomes. In 1949, she developed a classification scheme based on these parameters. The initial scheme was developed for women with type 1 diabetes; there is no separate classification for type 2 diabetes.

26. Why is the White classification used by obstetricians?

Its predictive value allows identification of patients at greatest risk for obstetric complications during pregnancy so that physicians can intensify management and fetal surveillance. In the updated classification (Table 5-1), women with pregestational diabetes are designated by the letters B, C, D, F, R, T, and H according to duration of diabetes and complications. Class A1 or A2 is used to classify women with GDM that is controlled with diet alone or with medications, respectively. It is unclear whether the White classification is better at predicting adverse pregnancy outcomes than categorizing the patients with respect to the absence or presence of vascular disease. However, it is still used by obstetricians to classify the duration and complications of women with diabetes.

27. What are the goals of glucose control for pregnant women with diabetes?

The goals of glucose control during pregnancy are rigorous. Optimally, the premeal glucose level should be less than 90 to 95 mg/dL, the 1-hour postprandial glucose level less than 130 to 140 mg/dL, and the 2-hour postprandial glucose level less than 120 mg/dL. More intensive goals have not been tested in an adequately powered randomized controlled trial (RCT) to determine whether they can achieve a reduction in macrosomia without increasing the risk of small-for-gestational-age (SGA) status. The results from the multicenter HAPO (Hyperglycemia and Adverse Pregnancy Outcomes) trial, which studied 25,000 pregnant women in nine countries, suggest that abnormal fetal growth occurs along a continuum and at lower glucose values than previously recognized. They calculated that a 1.75-fold risk of LGA infants occurs at an FBG level of 92 mg/dL or higher. Because macrosomia is related to both fasting and postprandial blood glucose excursions, pregnant diabetic women

TABLE 5-1. MODIFIED WHITE CLASSIFICATION OF PREGNANT DIABETIC WOMEN

CLASS	AGE AT ONSET (YR)	DURATION (YR)	VASCULAR DISEASE	MEDICATION
Gestational Diabetes				
A1	Any	Pregnancy	None	None
A2	Any	Pregnancy	None	Yes
Pregestational Diabetes				
B	> 20	< 10	None	Yes
C	10-19	10-19	None	Yes
D	< 10	> 20	Benign retinopathy	Yes
F	Any	Any	Nephropathy	Yes
R	Any	Any	Proliferative retinopathy	Yes
T	Any	Any	Renal transplant	Yes
H	Any	Any	Coronary artery disease	Yes

need to monitor premeal and postprandial glucose values regularly. Patients with type 1 and type 2 diabetes usually require three or four insulin injections per day or an insulin pump to achieve adequate control during pregnancy.

28. What is the role of the continuous glucose monitoring system in pregnancy?

A continuous glucose monitoring system (CGMS) can be helpful, especially in patients with type 1 diabetes who are having frequent hypoglycemic episodes and have hypoglycemic unawareness, allowing better delineation of glucose patterns so that basal and/or bolus insulin can be appropriately adjusted. A CGMS can also reveal postprandial hyperglycemia that might be otherwise unrecognized and that is strongly associated with excess fetal growth. In one series, a mother had to check her glucose levels a minimum of 10 times per day to give an indication of the glucose patterns obtained during CGMS. Another study showed that utilizing CGMSs in pregnant women with preexisting diabetes may not be an effective tool to decrease LGA rates. However, CGMSs have been shown to be very useful in women with type 1 diabetes who may have hypoglycemic unawareness, wide glycemic swings, or difficulty reaching an optimal HbA_{1C} level despite checking their blood glucose values many times each day.

29. Discuss the role of the insulin pump during pregnancy.

Experience with the insulin pump in the treatment of type 1 diabetes in pregnancy is increasing. Most trials have found that continuous subcutaneous insulin infusion is equivalent to multiple daily injections using basal and bolus insulin. The pump may be advantageous in women with recurrent hypoglycemia, especially at night, because different basal rates can be programmed. However, there are reports of women who began using the pump in pregnancy in ketoacidosis developed from pump failure. Therefore it may be optimal to begin pump therapy before pregnancy, given the steep learning curve involved in its use and the continuous changes that must be made in dosing basal and bolus insulin because of the changing insulin resistance throughout pregnancy.

30. Discuss the role of glargine and detemir insulins during pregnancy.

Insulin detemir (Levemir) has been approved by the FDA for use in pregnancy and may result in less nocturnal hypoglycemia than NPH insulin. For women with severe hepatic insulin resistance, NPH insulin before bedtime may also be required to achieve sufficient fasting glucose control, although its peak can be variable. Experience with insulin glargine (Lantus) in pregnancy is fairly extensive, and although not yet approved by the FDA, such use has been approved by the European Medicine Agency. However, there are still some concerns about glargine's potential mitogenic effects and higher affinity for the insulin-like growth factor-1 (IGF-1) receptor, especially in women with proliferative retinopathy. Insulin glargine does not cross the placenta, and no evidence indicates reproductive toxicity or embryotoxicity. Similar pregnancy outcomes have been reported in women taking glargine and women taking NPH. If a patient without proliferative retinopathy is doing well on insulin glargine, it is probably not necessary to switch her to another insulin during pregnancy. Either glargine or detemir insulin may be useful in women who experience recurrent hypoglycemia with NPH insulin therapy.

31. What is the role of short-acting insulin analogs in pregnancy?

Insulins lispro (Humalog) and aspart (NovoLog) have been used in pregnancy and have been shown to be safe and effective. Both reduce postprandial hyperglycemia and the risk of hypoglycemia compared with regular insulin in patients with type 1 diabetes. They may be especially helpful in women with type 1 diabetes and gastroparesis, because they can be dosed after eating, ensuring that food is not immediately vomited after a full bolus is given. Dosing these rapid-acting insulin analogs according to carbohydrate ratios and a premeal correction factor is usually necessary to achieve adequate control in women type 1 diabetes. Their use is also often more successful than use of regular insulin in women with type 2 diabetes, especially if regular insulin cannot effectively lower the 1- or 2-hour postprandial glucose levels into the target range without causing hypoglycemia 3 to 4 hours after injection.

32. How common is hypoglycemia in pregnant women with type 1 diabetes during and after pregnancy?

Maternal hypoglycemia is common and often severe in pregnant women with type 1 diabetes. In one series, hypoglycemia requiring assistance occurred in 71% of patients, with a peak incidence at 10 to 16 weeks of gestation. One third of the women had at least one episode resulting in seizures, loss of consciousness, or injury, any of which could potentially result in long-term neurological effects in the offspring. Current data suggest that the counterregulatory hormonal response to hypoglycemia is diminished in pregnancy. The physician must have a low threshold for bringing the expectant mother into the hospital to optimize education and glycemic control. Occasional monitoring in the middle of the night is recommended in the woman with type 1 diabetes because of the increased risk of nocturnal hypoglycemia, especially if she has hypoglycemia unawareness. Immediately after delivery, the mother's need for insulin declines to approximately 60% of her pre-pregnancy dose as a result of the rapid cessation of the placental hormone influence; there is a concomitant higher risk of hypoglycemia at this time. Insulin doses typically rise over the next weeks nearer to pre-pregnancy doses unless the mother breastfeeds.

33. Discuss special concerns in pregnant women with type 2 diabetes as compared with type 1 diabetes.

Women with type 2 diabetes are at least as high a risk of pregnancy complications as women with type 1 diabetes, especially if they have hypertension, obesity, or are in poor glycemic control. Some series, in fact, show that pregnancy outcomes may be less favorable in women with type 2 than in those with type 1 diabetes, including a higher perinatal mortality rate. The reasons for this may include older age, a lower rate of preconception counseling, a higher incidence of poor glycemic control in the first trimester, the coexistence of the metabolic syndrome (hypertension and obesity), undiagnosed sleep apnea, and occult cardiopulmonary disease, all of which are significant risk factors for pregnancy complications. Failure to achieve optimal control in early pregnancy in women with any type of preexisting diabetes may have teratogenic effects or may lead to early fetal loss. Poor glycemic control later in pregnancy increases the risks of intrauterine fetal demise, LGA status, and metabolic complications in the newborn.

Stillbirths in women with type 1 or type 2 diabetes are fivefold more common and are unexplained in about 50% of cases. Fetal hypoxia and cardiac dysfunction, associated with cardiac enlargement and asymmetric septal hypertrophy, result from poor glycemic control and are probably the most important pathogenic factors. Fetal hyperglycemia and hyperinsulinemia result in excess fetal growth, increased fetal metabolism with increased fetal oxygen consumption, and relative tissue hypoxia. As in the case with type 1 diabetes, an early dating ultrasound is necessary to determine the gestational age of the fetus, and a formal anatomy scan should be performed at 18 to 20 weeks to evaluate for fetal anomalies. A fetal echocardiogram should be offered at 20 to 22 weeks if the HbA_{1C} was elevated during the first trimester. Daily fetal movement monitoring should start at around 28 weeks, and women with type 1 or type 2 diabetes should be offered fetal surveillance beginning at about 32 weeks of gestation with twice-weekly non-stress tests (NSTs). A fetal ultrasound for growth should be considered at 28 to 32 weeks and before term. An earlier delivery should be offered to women who have either preexisting diabetes of longer duration or with vascular disease, especially if glucose control is suboptimal; at this time an amniocentesis may be done to confirm fetal lung maturity.

34. What is the risk of diabetic ketoacidosis in pregnancy?

Pregnancy predisposes to accelerated starvation, which can result in ketonuria after an overnight fast. Diabetic ketoacidosis (DKA) may occur at lower glucose levels (often referred to as "euglycemic DKA") because of the increased glomerular glucose filtration, continuous glucose utilization by the fetal-placental unit, and greater volume of distribution of glucose due to a 30% to 40% expansion of plasma volume. Women also have a lower buffering capacity because of progesterone-induced respiratory alkalosis, which results in a compensatory metabolic acidosis. An early switch from carbohydrate metabolism to lipolysis occurs in pregnant women who have depleted their glycogen stores after a 12-hour fast, resulting in a starvation ketoacidosis.

35. How should the risk of DKA be managed?

Any pregnant women with type 1 diabetes who is unable to keep down food or fluids or has persistent severe hyperglycemia should check for urinary ketones at home. If the urinary ketones cannot be cleared quickly, a blood chemistry panel should be ordered to rule out an anion gap, even if the maternal glucose value is less than 200 mg/dL. Often the only precipitant for DKA in pregnancy is nausea and vomiting, but the possibility of an infection, particularly urinary tract infections, should be aggressively investigated. Women with type 2 diabetes and even women with gestational diabetes can also experience DKA, especially in the context of prolonged fasting, infections, use of beta-agonists for preterm labor, or steroids to promote fetal lung maturity.

36. How does maternal DKA affect the fetus?

In a study of 20 consecutive cases of DKA, only 65% of the fetuses were alive on admission to the hospital. Risk factors for fetal loss included DKA manifesting later in pregnancy (32 weeks vs. 24 weeks), high insulin requirements, and longer duration of DKA. Electrolyte disturbances and fetal hypoxemia are additional risk factors for fetal death. The fetal heart rate must therefore be monitored continuously until the acidosis has resolved.

37. What must the physician remember about DKA in pregnant women?

Pregnant women unable to take oral nutrients require an additional 100 to 150 g/day of intravenous glucose to meet the metabolic demands of the fetal-placental unit. Without adequate carbohydrate (often a 10% dextrose solution is necessary), fat will be burned for fuel, and the patient in DKA will remain ketotic.

KEY POINTS 1: DIABETES IN PREGNANCY

1. Although hyperglycemia is a major teratogen, the fetal malformation rate can be decreased from up to 30% to the normal baseline risk with optimal glycemic control before pregnancy and during the first 10 weeks of gestation.
2. Diabetic ketoacidosis may occur at blood glucose levels less than 200 mg/dL in pregnancy and may also occur in women with gestational diabetes.
3. Inadequately controlled diabetes may put the fetus at risk for development of childhood obesity and glucose intolerance.
4. Women in whom gestational diabetes develops have a 30% to 50% risk for development of type 2 diabetes within 5 to 10 years.
5. Pregnancy does not usually accelerate the progression of diabetic nephropathy unless the disease is severe; however, proteinuria, diabetic retinopathy, and autonomic neuropathy may worsen.
6. Insulin requirements often decrease in the first trimester, putting the mother at high risk of severe hypoglycemia, but requirements may double or triple in the late second and third trimesters owing to the insulin resistance of pregnancy.
7. Currently there is no consensus between the ACOG and the ADA about which criteria to use for the screening for and diagnosis of gestational diabetes.

38. What is gestational diabetes mellitus and why is there no consensus on its diagnosis between the ACOG and the ADA?

The previous definition of GDM as a glucose-intolerant state with onset or first recognition during pregnancy has been challenged by the IADPSG and the American Diabetes Association (ADA). They recognized that many women with undiagnosed preexisting (overt) diabetes were being referred to as having GDM even though the degree of their hyperglycemia or its early manifestation (before

24 weeks of gestation) clearly indicated that these women had diabetes that was simply not identified until GDM screening was performed in pregnancy. Given that such women have a much higher risk of maternal and fetal complications, including major malformations if their HbA_{1C} levels are 6.5% or higher, the IADPSG and ADA now recommend that GDM be diagnosed only if the glucose intolerance was identified during pregnancy *AND* the woman did not qualify for preexisting (overt) diabetes. The IADPSG and ADA recommend that women diagnosed for the first time in pregnancy should be considered as having overt diabetes (and not GDM) if any of the following criteria is fulfilled—$HbA_{1C} \geq 6.5\%$, FBG level $\geq$ 126 mg/dL, or random glucose level $\geq$ 200 mg/dL—which are the same criteria for diagnosis of diabetes outside of pregnancy (Table 5-2).

The ADA also adopted the IADPSG recommendations to diagnose GDM at lower blood glucose thresholds than what has been used by the ACOG, on the basis of findings from the HAPO (Hyperglycemia and Adverse Pregnancy Outcomes) trial. Further, because the HAPO trial showed an increased risk of LGA status using a single abnormal threshold glucose value on a 75-g 2-hour oral glucose tolerance test (OGTT), the ADA now recommends that this test be used to diagnose GDM (Table 5-3) rather than two abnormal values on the 100-g 3-hour OGTT traditionally used by ACOG (Table 5-4). However, adopting the new ADA criteria will result in a tripling of the prevalence of GDM—to an estimated 18% of the pregnant population—in comparison with the 5% to 6% currently estimated prevalence according to the ACOG criteria (see Table 5-4). This prevalence increase could be even higher in some ethnic groups (Hispanic Americans, Native Americans, Pacific Islanders, and Asian Americans). Asian women have a higher risk of development of GDM at a lower BMI. Interestingly, women of African ancestry have a high prevalence of obesity but lower GDM rates than other groups. However, postpartum they have a higher rate of development of diabetes after GDM. Even prior to the changes in the ADA guidelines on the diagnosis of GDM, the prevalence of GDM had doubled in the past 10 to 15 years because of the obesity epidemic.

TABLE 5-2. CRITERIA FOR DIAGNOSIS OF OVERT DIABETES*

Fasting glucose measurement	$\geq$ 125 mg/dL
Hemoglobin A_{1C} measurement	$\geq$ 6.5%
Random glucose	$\geq$ 200 mg/dL

*Any of these findings makes the diagnosis.

TABLE 5-3. AMERICAN DIABETIC ASSOCIATION CRITERIA FOR A POSITIVE 75-G ORAL GLUCOSE TOLERANCE TEST RESULT*

Fasting glucose	$\geq$ 92 mg/dL
1-hour glucose	$\geq$ 180 mg/dL
2-hour glucose	153 mg/dL

*One abnormal value needed for positive result.

TABLE 5-4. AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS CRITERIA FOR A POSITIVE 100-G ORAL GLUCOSE TOLERANCE TEST RESULT*

Fasting glucose	$\geq$ 95 mg/dL
1-hour glucose	$\geq$ 180 mg/dL
2-hour glucose	$\geq$ 155 mg/dL
3-hour glucose	$\geq$ 140 mg/dL

*Two abnormal values needed for a positive result.

Currently there is no consensus about the adoption of the ADA criteria over the ACOG criteria. Critics of the ADA criteria argue that adopting it will triple the prevalence of GDM, potentially outstripping the resources to treat it. They also argue that it is not clear how much the increased risk of LGA status at lower glucose thresholds observed in the HAPO trial on which it was based was due to maternal obesity or mild hyperglycemia. Further, there are no randomized controlled trials pitting the diagnostic criteria against each other and showing that implementation of and treatment based on the new ADA criteria will result in lower rates of LGA infants or other adverse pregnancy outcomes.

39. What are the different diagnostic criteria for GDM according to the ACOG and the ADA?

The lack of a consensus for the diagnosis of GDM in the United States between the ACOG and the ADA is unfortunately forcing practitioners to choose to use one criterion over the other, resulting in a complete lack of standardization. A National Institutes of Health (NIH) consensus conference has selected a committee of members who have not published in the area of GDM in an effort to avoid bias, and it is hoped that this conference can resolve this lack of consensus in the near future. The Carpenter and Coustan criteria continue to be used by the ACOG; they require two abnormal glucose values out of four values on a 100-g 3-hour OGTT. However, the ADA adopted the IADPSG recommendations based on the HAPO trial, which showed that an FBG 92 mg/dL or higher, a 1-hour glucose level 180 mg/dL or higher, *OR* a 2-hour glucose level 153 mg/dL or higher (only one abnormal value required) on a 75-g 2-hour OGTT resulted in a 1.75-fold higher risk of an LGA infant and should be the basis for the diagnosis (see Table 5-2). The HAPO trial, performed in 25,000 women in nine countries, suggested that fetal overgrowth occurs at lower glucose targets than previously used and that the diagnostic glucose targets should be lowered. The values listed in Table 5-2 were statistically chosen because they resulted in a 1.75-fold increase in LGA status. Because the increased risk of LGA status occurred along a continuum, there was no clear threshold to adopt on the basis of the trial results. Further, obesity itself increased the risk of LGA status, and there is argument as to how much of the higher LGA risk was due to obesity and how much to mild hyperglycemia. Opponents argue that adopting a 1.75-fold higher risk about the mean versus a twofold or threefold increased risk was also somewhat arbitrary and will result in a tripling of the prevalence of GDM without compelling data from an RCT that adopting the new criteria would result in a benefit.

Nearly 95% of all women in the HAPO trial who met criteria for GDM using the 75-g 2-hour OGTT were diagnosed on the basis of the FBG and 1-hour glucose values, raising the question of whether the 2-hour value is worth the extra time and cost. Some countries are considering basing the GDM diagnostic criteria only on the fasting and 1-hour values to reduce subject burden and possibly the cost. There is also debate about early screening of high-risk women for GDM (see later) because the ADA has abandoned the use of the 50-g glucose challenge (1-hour Glucola test), which continues to be used by the ACOG, to screen women for GDM.

40. Explain the differences in early screening between the ACOG and ADA guidelines.

According to the ACOG, women who have *NO* risk factors do not require any screening or diagnostic testing at 24 to 28 weeks of gestation, but this category is limited to women meeting *all* of the following criteria: age under 25 years, normal weight before pregnancy, member of an ethnic group with a low prevalence of GDM, no known diabetes in first-degree relatives, no history of abnormal glucose tolerance, and no history of poor obstetric outcome or macrosomic infant ($>$ 9 lb). Most obstetricians advocate for universal screening because few women meet all of these criteria. The ADA recommends diagnostic testing at 24 to 28 weeks for everyone with the 75-g 2-hour OGTT (and no screening using a 1-hour 50-g glucose challenge).

41. What are the differences in recommendations for testing high-risk women early in pregnancy?

High-risk status requires glucose testing as soon as pregnancy is diagnosed and again at 24 to 28 weeks if the early test result is normal. Women meeting *any* of the following criteria should be

tested early: obesity, personal history of GDM (recurrence rate 30%-50%), previous macrosomic infant (> 9 lb), glycosuria, family history of diabetes in a first-degree relative, and polycystic ovary syndrome (PCOS). The ACOG recommends that these high-risk women be screened on their first prenatal visit with a 50-g oral glucose load and that, if the 1-hour glucose value exceeds 130 to 140 mg/dL, a diagnostic 3-hour 100-g OGTT be performed. The new ADA criteria do not use a 50-g OGTT test for screening. Instead, they advocate that high-risk women be tested on the first prenatal visit with either measurement of HbA_{1C} *or* performance of an FBG *or* a 75-g 2-hour OGTT, primarily to rule out overt diabetes. In any woman who meets criteria for overt diabetes ($HbA_{1C} \geq 6.5\%$; FBG $\geq$ 126 mg/dL or random glucose $\geq$ 200 mg/dL), a diagnosis of preexisting diabetes rather than GDM should be made. If the fasting glucose value is 92 mg/dL or higher, a diagnosis of GDM can be made. A 75-g 2-hour OGTT to determine whether the 1-hour or 2-hour glucose value exceeds or equals 180 mg/dL or 153 mg/dL, respectively, is optional and not mandated in all high-risk women *early* in pregnancy.

The recommendations given by the ADA to diagnose overt diabetes in early pregnancy have resulted in opponents underscoring that some high-risk women with only impaired glucose tolerance (IGT) (by OGTT) will be missed early using the new criteria because a practitioner can choose whether to obtain an HbA_{1C} measurement, FBG test, or 75-g 2-hour OGTT early in pregnancy. Some practitioners recommend that an HbA_{1C} value of 5.7% or greater be used to diagnose GDM early because prediabetes outside pregnancy is diagnosed with this value. However, an HbA_{1C} of 5.7% or greater was not given as an optional criterion by either the IADPSG or the ADA to diagnose GDM. Further, many studies outside of pregnancy have demonstrated that the HbA_{1C} measurement is the least sensitive test to diagnose either prediabetes or diabetes, especially because anemia is common in pregnancy and the HbA_{1C} result will be falsely low in states involving high red blood cell turnover.

Also, it has been demonstrated that the FBG value is less sensitive than the post–glucose load value on a 75-g 2-hour OGTT for diagnosing prediabetes or diabetes. One article has underscored the profound difference among different ethnic populations studied in the HAPO trial in regard to the sensitivities of an FBG value and a 1-hour or 2-hour 75-g glucose value in diagnosing GDM. Especially in the Asian population, an FBG value is unlikely to identify a woman as having GDM because most Asian women have only IGT after a glucose load. In Hong Kong, of all the women in the HAPO trial who were diagnosed as having GDM using the new criteria, only 26% had an abnormal FBG value, and the remainder were diagnosed by either an abnormal value on a 1-hour (45%) or 2-hour (29%) OGTT. This finding raises the question as to whether early diagnostic testing recommended by the ADA for high-risk women will miss many with only IGT, because administering the 75-g 2-hour OGTT is optional according to ADA criteria (women can be screened with *either* HbA_{1C} measurement or FBG test). Both the ACOG and the ADA agree that if initial test results are normal (using their different recommendations), repeat testing should be done at 24 to 28 weeks of gestation using either the 100-g 3-hour OGTT (ACOG) or the 75-g 2-hour OGTT (ADA).

42. Describe the 50-g glucose challenge used by ACOG.

The 50-g glucose challenge is the accepted screen by the ACOG for the presence of GDM, but a positive result must be followed by a diagnostic 100-g 3-hour OGTT. A positive screen result is in the range of 130 to140 mg/dL or above. The sensitivity and specificity of the test depend on what threshold value is chosen, and the cutoff may be selected according to the prevalence of GDM in the population being screened. The test does not have to be performed during a fasting state, but a serum sample must be drawn exactly 1 hour after administration of the oral glucose. Owing to the poor reproducibility of this test from one day to the next and the lack of any sensitivity cutoffs based on a diagnostic 75-g 2-hour OGTT result rather than the 100-g 3-hour OGTT, the ADA has abandoned the use of the 50-g glucose test as a screening tool.

43. Describe the 100-g 3-hour and the 75-g 2-hour OGTTs.

Both tests should be performed after 3 days of an unrestricted carbohydrate diet and while the patient is fasting. For the 100-g 3-hour OGTT, two abnormal blood glucose values are required, and for the 75-g 2-hour OGTT, only one abnormal value is required (see Tables 5-e3 and 5-4). If the 100-g 3-hour OGTT test is performed and only one value is abnormal, a second 100-g 3-hour test

should be performed 1 month later because a single elevated glucose value increases the risk of LGA status and one third of patients with such a result will ultimately meet the diagnostic criteria for GDM (see Table 5-4). Implementing the diagnostic criteria for the 75-g 2-hour OGTT instead of the 100-g 3-hour OGTT is estimated to increase the prevalence of GDM by threefold (from ~5%-6% to ~18%), and it is not yet clear whether such implementation will ultimately decrease risk of LGA infants. Obviously, the lack of consensus regarding which criterion to use from one institution to the next is extremely confusing for patient management as well as for clinical research trials for which either diagnostic criteria could be used.

44. Summarize the risks to the mother with GDM.

The immediate risks to the mother with GDM are increased incidences of cesarean delivery (~30%), preeclampsia (10%-30%), and polyhydramnios (~10%-20%), which can result in preterm labor. The long-term risks to the mother are related to recurrent GDM pregnancies (30%-50% recurrence) and the substantial risk for development of type 2 diabetes mellitus.

45. What factors increase the risk of subsequent development of type 2 diabetes?

Women with GDM have an extremely high risk (33%-50%) for development of type 2 diabetes in the subsequent 5 to 10 years. Risk factors include fasting hyperglycemia, an insulin requirement, GDM diagnosed before 24 weeks of gestation (preexisting glucose intolerance), obesity, membership in an ethnic group with a high prevalence of type 2 diabetes, and IGT at 6 weeks postpartum. Women with GDM who have multiple subsequent pregnancies also have a higher risk for development of type 2 diabetes.

46. What interventions may reduce the risk for development of type 2 diabetes?

Counseling with regard to diet, exercise, and weight loss is essential and is likely to improve insulin sensitivity, according to the findings of the Diabetes Prevention Program (DPP) trial. A subgroup analysis examining women in the DPP with a history of GDM showed that they had a much higher risk for development of type 2 diabetes (17% per year) than women with IGT but without a history of GDM. This risk could be halved to approximately 8% per year with diet and exercise or metformin. Such dietary modifications should be adopted by the family, because the infant of a woman with GDM is also at risk for obesity and the metabolic syndrome. One trial also demonstrated that the use of a thiazolidinedione, versus placebo, postpartum decreased the rate of development of type 2 diabetes in 30 months from 12.1% to 5.4% in the 133 randomly assigned women, apparently by decreasing insulin secretion and preserving beta-cell function. At this time, it is recommended that intensified efforts through diet and exercise be made to help a woman with GDM return to her pre-pregnancy weight and to lose additional weight if her BMI is still elevated. If diet and exercise are unsuccessful or do not normalize glucose tolerance, metformin should be considered, especially in women with both impaired fasting glucose (IFG) and IGT.

47. What is the incidence of complications in the infant of a mother with GDM?

Even with the advent of screening and aggressive GDM management, the incidence of neonatal complications for women with GDM ranges from 12% to 28%.

48. Summarize the basic mechanism behind fetal complications related to GDM.

Excessive transfer of glucose, amino acids, FFAs, and triglycerides from mother to fetus provides an overabundance of nutrients, resulting in excess fetal fat accretion. Maternal hyperglycemia induces fetal hyperglycemia, which results in fetal pancreatic islet hypertrophy and beta-cell hyperplasia with consequent fetal hyperinsulinemia. Fetal insulin is a potent growth hormone.

49. What is the most common complication of GDM?

The placenta plays a key role in the regulation of nutrient transport in GDM, contributing to the most common complication, which is macrosomia or LGA status (Fig. 5-1). Although transplacental glucose flux is flow limited, transport of essential and nonessential fatty acids is regulated. The expression of genes involved with inflammation and lipid transport and metabolism are significantly altered in the

placentas of women with GDM, favoring excess fetal fat accretion. Increased fat availability to the fetus leads to adiposity and visceromegaly (especially heart, liver, and pancreas), which put the mother at increased risk of requiring a cesarean section and the infant at risk for shoulder dystocia. The excessive supply of nutrients also causes an increase in fetal abdominal girth disproportionate to other body measurements (body-to-head disproportion), resulting in a difficult delivery.

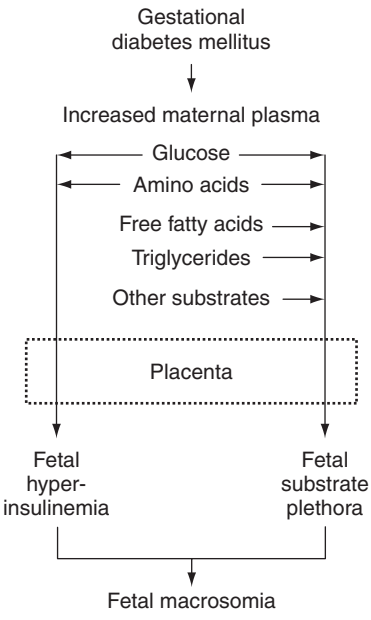

Figure 5-1. The mechanism by which gestational diabetes mellitus leads to fetal macrosomia.

50. What other complications may result from GDM or preexisting diabetes?

- Shoulder dystocia with Erb's palsy and clavicular fractures, fetal distress, low Apgar scores, and birth asphyxia when GDM is unrecognized.
- If mothers have poor glycemic control, respiratory distress syndrome may occur in up to 30% of infants because of decreased lung surfactant synthesis.
- Cardiac septal hypertrophy may be seen in 35% to 40%.
- With extremely poor glucose control, especially in women with type 1 or type 2 diabetes, there is also an increased risk of fetal mortality as a result of fetal acidemia and hypoxia.
- Common metabolic abnormalities in the infant of a mother with diabetes include neonatal hypoglycemia from sustained hyperinsulinemia as well as hypocalcemia, polycythemia, and hyperbilirubinemia.
- Excess FFAs and triglycerides delivered to the fetus may also contribute to excess fetal growth and is now the subject of increased research to discern whether these substrates may need to be targeted for lowering.

51. Why can macrosomia still occur despite adequate maternal glycemic control? Role of triglycerides and free fatty acids.

Fetal hyperinsulinemia may cause exaggerated fetal siphoning of glucose from the mother, which blunts the maternal postload glucose peaks, resulting in what appears to be optimal glycemic control

in the mother. Further, triglycerides and FFAs are now recognized as important nutrients for fetal fat accretion and the placenta has a lipoprotein lipase (LPL) that hydrolyzes maternal triglycerides to FFAs, which can be transported across the placenta. Triglyceride levels are higher in women with GDM and have been shown to be stronger predictors than glucose levels of excess neonatal fat in the offspring of who are obese or have GDM with adequate glycemic control. Upregulation of many genes involved with lipid transport and storage as well as inflammation and oxidative stress have been shown to characterize the placentas in women with GDM and may affect nutrient transport and fetal fat accretion.

52. Describe the fetal-based management strategy and fetal surveillance in GDM.

A number of RCTs have demonstrated that using fetal overgrowth as an indicator of optimal diabetes management is beneficial. Because measurements of maternal glucose may be deceptive and other nutrients such as excess lipids may also contribute to fetal fat accretion, assessing fetal growth as a gauge for the adequacy of treatment is now recommended. Amniotic fluid insulin levels, a marker of fetal hyperinsulinemia (because maternal insulin does not cross the placenta in appreciable quantities) correlates strongly with the fetal abdominal circumference at 28 to 32 weeks of gestation. These RCTs support intensifying maternal medical therapy when fetuses have an abdominal circumference above the 70th percentile because the latter feature is associated with increased abdominal fat accretion. The trials that were successful in reducing LGA status used insulin as a treatment, but it is unclear how much of the benefit of maternal insulin therapy was due to reducing very mild maternal hyperglycemia or suppressing FFAs. It is recommended that women with GDM who require medical therapy or have suboptimal glycemic control undergo fetal surveillance beginning at 32 to 34 weeks of gestation. Delivery may be considered at around 39 weeks if the woman has good dating criteria and favorable cervical status, but delivery at 40 weeks is an option if glycemic control continues to be optimal and fetal test results are reassuring. An estimated fetal weight of greater than 4500 g carries such a high risk of shoulder dystocia that an elective cesarean delivery is usually recommended in women with GDM or preexisting diabetes.

53. Discuss the long-term sequelae of GDM or preexisting diabetes in offspring of affected mothers.

The long-term sequelae of diabetes for offspring are concerning. Proliferation of fetal adipocytes and pancreatic beta cells may be responsible for “fetal programming” of the later development of obesity and the metabolic syndrome. Reports of an increased risk of adolescent obesity and type 2 diabetes in infants of mothers with GDM or preexisting diabetes are compelling. The incidence of childhood type 2 diabetes was approximately tenfold higher in Pima Indian offspring born to mothers with diabetes than in offspring whose mothers did not have diabetes until after pregnancy. Furthermore, despite similar incidences of obesity at 20 years of age in the two offspring groups, the incidence of type 2 diabetes was nearly 70% at age 25 to 29 years in the offspring of diabetic mothers, compared with approximately 10% in the offspring of prediabetic mothers (those in whom diabetes did not develop until after the pregnancy).

54. How does in utero hyperglycemia or other metabolic risk factors affect the long-term sequelae of infants born to diabetic mothers?

In utero hyperglycemia appears to be an independent risk factor for the development of childhood glucose intolerance. However, being born LGA or being born to an obese mother also increases the risk of childhood obesity and metabolic syndrome. Interestingly, women with severe obesity, many with a history of GDM, who undergo bariatric surgery before their next pregnancies have been shown to have far fewer maternal and fetal complications, and the offspring risk for childhood obesity is reduced. A maternal high-fat diet has also been associated with an increased risk of offspring metabolic disorders. Elevated insulin values in amniotic fluid (owing to fetal hyperinsulinemia) predicted teenage obesity in one study independently of fetal weight, and approximately 30% of these offspring had IGT by 17 years of age. Fetal programming or epigenetic influences appears to occur in this intrauterine environment of nutrient excess and may contribute to the

growing incidence of type 2 diabetes as children with IGT become mothers themselves, perpetuating the cycle.

55. What causes women to get GDM?

GDM is caused by abnormalities in at least three aspects of fuel metabolism: insulin resistance in fat and muscle, increased hepatic glucose production, and impaired insulin secretion. Although insulin levels may be high, the increased insulin resistance of pregnancy still results in inadequate compensation because impaired beta-cell function leads to insufficient insulin secretion to maintain euglycemia in the presence of insulin resistance. The insulin resistance is thought to be due primarily to the effects of increased production of human placental lactogen, placental growth hormone, tumor necrosis factor-α, and inflammatory cytokines. Women in whom GDM develops have lower pregravid insulin sensitivity than matched control groups, and some abnormalities may persist after delivery. The majority of women in whom GDM develops are overweight and many have characteristics of the metabolic syndrome before pregnancy. Thin or normal-weight women in whom GDM develops are in the minority and may display a maturity-onset diabetes of the young (MODY) gene or, more commonly, may be at risk for development of latent autoimmune diabetes of adulthood (LADA). Many of these unusual patients are found to be positive for glutamic acid decarboxylase (GAD) antibody or islet cell antibodies and have lowish C-peptide levels, putting them at increased risk for manifesting type 1 diabetes later.

56. What causes increased hepatic glucose production?

Increased hepatic glucose production results from inadequate insulin suppression of excessive hepatic gluconeogenesis. There are some women with GDM who primarily have fasting hyperglycemia, and it is thought that they have greater hepatic insulin resistance than peripheral (muscle and fat) insulin resistance. Beta-cell sensing of glucose is also abnormal and is manifested as an inadequate insulin response for a given degree of hyperglycemia.

57. Summarize the role of impaired insulin secretion in GDM.

Impaired insulin secretion renders the woman unable to meet the requirement for greater insulin production necessitated by the insulin resistance and increased hepatic glucose production. These same pathophysiologic disorders, which are in large part genetically determined, make the patient with GDM more likely to have type 2 diabetes mellitus later in life, when weight gain and aging often contribute further to insulin resistance and impaired insulin secretion. Pregnancy can be thought of as a "stress test" for the development of type 2 diabetes, because the marked insulin resistance of pregnancy necessitates a twofold to threefold increase in insulin secretion that the beta cell may not be able to achieve, resulting in a clinically evident abnormality in glucose metabolism. It has been demonstrated that this beta-cell defect persists postpartum, and the severity of the defect is predictive of the risk for development of type 2 diabetes.

58. What is the best therapy for women with GDM, and how much weight should they gain?

Women with GDM should be taught home blood glucose monitoring to ensure that glycemic goals are met throughout the duration of pregnancy. The best therapy for GDM depends entirely on the extent of the glucose intolerance and on the mother's response. In at least half of cases, diet alone maintains postprandial blood glucose values within the target range but is more likely to fail if fasting hyperglycemia also exists. Women should not exceed the Institute of Medicine (IOM) recommendations for weight gain in pregnancy (BMI $<$ 18.5 kg/m^2, 28-40 lb; BMI 18.5-24.9 kg/m^2, 25-35 lb; BMI 25-29.9 kg/m^2, 15-25 lb; BMI $\geq$ 30 kg/m^2, 11-20 lb) because both a higher maternal BMI and gestational weight gain independently increase the risk of an LGA infant. Further, many experts recommend targeting the lower end of the weight gain ranges. It has been shown that women with more severe obesity (BMI $>$ 35 kg/m^2) should gain even less weight and that many severely obese women do not need to gain any weight to deliver a normally grown infant. Postprandial glucose levels have been strongly associated with the risk of LGA infants, and

therefore restriction of simple carbohydrates may be helpful to blunt postprandial glucose excursions. However, saturated fats should also be limited because they increase insulin resistance and independently contribute to excess triglycerides and FFAs for fetal fat accretion. Women with a BMI greater than 30 kg/m^2 may benefit from a 30% to 33% caloric restriction to approximately 20-25 kcal/kg or approximately 1800 kcal per day, which has been shown to reduce hyperglycemia and serum triglycerides with no increase in ketonuria. Weight loss during pregnancy is not advocated at this time.

59. Discuss the role of oral sulfonylureas in GDM.

The only oral hypoglycemic drugs approved for use in women with GDM are glyburide and acarbose; the latter is usually problematic because of gastrointestinal side effects. None of the other insulin secretagogues is approved, nor is metformin or thiazolidinediones. In a landmark multicenter trial, 400 women with GDM were randomly assigned to receive either insulin or glyburide after 24 weeks of gestation. Maternal glycemic control, macrosomia, neonatal hypoglycemia, and neonatal outcomes were no different between the groups. Most important, the cord serum insulin concentrations were similar in the two groups, and glyburide was not detected in the cord serum of any infant tested. However, subsequent studies suggested that a very small amount of glyburide may cross the placenta. Overall, glyburide therapy will fail in approximately 20% of women with GDM and they will require insulin treatment to achieve adequate glycemic control. Risk factors associated with glyburide failure include diagnosis of GDM before 24 weeks, fasting hyperglycemia, recurrent pregnancies, and more severe hyperglycemia.

60. Discuss the role of metformin in pregnancy.

The MiG (Metformin in Gestation) trial was an RCT of 751 women with GDM randomly assigned to receive metformin or insulin. Because of concerns about the possible risk of fetal lactic acidosis, women with a contraindication to metformin, fetal anomalies, gestational hypertension, preeclampsia, fetal growth restriction, or ruptured membranes were excluded from the study. Women with preexisting diabetes were also excluded. Metformin did not appear to increase the rates of any adverse outcomes, although it was associated with a slight increase in preterm birth rate and 46% of women in the metformin group required supplemental insulin. The 2-year-old offspring data have been reported in a follow-up trial (Metformin in Gestation—The Offspring Follow Up [MiG-TOFU]). There was some evidence of increased subcutaneous fat in the offspring exposed to metformin in utero but total fat as measured by dual-energy x-ray absorptiometry (DXA) scan did not appear to be different in the two groups, even though only a minority of the offspring underwent DXA. Although the researchers of the trial speculated that metformin might be of value in decreasing visceral fat in the offspring, no good visceral fat measures were made because DXA is insensitive in measuring visceral fat and magnetic resonance imaging was not performed. Metformin should not be used in women at risk for placental insufficiency because it crosses the placenta and it has not been approved in pregnancy for the routine treatment of GDM. It is recommended that its use be limited to prospective trials, although many practitioners are using it because of its lower risk of hypoglycemia, its ease of use, and the challenges of treating a rapidly growing GDM population.

61. When should insulin be used to treat GDM?

Women who have fasting blood glucose levels greater than 95 mg/dL, 1-hour postprandial glucose levels greater than 140 mg/dL, or 2-hour postprandial glucose levels greater than 120 mg/dL should be started on insulin therapy. Those who are unwilling to start insulin and who exhibit mild hyperglycemia without substantial increases in fasting blood glucose may be candidates for glyburide therapy or possibly metformin, although the latter is not yet approved by the FDA for use in GDM. A woman with a fetus that is LGA, as demonstrated by ultrasound, is also a candidate for medical management. Often GDM can be treated with twice-daily injections of NPH and regular insulin, but occasionally, postprandial glycemic excursions are so excessive that mealtime injections of a short-acting insulin analog are necessary. Serious hypoglycemia tends to be an infrequent occurrence in such patients because of their underlying insulin resistance and symptomatic awareness of hypoglycemia.

62. What is the role of exercise in patients with GDM or preexisting diabetes?

Both the ACOG and the ADA advise that pregnant women adopt the national guidelines of exercising 30 minutes daily as long as there is not an obstetric contraindication. Moderate exercise is well tolerated in pregnancy. Exercise also improves insulin sensitivity in women with type 2 diabetes and may limit excess weight gain. Fetal safety of such exercise has been established, especially if the maternal heart rate is kept under 140 to 160 beats/minute at durations of 30 minutes and if the mother is well hydrated and does not get overheated. Two of three small trials in GDM pregnancies have shown that exercise three times a week can achieve glycemic control and infant birth weights that are similar to those seen in women who are treated with insulin. Unfortunately, exercise has been shown in one meta-analysis not to effectively decrease LGA and to be only marginally effective in limiting excess gestational weight gain. However, if women increase their physical activity by walking after they eat, postprandial glucose rises can be significantly blunted. Additionally, establishing a regular routine of modest exercise during pregnancy may also have long-lasting benefits for the mother with GDM, who clearly has an appreciable risk for development of type 2 diabetes in the future.

63. When is a controlled exercise program contraindicated?

Women at risk for preterm labor, vaginal bleeding, or conditions predisposing to growth restriction are not candidates for a controlled exercise program. Women with poorly controlled hypertension and preeclampsia are usually advised to adhere to bed rest. Some women, especially women with a low BMI and long-standing type 1 diabetes with vascular disease, may be at risk for placental insufficiency or growth restriction and may not be candidates for exercise.

64. What important postpartum management issues should be addressed in women with pregestational or gestational diabetes?

Critical issues in the postpartum period include maintenance of glycemic control, diet, exercise, weight loss, blood pressure and renal protection management, breastfeeding, and contraception. Women with type 1 diabetes should be checked for TPO antibodies which, if present, confer up to a 50% risk for development of postpartum thyroiditis. Breastfeeding has been shown to be advantageous to mothers with type 2 diabetes and GDM by facilitating weight loss. Inability to lose the weight gained in pregnancy is one of the strongest risk factors for progressing to type 2 diabetes in women with GDM. The majority of women with preexisting diabetes has dramatic decreases in their insulin requirements immediately postpartum and are likely to require significantly less than their pre-pregnancy doses, especially those who breastfeed. Glycemic goals need to be relaxed, especially given erratic eating and sleeping schedules and the improved insulin sensitivity. Women with preexisting diabetes, even those who have been extremely compliant and have had optimal glycemic control during pregnancy, experience a dramatic worsening of glucose control after delivery. Furthermore, many stop seeking medical care for their diabetes. The postpartum period is relatively neglected as both the new mother and her physician relax their vigilance. However, this period offers a unique opportunity to institute health habits that can have highly beneficial effects on the quality of life of both the mother and her infant. The importance of effective contraception cannot be overstated, because 50% of pregnancies are unplanned and each subsequent pregnancy in a woman with GDM increases her risk for development of type 2 diabetes.

65. Explain the value of diet and exercise in the postpartum period.

A weight loss program consisting of diet and exercise should be instituted for women with GDM to improve insulin sensitivity and prevent the development of type 2 diabetes. It has been shown that most women with GDM or type 2 diabetes do not lose their pregnancy weight gain and often enter a subsequent pregnancy at an even higher weight. Diet and exercise reduced the development of type 2 diabetes by approximately 50% in the subgroup of women with GDM in the DPP trial, and therefore every effort must be made to intervene in this exceedingly high-risk population. Overweight women with type 2 diabetes are likely to be able to change from insulin to oral medications if they can also reduce their weight.

66. Discuss the importance of glucose monitoring and subsequent testing during the postpartum period.

Vigilant home blood glucose monitoring should be continued in the postpartum period by women with pregestational diabetes because insulin requirements drop almost immediately and often dramatically at this time, increasing the risk of hypoglycemia. For women with GDM who required insulin, occasional home blood glucose monitoring may be useful because about 10% of such patients have been shown to meet the criteria for diabetes on postpartum testing. In all women with a history of GDM, glycemic status should be reassessed 6 to 12 weeks after delivery. At a minimum, an FBG test should be performed to determine whether the woman has persistent diabetes (FBG $>$ 126 mg/dL) or IFG (FBG 100-125 mg/dL). A 75-g 2-hour OGTT is recommended by the ADA and IADPSG because a 2-hour glucose value of 200 mg/dL or higher establishes a diagnosis of diabetes and a 2-hour value of 140-199 mg/dL makes the diagnosis of IGT. The majority of women with persistent IGT is missed if only an FBG measurement is checked. An HbA_{1C} measurement is not sensitive in diagnosing prediabetes at 6 weeks postpartum because it is often low owing to iron deficiency anemia or postpartum blood loss and because it reflects glycemia over a 3-month period (which would include the last 6 weeks of pregnancy).

67. Why is a diagnosis of impaired glucose tolerance or prediabetes of critical importance?

The importance of diagnosing impaired glucose intolerance or prediabetes lies in its value in predicting the future development of type 2 diabetes. In one series, a diagnosis of IGT was the most potent predictor of the development of type 2 diabetes in Latino women with a history of GDM; diabetes developed in 80% of such women in the subsequent 5 to 7 years. Intensified efforts promoting diet, exercise, and weight loss, and possibly metformin if lifestyle changes fail, should be instituted in this extraordinarily high-risk group of women.

68. Summarize the role of ACE inhibitors or other antihypertensives in the postpartum period.

Postpartum women who are candidates for an ACE inhibitor can be started on enalapril or captopril, which have not been shown to appear in breast milk in appreciable concentrations. There are few data on ARBs, but calcium channel blockers are also compatible with breastfeeding. Diuretics should be avoided because of their possible suppressive effects on breast milk production, and beta-blockers such as atenolol with a low degree of protein binding can reach breast milk and so should be avoided.

69. Should women with diabetes breastfeed their infants?

Women should be encouraged to breastfeed unless difficulties in glycemic control arise. Women with type 1 diabetes who breastfeed have even lower insulin requirements than those who do not, necessitating a reduction of insulin dosing to 50-60% of pre-pregnancy requirements. Due to fluctuating glucose levels during breastfeeding, which often occurs at night in the fasted state, women are at high risk for severe maternal hypoglycemia and therefore glucose goals should be relaxed. For women with insulin-resistant type 1 diabetes, type 2 diabetes, or GDM, breastfeeding promotes loss of maternal weight gain and also decreases the risk of childhood obesity, especially if continued for at least 6 months. There are reports suggesting that modest doses of glyburide and metformin can be used in breastfeeding mothers, but the sample sizes of these studies are small; the pediatrician should be notified, especially if glyburide is used. Women with a history of GDM who breastfeed appear to have a lower incidence for development of type 2 diabetes, partly because of enhanced weight loss since breastfeeding requires approximately 300-400 kcal per day. The mother must also ensure that her calcium intake is at least 1500 mg/day.

70. How common is postpartum thyroiditis in women with type 1 diabetes? When does it appear?

Women with type 1 diabetes have been reported to have a 20% to 25% incidence of postpartum thyroiditis, the risk being highest in women who test positive for TPO antibodies. Hyperthyroidism can

occur in the 2- to 4-month postpartum period, and hypothyroidism may present in the subsequent 4 to 8 months. Given the significance of this disorder, measurement of thyroid-stimulating hormone is recommended in patients with type 1 diabetes and TPO antibodies at 3 months and at 6 months after delivery or with any suggestive symptoms.

71. Summarize the long-term follow-up of nondiabetic women with a history of GDM.

Women with a history of GDM should undergo a 75-g 2-hour OGTT at approximately 6 to 12 weeks postpartum so they can be determined to be normal or to have prediabetes (IFG, IGT) or diabetes. The ADA recommends retesting every 1 to 3 years using an FBG HbA_{1C} measurement or 75-g 2-hour OGTT; but it has recently been shown that an HbA_{1C} value of 5.7% or higher has been shown to have poorer sensitivity than an abnormal FBG value or 75-g 2-hour OGTT result at 6 weeks to 1 year. The 75-g 2-hour OGTT remains the most sensitive method for detecting any glucose intolerance, especially in some ethnic groups, such as Asian American women, who typically have normal FBG values. There are definite racial-ethnic differences in hemoglobin glycation. A number of women with GDM will go from having GDM to having type 1 or type 2 diabetes between pregnancies. If such a woman enters the next pregnancy with an HbA_{1C} value of 6.5% or higher, her fetus will carry an increased risk of a major malformations, underscoring the importance of repeat testing and effective contraception.

72. Which contraceptive agents can be used by women with diabetes or a history of GDM?

It should be documented at every visit that women are using or have been offered an effective birth control method. The vast majority of contraceptive methods are relatively safe in women with diabetes, including combined oral contraceptives, except for women who have poorly controlled hypertension or hypertriglyceridemia or are at risk for thromboembolic disease. Triglycerides should be measured after the initiation of oral contraceptives in all women with diabetes or a history of GDM because of the significant incidence of hypertriglyceridemia and the associated risk of pancreatitis with oral estrogen use.

73. Summarize the role of low-dose combined oral contraceptives in women with diabetes or a history of GDM.

Low-dose combined oral contraceptives have been shown to be effective and to have minimal metabolic effects in women with diabetes. The ORTHO EVRA patch and the estrogen-progestin contraception ring (NuvaRing) are also options, but the patch has been associated with a higher risk of thromboembolism. In a retrospective cohort of 904 women with GDM, combined oral contraceptives did not influence the development of type 2 diabetes.

74. What other contraceptive options are appropriate in women with diabetes or a history of GDM?

Progestational agents, such as Depo-Provera (medroxyprogesterone acetate) and norethindrone, are less favorable alternatives because Depo-Provera may affect carbohydrate tolerance and norethindrone alone (Minipill) is less efficacious. Depo-Provera has been associated with an increased risk of type 2 diabetes in nursing mothers with a history of GDM, primarily because of excess weight gain. The etonogestrel implant (Implanon) has not been shown to worsen carbohydrate intolerance and may be a good choice for women who want contraception for 3 years. There is no increase in pelvic inflammatory disease with the use of intrauterine devices (IUDs) in women with well-controlled type 1 or type 2 diabetes after the postinsertion period. Therefore an IUD (containing either copper or progestin) is a very attractive choice in women who do not desire pregnancies in the near future. Nearly any contraceptive method is superior to an unwanted pregnancy, given the risks to the mother with pregestational diabetes and the increased risk for development of type 2 diabetes in mothers with a history of GDM.

BIBLIOGRAPHY

ACOG Committee Opinion: Postpartum screening for abnormal glucose tolerance in women who had gestational diabetes mellitus. June, Number 435, 2009.

ACOG Committee Opinion: Screening and diagnosis of gestational diabetes mellitus, Sept, Number 504, 1–3, 2011.

American Diabetes Association: Diagnosis and classification of diabetes mellitus, *Diabetes Care* 34:S62–S69, 2011.

Ballas J, Moore TR, Ramos GA: Management of diabetes in pregnancy, *Curr Diab Rep* 12:33–42, 2012.

Baptiste-Roberts K, Barone BB, Gary TL, et al: Risk factors for type 2 diabetes among women with gestational diabetes: a systematic review, *Am J Med* 122:207–214, 2009.

Barbour LA, McCundy CE, Hernandez TL, et al: Cellular mechanisms in gestational diabetes, *Diabetes Care* 30(Suppl 2): S112–S119, 2007.

Barbour LA: Weight gain in pregnancy: is less truly more for mother and infant?, *Obstetric Medicine* 5:58–64, 2012.

Buchanan TA, Xiang AH, Page KA: Gestational diabetes mellitus: risks and management during and after pregnancy, *Nat Rev Endocrinol* 8:639–649, 2012.

Buchanan TA, Xiang A, Kjos SL, Watanabe R: What is gestational diabetes? *Diabetes Care* 30(Suppl 2):S105–S111, 2007.

Castorino K, Paband R, Zisser H, Jovanovic L: Insulin pumps in pregnancy: using technology to achieve normoglycemia in women with diabetes, *Curr Diab Rep* 12:53–59, 2011.

Catalano PM, Thomas A, Huston-Presley L, Amini SB: Phenotype of infants of mothers with gestational diabetes, *Diabetes Care* 30(Suppl 2):S156–S160, 2007.

Clausen TD, Mathiesen E, Ekbom P, et al: Poor pregnancy outcome in women with type 2 diabetes, *Diabetes Care* 28: 323–328, 2005.

Cooper WO, Hernandez-Diaz S, Arbogast PG, et al: Major congenital malformations after first-trimester exposure to ACE inhibitors, *N Engl J Med* 354:2443–2451, 2006.

Cormier CM, Martinez CA, Refuerzo JS, et al: White's classification of diabetes in pregnancy in the 21st century: is it still valid? *Am J Perinatol* 27:349–352, 2012.

Crowther CA, Hiller JE, Moses JR, et al: for the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) Trial Group: Effect of treatment of gestational diabetes mellitus on pregnancy outcomes, *N Engl J Med* 352:2477–2486, 2005.

Crume TL, Ogden LG, Mayer-Davis EJ, et al: The impact of neonatal breast-feeding on growth trajectories of youth exposed and unexposed to diabetes in utero: the EPOCH study, *Internat J Obesity* 36:529–534, 2012.

Dabelea D, Crume T: Maternal environment and the transgenerational cycle of obesity and diabetes, *Diabetes* 60:1849–1855, 2011.

England LJ, Dieta PM, Njoroge T, et al: Preventing type 2 diabetes: public health implications for women with a history of gestational diabetes, *Am J Obstet Gynecol* 200:365, 2009.

Garcia-Patterson A, Gich I, Amini SB, et al: Insulin requirements throughout pregnancy in women with type 1 diabetes mellitus: three changes of direction, *Diabetologia* 53:446–451, 2010.

Gauster M, Desoye G, Totsch M, Hiden U: The placenta and gestational diabetes mellitus, *Curr Diab Rep* 12:16–23, 2012.

Glatstein M, Djokanovic N, Garcia-Bournissen F, et al: Use of hypoglycemic drugs during lactation, *Canadian Family Physician* 55:371–373, 2009.

Harmon KA, Gerard L, Jensen DR, et al: Continuous glucose profiles in obese and normal-weight pregnant women on a controlled diet, *Diabetes Care* 34:1–7, 2011.

Hernandez TL, Friedman JE, Van Pelt RE, Barbour LA: Patterns of glycemia in normal pregnancy: should the current therapeutic targets be challenged?, *Diabetes Care* 34:1660–1668, 2011.

Holmes VA, Young IS, Patterson CC: Optimal glycemic control, pre-eclampsia, and gestational hypertension in women with type 1 diabetes in the diabetes and pre-eclampsia intervention trial, *Diabetes Care* 34:1683–1688, 2011.

IADPSG Consensus Panel: International Association of Diabetes and Pregnancy Study Groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy, *Diabetes Care* 33:676–682, 2012.

Kahn B, Davies JK, Lynch AM, et al: Predictors of glyburide failure in women with gestational diabetes, *Obstet Gynecol* 107:1306–1309, 2006.

Kim C, Herman WH, Cheung NW, et al: Comparison of hemoglobin A1C with fasting glucose and 2-h postchallenge glucose for risk stratification among women with recent gestational diabetes, *Diabetes Care* 34:1949–1951, 2011.

Kitzmiller JL, Block JM, Brown FM, et al: Managing preexisting diabetes for pregnancy, *Diabetes Care* 31:1060–1079, 2008.

Kjos SL, Schaeffer-Graf UM: Modified therapy for gestational diabetes using high-risk and low-risk fetal abdominal circumference growth to select strict versus relaxed maternal glycemic targets, *Diabetes Care* 30(Suppl 2):S200–S205, 2007.

Kjos SL: After pregnancy complicated by diabetes: postpartum care and education, *Obstet Gynecol Clinics North Am* 34:335–349, 2007.

Landon MB, Gabbe SG: Gestational diabetes mellitus, *Obstet Gynecol* 118:1379–1393, 2011.

Langer O, Conway DL, Berkus MD, et al: A comparison of glyburide and insulin in women with gestational diabetes, *N Engl J Med* 343:1134–1138, 2000.

Li D-K, Yang C, Andrade S, et al: Maternal exposure to angiotensin converting enzyme inhibitors in the first trimester and risk of malformations in offspring: a retrospective cohort study, *BMJ* 343:1–10, 2011.

Malcolm N: Through the looking glass: gestational diabetes as a predictor of maternal and offspring long-term health, *Diab Metab Res Rev* 28:307–311, 2012.

Mathiesen E, Kinsley B, Amiel SA, et al: The Insulin Aspart Pregnancy Study Group: Maternal glycemic control and hypoglycemia in type 1 diabetes pregnancy: a randomized trial of insulin aspart versus human insulin in 322 pregnant women, *Diabetes Care* 30:771–776, 2007.

Mathiesen ER, Ringholm L, Damm P: Stillbirth in diabetic pregnancies, *Best Practice Res Clin Obstet Gynaecol* 25:105–111, 2011.
Metzger BE, Buchanan TA, Coustan DR, et al: Summary and recommendations of the Fifth International Workshop-Conference on Gestational Diabetes Mellitus, *Diabetes Care* 30(Suppl 2):S251–S260, 2007.
Murphy HR, Kumareswaran K, Elleri D, et al: Safety and efficacy of 24-h closed-loop insulin delivery in well-controlled pregnant women with type 1 diabetes, *Diabetes Care* 34:2527–2529, 2011.
Nielsen GL, Moller M, Sorenson HT: HbA1C in early diabetic pregnancy and pregnancy outcomes: a Danish population-based cohort study of 573 pregnancies in women with type 1 diabetes, *Diabetes Care* 29:2612–2616, 2006.
Price N, Bartlett C, Gillmer M: Use of insulin glargine during pregnancy: a case-control study, *BJOG* 114:453–457, 2007.
Ratner RE, Christophi CA, Metzger BE, et al: Prevention of diabetes in women with a history of gestational diabetes: effects of metformin and lifestyle interventions, *J Clin Endocrinol Metab* 93:4774–4779.
Reece EA, Leguizamon G, Wiznitzer A: Gestational diabetes: the need for common ground, *Lancet* 373:1789–1797, 2009.
Ringholm L, Mathiesen ER, Kelstrup L, Damm P: Managing type 1 diabetes mellitus in pregnancy—from planning to breastfeeding, *Nat Rev Endocrinol* 8:659–667, 2012.
Roland JM, Murphy HR, Northcote-Wright J, Temple RC: The pregnancies of women with type 2 diabetes: poor outcomes but opportunities for improvement, *Diabetes Med* 22:1774–1777, 2005.
Rowan JA, Hague WM, Gao W, et al: Metformin versus insulin for the treatment of gestational diabetes, *N Engl J Med* 358:2003–2015, 2008.
Rowan JA, Rush EC, Obolonkin V, et al: Metformin in gestational diabetes: the offspring follow-up (MiG TOFU), *Diabetes Care* 34:2279–2284, 2011.
Ryan EA: Diagnosing gestational diabetes, *Diabetologia* 54:480–486, 2011.
Sacks DA, Hadden DR, Maresh M, et al: Frequency of gestational diabetes mellitus at collaborating centers based on IADPSG consensus panel—recommended criteria, *Diabetes Care* 35:626–528, 2012.
Schaefer-Graf UM, Graf K, Kulbacka I, et al: Maternal lipid as strong determinants of fetal environment and growth in pregnancies with gestational diabetes mellitus, *Diabetes Care* 31:1858–1863, 2008.
Schaefer-Graf UM, Hartman R, Pawliczak J: Association of breast-feeding and early childhood overweight in children from mothers with gestational diabetes mellitus, *Diabetes Care* 29:1105–1107, 2006.
Seely EW, Ecker J: Chronic hypertension in pregnancy, *N Engl J Med* 365:439–436, 2011.
Temple RC, Aldridge VJ, Murphy HR: Prepregnancy care and pregnancy outcomes in women with type 1 diabetes, *Diabetes Care* 29:1744–1749, 2007.
The HAPO Study Cooperative Research Group: Hyperglycemia and adverse pregnancy outcomes, *N Engl J Med* 358: 1991–2002, 2008.
Xiang AH, Peters RK, Kjos S, et al: Effect of pioglitazone on pancreatic b-cell function and diabetes risk in Hispanic women with prior gestational diabetes, *Diabetes* 55:517–522, 2006.

CHAPTER 6

LIPID DISORDERS

Emily Schroeder and Michael T. McDermott

1. What are the major lipids in the bloodstream?

Cholesterol and triglycerides (TGs) are the major circulating lipids. Cholesterol is used by all cells for the synthesis and repair of membranes and intracellular organelles and by the adrenal glands and gonads as a substrate to synthesize adrenal and gonadal steroid hormones. TGs are an energy source that can be stored as fat in adipose tissue or used as fuel by muscle and other tissues.

2. What are lipoproteins?

Cholesterol and TGs are not water soluble and thus cannot be transported through the circulation as individual molecules. Lipoproteins are large, spherical particles that package these lipids into a core surrounded by a shell of water-soluble proteins and phospholipids. Lipoproteins serve as vehicles that transport cholesterol and TGs from one part of the body to another.

3. What are the major lipoproteins in the bloodstream?

Chylomicrons, very-low-density lipoproteins (VLDLs), low-density lipoproteins (LDLs), and high-density lipoproteins (HDLs) are the major circulating lipoproteins. Their functions are as follows:

Chylomicrons	Transport exogenous TGs from the gut to adipose tissue and muscle
VLDLs	Transport endogenous TGs from the liver to adipose tissue and muscle
LDLs	Transport cholesterol from the liver to peripheral tissues
HDLs	Transport cholesterol from peripheral tissues to the liver

4. What are the apolipoproteins?

Apolipoproteins are located on the surfaces of the lipoproteins. They function as ligands for binding to lipoprotein receptors and as cofactors for metabolic enzymes. Their functions are as follows:

Apolipoprotein A	Ligand for peripheral HDL receptors
Apolipoprotein B	Ligand for peripheral LDL receptors
Apolipoprotein E	Ligand for hepatic receptors for remnant particles
Apolipoprotein C-II	Cofactor for lipoprotein lipase (LPL)

5. Name other enzymes and transport proteins that are important in lipoprotein metabolism.

See Table 6-1 and Figure 6-1.

6. Explain the function and metabolism of TGs.

Food and hepatic synthesis are the major sources of TGs. They are transported by chylomicrons (dietary TGs) and VLDLs (endogenous TGs) to adipose tissue and muscle, where lipoprotein lipase and cofactor apolipoprotein C-II (Apo C-II) break down TGs into fatty acids (FAs) and monoglycerides. FAs enter adipose cells to be stored as fat or muscle cells to be used as fuel. The chylomicron and VLDL remnant particles return to the liver, where hepatic lipase converts VLDL remnants into LDL.

7. Describe the function and metabolism of LDL.

LDL transports cholesterol from the liver to peripheral tissues, where surface apolipoprotein B-100 binds to cellular LDL receptors (LDLRs). LDLR clustering in clathrin-coated pits on the cell membrane,

TABLE 6-1. ENZYMES AND TRANSPORT PROTEINS IMPORTANT IN LIPOPROTEIN METABOLISM

ENZYME/TRANSPORT PROTEIN	FUNCTION
Hydroxy-3-methyl-glutaryl-coenzyme A reductase	The rate-limiting enzyme in hepatic cholesterol synthesis
Lipoprotein lipase	Removes TGs from chylomicrons and VLDLs in adipose tissue, leaving remnant particles
Hepatic lipase	Removes additional TGs from remnant particles in the liver, converting them into LDLs
Lecithin cholesterol acyl transferase	Esterifies cholesterol molecules on the surface of HDLs, drawing them into the HDL core
Cholesterol ester transfer protein	Shuttles esterified cholesterol back and forth between HDLs and LDLs

HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride; VLDL, very-low-density lipoprotein.

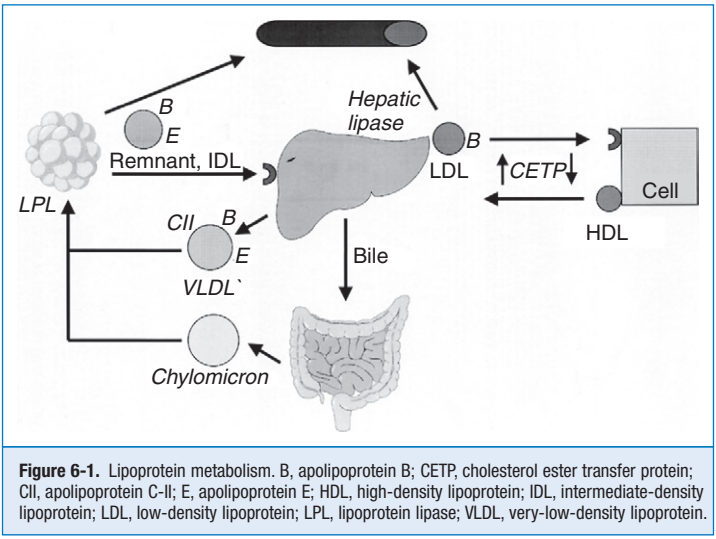

Figure 6-1. Lipoprotein metabolism. B, apolipoprotein B; CETP, cholesterol ester transfer protein; CII, apolipoprotein C-II; E, apolipoprotein E; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LPL, lipoprotein lipase; VLDL, very-low-density lipoprotein.

promoted by LDLR adaptor protein-1 (LDLRAP1), is necessary for efficient LDL uptake. After LDL is internalized, it is degraded to free cholesterol (FC) for intracellular use. Excess LDL is cleared from the circulation by scavenger macrophages.

8. What is the function of HDL?

HDL removes excess cholesterol from cells by two mechanisms. Nascent pre-βHDL is made in the liver and intestine. Surface Apo A1 on pre-βHDL acquires FC through the adenosine triphosphate (ATP)–binding cassette (ABC) transporter-A1 (ABCA1) on arterial wall macrophages. Plasma lecithin cholesterol acyl transferase (LCAT) then esterifies the FC to cholesterol ester (CE). In addition, HDL accepts additional FC from arterial macrophages through the ABCG1 transporter and the scavenger receptor, class B, type 1 (SR-B1) receptor. Cholesterol ester transfer protein (CETP) transfers some CE back to LDL particles, and the mature HDL transports the remaining CE to the liver, where transfer occurs through hepatic SR-B1 receptors. In addition to performing reverse cholesterol transport, HDL reduces LDL oxidation, inhibits vascular inflammation, and improves endothelial function. All of these functions make HDL a potent antiatherogenic lipoprotein.

9. Describe the pathogenesis of the atherosclerotic plaque and arterial thrombosis.

LDL can be modified by oxidation. Scavenger macrophages located beneath the intimal surface of arteries engulf oxidized LDL, becoming lipid-laden foam cells, which secrete growth factors that stimulate smooth muscle cell proliferation. These developing plaques also secrete cytokines that attract inflammatory cells, which secrete proteolytic enzymes that erode the fibromuscular plaque cap, making it prone to rupture. When rupture occurs, platelets aggregate and release chemicals that promote vasoconstriction and initiate thrombus formation, which may ultimately occlude the artery.

10. Are elevated serum TG values harmful?

Increased serum TG levels are associated with atherosclerosis and increased coronary disease. The American Heart Association states that triglycerides are not directly atherogenic but represent an important biomarker of cardiovascular risk because of their association with an atherogenic lipid profile (low HDL cholesterol levels and small, dense LDL particles), as well as obesity, insulin resistance, and the metabolic syndrome. It has not yet been shown that decreasing TG levels will reduce coronary disease risk. TG values greater than 1000 mg/dL significantly increase the risk of acute pancreatitis.

11. What is metabolic syndrome?

Metabolic syndrome (MS) is a condition that is diagnosed when a patient has any three of the following findings: elevated fasting blood glucose ($\geq$ 110 mg/dL), high TGs ($\geq$ 150 mg/dL), low HDL ($<$ 40 mg/dL for men, $<$ 50 mg/dL for women), hypertension ($\geq$ 130 mm Hg systolic/85 mm Hg diastolic), and abdominal obesity (waist $>$ 40 inches in men, $>$ 35 inches in women). The common thread among the disorders that constitute MS appears to be insulin resistance. MS carries a high risk for atherosclerotic vascular disease.

12. What is lipoprotein(a) [Lp(a)]?

Lipoprotein(a) [Lp(a)] has approximately 85% amino-acid sequence homology with plasminogen. When an Lp(a) molecule attaches to apoprotein B on the surface of an LDL particle, the new particle is referred to as Lp(a). Excessive Lp(a) promotes atherosclerosis, possibly because it is easily oxidized and engulfed by macrophages, because it inhibits thrombolysis, or both.

13. What are the primary dyslipidemias?

Primary dyslipidemias are inherited disorders of lipoprotein metabolism. The major primary dyslipidemias and their lipid phenotypes are as follows:

PRIMARY DYSLIPIDEMIA	PHENOTYPE
Familial hypercholesterolemia (FH)	↑↑Cholesterol
Polygenic hypercholesterolemia	↑Cholesterol
Familial combined hyperlipidemia (FCH)	↑Cholesterol and ↑TGs
Familial dysbetalipoproteinemia (FDL)	↑Cholesterol and ↑TGs
Familial hypertriglyceridemia (FHT)	↑TGs
Familial hyperchylomicronemia (FHC)	↑↑TGs

↑, elevated; ↑↑, extremely elevated.

14. What is familial hypercholesterolemia?

FH is an inherited disease characterized by extreme elevations of serum cholesterol but normal serum TG levels. The disorder has a population frequency of 1:500 for heterozygotes, who generally have serum cholesterol levels of 300 to 800 mg/dL, and 1:1,000,000 for homozygotes, who have serum cholesterol levels of 600 to 1000 mg/dL. Most patients have genetic mutations resulting in deficient or dysfunctional LDL receptors (LDLRs). Other less common monogenic hypercholesterolemic disorders include apoprotein B mutations that produce a defective apo B that cannot bind to LDLR, proprotein convertase subtilisin–like kexin type 9 (PCSK9) mutations that cause accelerated LDLR degradation, LDLR adaptor protein-1

(LDLRAP1) mutations that prevent normal clustering of LDLR in cell surface clathrin-coated pits, and ATP-binding cassette G5 or G8 (ABCG5/8) mutations that cause abnormal cellular transport of cholesterol and plant sterols (sitosterolemia). These disorders are characterized by premature coronary artery disease (CAD), often before age 20 in homozygous FH, and tendon xanthomas.

15. What is familial combined hyperlipidemia?

FCH is an inherited disorder characterized by variable elevations of both serum cholesterol and TG. Affected patients have excessive hepatic apolipoprotein B synthesis, with increased numbers of apolipoprotein B–containing VLDL and LDL particles. The genetic basis for the disorder has not yet been determined. These patients are prone to development of premature CAD.

16. What is familial dysbetalipoproteinemia?

Familial dysbetalipoproteinemia (FDL), also known as broad beta disease, is an inherited condition characterized by significant and relatively balanced elevations of both serum cholesterol and TGs. This disorder results from an abnormal apolipoprotein E phenotype (E2/E2), which binds poorly to hepatic receptors, resulting in impaired clearance of circulating VLDL remnants by the liver. Affected patients often have premature CAD. Planar xanthomas in the creases of the palms and soles of the feet are a characteristic finding in patients with FDL.

17. What is polygenic hypercholesterolemia?

Polygenic hypercholesterolemia, which is characterized by mild to moderate elevations of serum cholesterol alone, is the most common type of inherited hypercholesterolemia. This condition generally occurs when one or more mild defects of cholesterol metabolism combine to elevate the serum cholesterol value. Affected patients have an increased risk of CAD.

18. What are familial hypertriglyceridemia and familial hyperchylomicronemia?

Familial hypertriglyceridemia (FHT) is an inherited condition featuring moderate to severe elevations of serum TG levels with normal serum cholesterol levels. Familial hyperchylomicronemia (FHC) is characterized by extremely high serum TG and chylomicron levels. The genetic basis for FHT is unclear, but it may be polygenic or caused by milder forms of the mutations that cause FHC. FHC is due to inactivating mutations in the gene for LPL or Apo CII and mutations of the apolipoprotein AV (APOAV) gene. Severe hypertriglyceridemia with chylomicronemia may predispose to the development of eruptive xanthomas, lipemia retinalis, hepatosplenomegaly, and acute pancreatitis.

19. How do you distinguish between familial combined hyperlipidemia and familial dysbetalipoproteinemia?

Because FCH and FDL are characterized by combined elevations of both cholesterol and TGs, additional tests may be necessary to make the distinction. Patients with FCH have increased serum apolipoprotein B levels, whereas patients with FDL have an E2/E2 apolipoprotein E phenotype and a broad beta-band on lipoprotein electrophoresis. Family studies are also helpful.

20. What causes familial low HDL?

Familial hypoalphalipoproteinemia (familial low HDL), characterized by extremely low serum HDL levels and premature CAD, is caused by inactivating mutations in the genes that encode apolipoprotein A1 (APOA1), ABCA1, or lecithin cholesterol acyl transferase.

21. Name the secondary dyslipidemias.

The secondary dyslipidemias are serum lipid elevations that result from systemic diseases such as diabetes mellitus, hypothyroidism, nephrotic syndrome, renal disease, obstructive liver disease, dysproteinemias, and lipodystrophies. Lipids also may be increased by medications, such as beta-blockers, thiazide diuretics, estrogens, progestins, androgens, retinoids, corticosteroids, cyclosporin A, antipsychotics, and protease inhibitors. These disorders usually improve when the primary condition is treated or the offending drug is discontinued.

KEY POINTS 1: CAUSES OF LIPID DISORDERS

1. Elevation of low-density lipoprotein (LDL) cholesterol is a major risk factor for coronary artery disease (CAD).
2. A low level of high-density lipoprotein (HDL) cholesterol is also a significant risk factor for CAD.
3. High levels of serum triglycerides (TGs) are associated with increased CAD, but it is unclear whether lowering TG levels decreases CAD risk.
4. Serum TG levels greater than 1000 mg/dL significantly increase the risk of acute pancreatitis.
5. Inflammation within the atherosclerotic plaque plays a major role in plaque rupture and the occurrence of acute coronary events.

22. What is the cause of severe elevations of serum TGs?

TG levels above 1000 mg/dL pose a very high risk for the development of acute pancreatitis, a condition with a mortality rate of up to 10%. Most patients with such severe TG elevations have a primary TG disorder, such as FHT, FCH, or FDL, combined with a secondary disorder, most commonly poorly controlled diabetes mellitus, alcohol abuse, estrogen use, or the use of medications for the treatment of human immunodeficiency virus (HIV).

23. Summarize the revised (2004) Coronary Heart Disease (CHD) risk stratification from the Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (NCEP).

High Risk

1. Known CHD.
2. CHD risk equivalents:
   a. Peripheral arterial disease
   b. Cerebral arterial disease
   c. Abdominal aortic aneurysm
   d. Diabetes mellitus
   e. 2+ risk factors with CHD 10-year risk $>$ 20%*

Moderately High Risk

2+ risk factors with CHD 10-year risk = 10%-20%*

Moderate Risk

2+ risk factors with CHD 10-year risk $<$ 10%*

Low Risk

0-1 risk factor with CHD 10-year risk $<$ 10%*

*Risk factors: smoking, hypertension (blood pressure $\geq$ 140/90 mm Hg or on antihypertensive medication), HDL $<$ 40 mg/dL, age $\geq$ 45 years (men) or $\geq$ 55 years (women), CHD in first-degree relative (diagnosed at $<$ 55 years of age [men] or $<$ 65 years [women]).
CHD 10-year risk calculation: http://www.nhlbi.nih.gov/guidelines/cholesterol

24. What are the revised (2004) LDL cholesterol treatment goals from the ATP III?

PATIENT RISK	LDL CHOLESTEROL GOAL (MG/DL)
High risk	$<$ 100 (optional $<$ 70)
Moderately high risk	$<$ 130 (optional $<$ 100)
Moderate risk	$<$ 130
Low risk	$<$ 160

25. What is therapeutic lifestyle change?

Therapeutic lifestyle change (TLC) should be encouraged for individuals with LDL cholesterol above their risk-stratified goal. Medications should be added. ATP III recommends therapeutic lifestyle change (TLC) for individuals with LDL cholesterol above their risk stratified goal. Medications can be added, as needed, but the TLC should continue. The components of TLC as recommended by ATP III are:

COMPONENT	GOALS
Total fat	25%-35% of total calories
Saturated fat	< 7% of total calories
Polyunsaturated fat	< 10% of total calories
Monounsaturated fat	< 20% of total calories
Carbohydrate	50%-60% of total calories
Protein	Approximately 15% of total calories
Total calories	Adjust to achieve and maintain ideal body weight
Dietary fiber	20-30 g/day
Physical activity	Expend at least 200 kcal/day

26. What medications most effectively improve dyslipidemia?

See Table 6-2.

27. How do the currently available statin medications differ?

The statins inhibit 3-hydroxy-3-methyl-glutaryl-CoA reductase, the rate-limiting enzyme in cholesterol synthesis. This leads to a decrease in cholesterol synthesis and an increase in LDL receptor–mediated removal of LDL. Some statins are naturally occurring compounds (lovastatin, pravastatin) and others are synthetic. Some are more hydrophilic (pravastatin, rosuvastatin), whereas the others are more lipophilic. The main differences of clinical interest, however, are their LDL-lowering potencies. The most commonly used statins, in order of relative LDL-lowering potencies, are fluvastatin < pravastatin < lovastatin < simvastatin < atorvastatin < rosuvastatin < pitavastatin. The initial statin dose produces the greatest LDL cholesterol reduction. Each subsequent doubling of the statin dose, on average, results only in an additional 6% decrease in serum LDL cholesterol level.

28. How should the statin-intolerant patient be approached?

Myopathy occurs in approximately 10% of patients treated with statins. Myopathy typically manifests as myalgias, with or without elevations in creatine kinase (CK). For CK elevations greater than five times the upper limit of normal or if the patient has moderate to severe symptoms, the statin should be stopped. Once the patient is asymptomatic and the CK level is reduced, reasonable approaches include a trial of low-dose fluvastatin or pravastatin, alternate-daily or weekly dosage of a more potent statin such as rosuvastatin or pitavastatin, or combination of a low-dose statin with a non-statin cholesterol

TABLE 6-2. MEDICATIONS THAT MOST EFFECTIVELY IMPROVE DYSLIPIDEMIA

	EFFECT ON LDL (%)	EFFECT ON TG (%)	EFFECT ON HDL (%)
Statins	↓20-60	↓10-30	↑5-15
Ezetimibe	↓15-25	None	↓10
Bile acid sequestrants	↓5-30	None or slight increase	None or slight increase
Niacin	↓10-20	↓10-30	↑10-40
Fibrates	↓5-20	↓30-50	↑10-20
Fish oil	variable	↓20-50	↑5-10

↑, increases (by); ↓, decreases (by); HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride; VLDL, very-low-density lipoprotein.

agent (ezetimibe or bile acid sequestrant). Over-the-counter preparations containing natural statin-like agents, such as red yeast rice, can also be tried, although they undergo limited quality control and have low efficacy. In patients with mild symptoms and CK elevations less than five times the upper limit of normal, the statin may be continued. If symptoms worsen, the CK level should be rechecked.

29. How effective and safe are combinations of lipid-lowering medications?

For severe cholesterol elevations, the addition of ezetimibe, niacin, or a bile acid resin to a statin often reduces serum LDL cholesterol by an additional 20%, compared with only 6% when the statin dose is doubled. These combinations are generally safe to use, but side effects can be additive. For elevations of both cholesterol and TGs, adding a fibrate to a statin can lower the serum TG level up to 50%. However, the risk of myositis and frank rhabdomyolysis increases. Fenofibrate appears to be significantly safer than gemfibrozil when combination with a statin is considered necessary.

30. Does aggressive cholesterol-lowering therapy effectively and safely reduce the risk of coronary artery disease?

Clinical trials have repeatedly demonstrated the efficacy of aggressive cholesterol-lowering with statins in reducing myocardial infarction, strokes, and cardiovascular mortality in patients with a previous history of CAD (secondary prevention—4S (Scandinavian Simvastatin Survival Study), CARE (Cholesterol and Recurrent Events), LIPID (Long-term Intervention with Pravastatin in Ischaemic Disease), HPS (Heart Protection Study), TNT (Treating to New Targets), PROVE IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy), AVERT (Atorvastatin Versus Revascularization Treatment), and ALLIANCE (Aggressive Lipid Lowering to Alleviate New Cardiovascular Endpoints). A meta-analysis from the Cholesterol Treatment Trialists' Collaboration suggests that each 1-mmol/L reduction in LDL cholesterol results in an approximately 20% reduction in the annual rate of cardiovascular disease.

The role of statins in the setting of primary prevention is less clear. Some trials have demonstrated a benefit—WOSCOPS (West of Scotland Coronary Prevention Study), AFCAPS (Air Force Coronary Atherosclerosis Prevention Study), HPS (Heart Protection Study), ASCOT-LLA, CARDS (Collaborative Atorvastatin Diabetes Study), and JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin). A Cochrane meta-analysis showed that statins can reduce all-cause mortality, cardiovascular mortality, and cardiovascular events. However, another meta-analysis did not find a reduction in all-cause mortality, and the cost effectiveness of statins and effects on quality of life are unclear.

The major safety concerns about statin therapy are hepatotoxicity and myopathy. Both of these problems were relatively rare in the clinical trials but occur more commonly in clinical practice in patients who require higher doses or take them in combination with other medications that may interfere with statin metabolism. In particular, high-dose simvastatin therapy has been associated with an increased risk of myopathy.

31. What is the appropriate role for niacin?

Niacin, which decreases VLDL production, is often used in combination with statins in order to further decrease LDL cholesterol levels, decrease TGs, and increase HDL cholesterol levels. Niacin also decreases lipoprotein(a) [Lp(a)] levels. However, a meta-analysis found no effect of niacin on total mortality or cardiac mortality. The ARBITER 6-HALTS (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6: HDL and LDL Treatment Strategies in Atherosclerosis) study found that among patients taking statins, niacin was superior to ezetimibe on the surrogate end point of regression of carotid intima-media thickness. The later AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL Cholesterol/High Triglyceride and Impact on Global Health Outcomes) study found no benefit to adding niacin to statin therapy. Thus the appropriate role for niacin in the treatment of dyslipidemia is currently unclear.

32. What is the appropriate role for ezetimibe?

Ezetimibe, which inhibits intestinal cholesterol absorption, is commonly used in combination with statins and effectively lowers LDL cholesterol levels. However, ezetimibe in combination with statins has not been conclusively shown to decrease mortality or cardiovascular events. The ENHANCE

(Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression) study of individuals with familial hypercholesterolemia did not show any improvement in their surrogate end point of carotid intima-media thickness. The IMPROVE-IT (The Improved Reduction of Outcomes: Vytorin Efficacy International Trial) study, which is currently comparing simvastatin with and without ezetimibe, should provide additional information about the appropriate role for ezetimibe.

33. What is the appropriate role for fibrates?

Fibrates, which decrease VLDL production, are the most effective TG-lowering agents. They also increase HDL cholesterol and modestly decrease LDL cholesterol. A meta-analysis showed that fibrates decreased cardiovascular events but had no effect on stroke, cardiac mortality, or total mortality. The FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) study of fenofibrate in patients with type 2 diabetes reported a nonsignificant 11% reduction in cardiovascular events. The ACCORD (Action to Control Cardiovascular Risk in Diabetes) Lipid Trial in patients with type 2 diabetes did not find any reduction in cardiovascular end points when fenofibrate was added to simvastatin. Given the fact that elevated TGs have not yet been shown to be causally related to cardiovascular risk, the appropriate role for fibrates is still somewhat unclear.

34. What are CETP inhibitors?

CETP inhibitors interfere with the protein that transfers esterified cholesterol between HDL and LDL, resulting in an increase in HDL of more than 50%. Several CETP inhibitors are currently under development and in clinical trials. Unfortunately, to date these trials have been unable to show an increase in cardiovascular events and mortality, and a trial of torcetrapib was terminated because of an increase in coronary events and mortality in treated patients (see Cannon, 2011, in Bibliography).

KEY POINTS 2: TREATMENT OF LIPID DISORDERS

1. Statins are the most effective low-density lipoprotein (LDL) cholesterol–lowering agents and have the strongest evidence base for reducing cardiovascular events.
2. Additional LDL reduction can be achieved by adding ezetimibe, niacin, and bile acid resins.
3. Fibrates are the most effective triglyceride (TG)–lowering agents, but additional reductions can be achieved by adding niacin, fish oils, and high-dose statins.
4. The Adult Treatment Panel III (ATP III) recommends LDL goals of less than 100 mg/dL for patients with coronary heart disease (CHD) or CHD equivalents, less than 130 mg/dL for patients with two or more CHD risk factors, and less than 160 mg/dL for patients with no or one CHD risk factor. An optional LDL goal of less than 70 mg/dL may be more appropriate for the highest risk patients.
5. The ATP III also recommends a non–high-density lipoprotein cholesterol goal of 30 mg/dL above the LDL cholesterol goal in the patient whose serum TG level is greater than 200 mg/dL after the LDL goal has been achieved.

35. Is measurement of inflammatory markers a useful tool in CAD risk assessment?

Inflammation within an atherosclerotic plaque makes the plaque more likely to rupture, precipitating an acute ischemic event. Highly sensitive C-reactive protein (hsCRP), a nonspecific marker of inflammation, appears to predict CAD risk, as do LDL cholesterol levels. The JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) trial showed a benefit to treatment with rosuvastatin in individuals with LDL cholesterol levels lower than 130 mg/dL and hsCRP levels of 2.0 mg/L or less. Thus information on LDL cholesterol and hsCRP together can be useful to providers making decisions about which patients to treat more aggressively but need not be performed routinely in all patients.

An indirect measure of inflammation is lipoprotein-associated phospholipase A_2 (Lp-PLA_2), an enzyme produced by inflammatory cells and liver cells that circulates in the plasma primarily bound

to LDL particles. It hydrolyzes oxidized phospholipids on LDL particles, producing two inflammatory mediators, lysophosphatidylcholine and oxidized fatty acids, which have been linked to atherosclerotic plaque formation. Measurement of Lp-PLA_2 may be considered for selected patients at increased cardiovascular risk as part of the initial clinical assessment. Studies of daraplabid, an Lp-PLA_2 inhibitor, are ongoing, but there is no current evidence that lowering Lp-PLA_2 will reduce cardiovascular risk.

36. Should we be using measurements of lipoprotein size and number?

Lipoprotein size and number can now be assessed by a variety of commercially available techniques. These analyses provide additional information about the atherogenicity of a lipoprotein profile. The cost-effectiveness of obtaining this additional information has not yet been demonstrated. Decisions regarding the need for treatment and the choice of agents can be made on the basis of the clinical risk factor profile and standard lipid profile in the majority of patients. Therefore these additional tests should be limited to situations in which they are likely to have a clear impact on the choice and aggressiveness of therapy.

37. How should the patient with severe hypertriglyceridemia be managed?

Serum TG levels above 1000 mg/dL must be lowered quickly because of the high risk of precipitating acute pancreatitis. Medications alone are not effective when TG levels are this high. Patients must immediately be started on a very-low-fat (less than 5% fat) diet until the TG level is less than 1000 mg/dL. Such a diet lowers serum TGs approximately 20% each day. Contributing factors, most commonly uncontrolled diabetes mellitus, alcohol abuse, estrogen use, and medications for treatment of human immunodeficiency virus, must simultaneously be addressed. After serum TG levels are less than 1000 mg/dL, the most effective medications to reduce serum TGs further are the fibrates. If these medications do not lower serum TG sufficiently, niacin, fish oils, or a statin may be added to the regimen.

BIBLIOGRAPHY

ACCORD Study Group: Effects of combination lipid therapy in type 2 diabetes mellitus, *N Engl J Med* 362:1563–1574, 2010.

AIM-HIGH Investigators: Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy, *N Engl J Med* 365:2255–2267, 2011.

Cannon CP: High-density lipoprotein cholesterol as the Holy Grail, *JAMA* 306:2153–2155, 2011.

Cannon CP, Giugliano RP, Blazing MA, et al: Rationale and design of IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial): comparison of ezetimibe/simvastatin versus simvastatin monotherapy on cardiovascular outcomes in patients with acute coronary syndromes, *Am Heart J* 156:826–832, 2008.

Cholesterol Treatment Trialists' (CTT) Collaboration: Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials, *Lancet* 376:1670–1681, 2010.

Colhoun HM, Betteridge DJ, Durrington PN, et al: Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial, *Lancet* 364:685–696, 2004.

Davidson MH, Ballantyne C, Jacobson TA, et al: Clinical utility of inflammatory markers and advanced lipoprotein testing: advice from an expert panel of lipid specialists, *J Clin Lipidology* 5:338–367, 2011.

Downs JR, Clearfield M, Weis S, et al: Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study, *JAMA* 279:1615–1622, 1995.

Eckel RH: Approach to the patient who is intolerant of statin therapy, *J Clin Endocrinol Metab* 95:2015–2022, 2010.

Emerging Risk Factors Collaboration: Lipid-related markers and cardiovascular disease prediction, *JAMA* 307:2499–2506, 2012.

Executive Summary of the Third Report of the National Education Program (NCEP): 2001 expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III), *JAMA* 285:2486–2497.

Ford I, Murray H, Packard CJ, et al: Long-term follow-up of the West of Scotland Coronary Prevention Study, *N Engl J Med* 357:1477–1486, 2007.

Greving JP, Visseren FLJ, De Wit GA, et al: Statin treatment for primary prevention of vascular disease: whom to treat? Cost-effectiveness analysis, *BMJ* 342:1672, 2011.

Grundy SM, Cleeman JI, Merz CNB, et al: Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines, *Circulation* 110:227–239, 2004.

Heart Protection Collaborative Group: MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomized placebo-controlled trial, *Lancet* 360:7–22, 2002.

Heart Protection Study Collaborative Group: C-reactive protein concentration and the vascular benefits of statin therapy: an analysis of 20,536 patients in the Heart Protection Study, *Lancet* 377:469–476, 2011.

Hou R, Goldberg AC: Lowering low-density lipoprotein cholesterol: statins, ezetimibe, bile acid sequestrants, and combinations: comparative efficacy and safety, *Endocrinol Metab Clin N Am* 38:79–97, 2009.

Jun M, Foote C, Lv J, et al: Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis, *Lancet* 375:1875–1884, 2010.

Kastelein JJ, Akdim F, Stroes ESG, et al: Simvastatin with or without ezetimibe in familial hypercholesterolemia. *N Engl J Med* 358:1431–1443, 2008.

Keech A, Simes RJ, Barter P, et al: Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD Study): randomised controlled trial, *Lancet* 366:1849–1861, 2005.

Koren MJ, Hunninghake DB, for the ALLIANCE Investigators: Clinical outcomes in managed care patients with coronary heart disease treated aggressively in lipid lowering disease management clinics, *J Am Coll Cardiol* 44:1772–1779, 2004.

LaRosa J, Grundy SM, Waters DD, et al: Intensive lipid lowering with atorvastatin in patients with stable coronary disease, *N Engl J Med* 352:1425–1435, 2005.

Lipid Study Group: Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels, *N Engl J Med* 339:1349–1357, 1998.

Miller M, Stone NJ, Ballantyne C, et al: Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association, *Circulation* 123:2292–2333, 2011.

Pitt B, Waters D, Brown WV, et al: Aggressive lipid-lowering therapy compared with angioplasty in stable coronary artery disease, *N Engl J Med* 341:70–76, 1999.

Ray KK, Seshasai SRK, Erqou S, et al: Statins and all-cause mortality in high-risk primary prevention: a meta-analysis of 11 randomized controlled trials, *Arch Intern Med* 170:1024–1031, 2010.

Ridker PM, Danielson E, Fonseca FAH, et al: Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein, *N Engl J Med* 359:2195–2207, 2008.

Sacks FM, Pfeffer MA, Moye LA, et al: The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels, *N Engl J Med* 335:1001–1009, 1996.

Scandinavian Simvastatin Survival Study Group: Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S), *Lancet* 344:1383–1389, 1994.

Semenkovich CF, Goldberg AC, Goldberg IJ: Disorders of lipid metabolism. In Melmed S, Polonsky KS, Larsen PR, editors: Williams Textbook of Endocrinology, 12th edition. Philadelphia, 2011, Elsevier Saunders.

Sever PS, Dahlof B, Poulter NR, et al: Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower than average cholesterol concentrations, in the Anglo-22 Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): a multicenter randomized controlled trial, *Lancet* 361:1149–1158, 2003.

Shepherd J, Cobbe SM, Ford I, et al: Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia, *N Engl J Med* 333:1301–1307, 1995.

Studer M, Briel M, Leimenstoll B, et al: Effect of different antilipidemic agents and diets on mortality: a systematic review, *Arch Inter Med* 165:725–730, 2005.

Study of Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Group: Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12,064 survivors of myocardial infarction: a double-blind randomized trial, *Lancet* 376:1658–1669, 2010.

Taylor AJ, Villines TC, Stanek EJ, et al: Extended-release niacin or ezetimibe and carotid intima-media thickness, *N Engl J Med* 361:2113–2122, 2009.

Taylor F, Ward K, Moore THM, et al: Statins for the primary prevention of cardiovascular disease, *Cochrane Database of Systematic Reviews* 1:CD004816, 2011.

Third Report of the National Education Program (NCEP): Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report, *Circulation* 106:3143–3421, 2002.

CHAPTER 7

OBESITY

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1. Define the terms "overweight" and "obesity."

Overweight and *obesity* are defined as degrees of excess weight that are associated with increases in morbidity and mortality. In 1998, the National Heart, Lung, and Blood Institute of the National Institutes of Health (NIH) published guidelines on the diagnosis and treatment of overweight and obesity. The expert panel advocated using specific body mass index (BMI) cutoff points to diagnose both conditions. The BMI is calculated by dividing a person's weight in kilograms by his or her height in meters squared. A BMI (kg/m^2) of 25 or less is defined as normal; 25 to 29.9, as overweight; 30 to 34.9, as mild obesity; 35 to 39.9, as moderate obesity; and greater than 40, as severe or morbid obesity.

2. Does fat distribution affect the assessment of risk in an overweight or obese patient?

Yes. Accumulation of excessive adipose tissue in a central—or upper—body distribution (android or male pattern) is associated with a greater risk of adverse metabolic health consequences than lower-body obesity (gynoid or female pattern). Abdominal adiposity is an independent predictor of risk for diabetes, hypertension, dyslipidemia, and coronary artery disease. The absolute amount of intraabdominal or visceral fat is most closely linked to these adverse health risks.

3. Explain the role of waist circumference in risk stratification.

For this reason, the waist circumference is the favored measure for risk stratification on the basis of fat distribution. Men with a waist circumference greater than 40 inches ($>$ 102 cm) and women whose waist circumference is greater than 35 inches ($>$ 88 cm) have increased risk. Waist circumference is most useful for risk stratification in people with a BMI between 25 and 30 kg/m^2. In this intermediate-risk group, those with increased waist circumference should undertake greater efforts directed at preventing further weight gain, whereas those with a smaller waist circumference can be reassured that their weight does not pose major health hazards.

4. How is waist circumference measured?

Waist circumference should be measured with a tape measure parallel to the floor at the level of the iliac crest at the end of a relaxed expiration.

5. What adverse health consequences are associated with obesity?

Obesity is clearly associated with diabetes, hypertension, hyperlipidemia, coronary artery disease, degenerative arthritis, gallbladder disease, and cancer of the endometrium, breast, prostate, and colon. It has also been associated with urinary incontinence, gastroesophageal reflux, infertility, sleep apnea, and congestive heart failure. The incidence of these conditions rises steadily as body weight increases (Figs. 7-1 and 7-2). Risks increase with even modest weight gain. Health risks are magnified with advancing age and a positive family history of obesity-related diseases.

6. Summarize the economic consequences of obesity.

The total direct and indirect health care costs associated with obesity were estimated to be $147 billion in 2008. In 2006, annual medical spending was $1429 (42%) greater for obese people than for normal-weight people. Almost 90% of the increase in costs attributable to the care of obese people is due to the rise in the prevalence of obesity. In addition, the NIH estimated that Americans pay $44 billion for weight loss products and services.

Figure 7-1. Body mass index and the risk of hypertension. *(From Expert Group on Weight Standards: Canadian Guidelines for Healthy Weights, Canada: Ottawa, ON, 1988, Minister of Supply and Services, p 69.)*

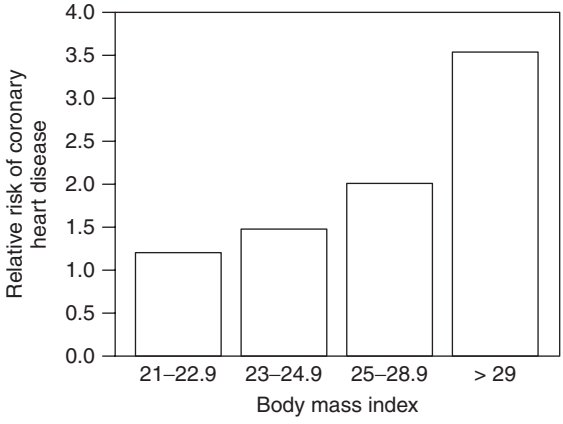


Figure 7-2. Body mass index and the risk of coronary disease.

7. What are the psychological complications of obesity?

Situational depression and anxiety related to obesity are common. The obese person may suffer from discrimination, which contributes further to difficulty with poor self-image and social isolation. It may be difficult in some patients to determine whether depression is accelerating weight gain or whether weight gain is exacerbating an underlying depression, but treating both conditions may improve quality of life. Work by the Rudd Center and other groups has highlighted the bias that obese patients experience even from doctors who care for them. It is important for treating physicians to at least be aware of a tendency to blame obese patients for their condition and to compensate for this common bias as best they can if present.

8. How common is obesity?

Obesity has reached epidemic proportions in the United States. The National Health and Nutrition Examination Survey (NHANES) conducted by the federal government uses direct measures of height and

weight in a representative sample of Americans to estimate the prevalence of obesity. The prevalence of obesity increased significantly during the 1980s and 1990s but has now leveled off. The latest data from the NHANES showed that in 2009 to 2010, 35.7% of adults in the United States had a BMI greater than 30 kg/m^2. This rate of obesity has not changed significantly from those in 2003 through 2008. The prevalence of overweight (BMI $>$ 25 kg/m^2) was found to be 68.8%. The prevalence of severe obesity (BMI $>$ 40 kg/m^2) was 6.3% in the latest dataset. In children and adolescents aged 2 to 19 years, the prevalence of obesity was found to be 16.9%, not changed from 2007 to 2008 prevalences.

9. What caused the dramatic rise in the prevalence of obesity in the 1980s and 1990s?

The prevalence of obesity indeed rose over this short period; it seems that the primary culprit is a changing environment that promotes increased food intake and reduced physical activity. This statement should not be taken to mean, however, that body weight is not subject to physiologic regulation. The control of body weight is complex, with multiple interrelated systems controlling caloric intake, macronutrient content of the diet, energy expenditure, and fuel metabolism.

10. Describe the current model for obesity as a chronic disease.

Obesity is now viewed as a chronic, often progressive metabolic disease much like diabetes or hypertension. This view requires a conceptual shift from the previous widely held belief that obesity is simply a cosmetic or behavioral problem. Development of obesity requires a period of positive energy balance during which energy intake exceeds energy expenditure. Maintaining energy balance is one of the most important survival mechanisms of any organism. A sustained negative imbalance between energy intake and expenditure is potentially life-threatening within a relatively short time. To maintain energy balance, the organism must assess energy stores within the body; assess the nutrient content of the diet; determine whether the body is in negative energy or nutrient balance; and adjust hormone levels, energy expenditure, nutrient movement, and ingestive behavior in response to these assessments.

11. Do abnormal genes cause obesity?

Obesity is clearly more common in people who have family members who are also obese. Genetics appears to be responsible for 30% to 60% of the variance in weight in most populations. The problem of human obesity, however, involves an interaction between genetic susceptibility and environmental triggers. The genes that we possess to regulate body weight evolved somewhere between 200,000 and 1 million years ago, at which time the environmental factors controlling nutrient acquisition and habitual physical activity were dramatically different. A number of single gene defects have been identified that cause severe childhood obesity. These include mutations in the leptin gene, leptin receptor, the MC4R gene, brain-derived neurotrophic factor (BDNF), and SIM-1. However, these mutations are quite rare, explaining less than 8% of severe early-onset obesity. Genome-wide association studies have identified more than 20 genes that are associated with common forms of human obesity. The most common of these is the FTO gene. The allele of this gene that is associated with weight gain is present in 15% of humans. However, the weight gain associated with this high-risk allele is only 3 kg. Thus, common human obesity appears to be the result of alterations in a large number of genes, each having relatively small effects (polygenic).

12. What is leptin?

Leptin is a hormone secreted exclusively by adipose tissue in direct proportion to fat mass. It was discovered in 1994. Leptin acts through receptors located on neurons in the arcuate nucleus of the hypothalamus and other brain regions to regulate both food intake and energy expenditure. Changes in leptin levels in the hypothalamus alter the production of a number of neuropeptides, including pro-opiomelanocortin (POMC) and Agouti-related peptide (AGRP).

13. Does leptin deficiency cause human obesity?

There are a handful of cases in which genetic deficiency of either leptin or its receptor has been found to cause severe early-onset obesity. Treating leptin-deficient humans with leptin results in

dramatic weight loss. However, leptin levels are typically higher in obese than in lean humans in proportion to the former's greater fat mass. Studies in which recombinant human leptin was administered to typical obese humans produced minimal weight loss. These findings suggest that common forms of human obesity are associated with leptin resistance, not leptin deficiency.

14. Explain how the melanocortin system is involved in weight regulation.

Alpha-melanocortin (alpha-melanocyte–stimulating hormone [α-MSH]) is one of the hormone products of the POMC gene. This neuropeptide acts in the hypothalamus on melanocortin receptors, particularly the MC4-R subtype, to regulate body weight. By stimulating the MC4-R, α-MSH inhibits food intake, whereas the natural antagonist, Agouti-related peptide (AGRP), which is also made in the hypothalamus, stimulates food intake. MC4-R agonists have been developed. Although these drugs decrease food intake and reduce body weight in obese rodents, they have not been found to be useful as single agents in obese humans. The failure of these drugs and others that work through hypothalamic regulatory pathways to produce significant weight loss in obese humans has raised questions about the role of these systems in common forms of human obesity.

15. What is ghrelin?

Ghrelin is a hormone originally identified as a growth hormone–releasing hormone produced by the stomach and proximal small intestine that appears to regulate appetite. Ghrelin levels rise before meals and promptly drop following food intake. Self-reported hunger mirrors serum ghrelin levels. Twenty-four-hour ghrelin levels rise when people go on an energy-restricted diet and are dramatically reduced after gastric bypass surgery. Ghrelin has been described as a "hunger hormone" and is another possible target for weight loss drugs. The bioactive form of the hormone, acylated ghrelin, has a fatty acid attached to the parent hormone. Drugs that alter the production of acylated ghrelin are also being investigated.

16. Does a decrease in energy expenditure play a role in the development of obesity?

The development of obesity requires an imbalance between caloric intake and caloric expenditure. For fat mass to increase, there must be an imbalance between the amount of fat deposited and the amount of fat oxidized. One possibility is that people become obese because of a reduction in their energy expenditure. Despite the common idea that a "low metabolic rate" predisposes to obesity, there is little evidence that this is true.

17. What are the components of energy expenditure?

- Basal metabolic rate (BMR): The amount of energy needed to maintain body homeostasis by maintaining body temperature, maintaining cardiopulmonary integrity, and maintaining electrolyte stability.
- Thermic effect of food: A relatively small component (5% to 10%) that represents the energy cost associated with the assimilation of a meal.
- Physical activity energy expenditure (PAEE): This is the most variable component. It can account for as little as 10% to 20% of total energy expenditure in people who are sedentary or as much as 60% to 80% of total energy expenditure in training athletes. PAEE increases with planned physical activity or with activities of daily living, such as stair climbing and even fidgeting. The unconscious component of physical activity has been termed non-exercise activity thermogenesis (NEAT) and may be a regulated parameter.

18. Explain the concept of energy balance.

When an individual is weight stable, total daily energy expenditure equals total daily energy intake. Total energy expenditure is linearly related to lean body mass. Studies that have used sophisticated methods for measuring energy expenditure have clearly shown that obese people consume more calories than lean people. The obese person who says that he or she eats only a small amount but is gaining weight may be telling the truth in the short term, but over longer periods, high caloric intakes

are required to maintain the obese state. Although reduced levels of PAEE may predispose to obesity, BMR is not reduced in obese people. The central cause of obesity is the failure to couple energy intake to energy expenditure accurately over time.

19. Are there other factors involved in the increase in the prevalence of obesity?

Over the past 10 years, investigators have identified a range of novel environmental factors that may be related to the increase in obesity seen over the past 40 years. One area that has received a good deal of attention is reduced sleep time. It is clear that on average Americans are sleeping less than they did 50 years ago. Epidemiologic studies have shown that shortened sleep time is associated with obesity, and experimental studies have shown that sleep restriction is associated with insulin resistance, increased appetite, and a change in fat oxidation. Medication use is another factor that may be involved in promoting obesity. Widely used medications that promote weight gain include newer antipsychotic medications, sulfonylureas, insulin, thiazolidinediones, and progesterone-containing birth control medications. Other novel factors that are potentially involved include the aging of the population as well as increases in the number of ethnic minorities in the United States, the use of climate control systems in houses and public buildings (mice housed in thermoneutral environments weigh more than mice housed at lower temperatures), and environmental toxins (some studies suggest that adipose tissue increases in response to environmental toxins in an effort to sequester them).

20. What options are available for treating the obese patient?

Treatment options for overweight or obese patients include diet, exercise, pharmacotherapy, surgery, and combinations of these modalities. The specific modality should be based on the individual's BMI and associated health problems. A more aggressive treatment approach is warranted in those whose BMI is higher and those with weight-related health problems. Behavioral approaches can be advocated for all overweight and obese patients. Pharmacologic treatment should be considered in those whose BMI is greater than 27 kg/m^2 in the presence of medical complications or greater than 30 kg/m^2 in the absence of medical complications. Surgical treatment is currently reserved for those with a BMI greater than 40 kg/m^2 and those with a BMI greater than 35 kg/m^2 and comorbidities. Evidence suggests that bariatric surgery is also helpful for patients with diabetes whose BMI is less than 35 kg/m^2.

21. What is the goal of a weight loss program?

Before discussing the treatment options with a patient, it is important to decide the goal of the treatment program. Many obese patients have unrealistic expectations about the amount of weight that they might lose through a weight loss program. Most would like to achieve ideal body weight and are disappointed if they lose only 5% to 10% of their initial weight. These desires stand in stark contrast to the magnitude of weight loss that has been seen with all treatment modalities short of bariatric surgery. The most effective diet, exercise, or drug treatment programs available result in roughly a 5% to 10% weight loss in most people.

22. Is a 5% to 10% reduction helpful in terms of health improvement?

Loss of 5% to 10% of body weight has been associated with improvements in health-related measures, such as lower blood pressure, reductions in low-density lipoprotein (LDL) cholesterol levels, improved functional capacity, and a markedly lower risk of diabetes. Most experts now believe that a sustained 5% to 10% weight loss (e.g., a weight loss of 11 to 12 lb for someone who initially weighed 220 lb) is a realistic goal with measurable health benefits. Alternatively, prevention of further weight gain may be a reasonable and attainable goal, or the health care provider may simply encourage the patient to focus on eating and activity habits and not on a weight goal at all.

23. How can a patient's readiness to change his or her diet or physical activity be assessed?

Stages of change theory can help the clinician focus counseling activities within the context of a brief office visit. Prochazka has hypothesized six predictable stages through which a person passes before he or she is able to change a long-standing behavior, such as diet, physical activity pattern, or

smoking: precontemplative, contemplative, planning, action, maintenance, and relapse. Identifying the stage that the patient is in and targeting counseling efforts to that stage may improve the effectiveness of the counseling activities.

24. What is "motivational interviewing," and how is it used in counseling an obese patient?

Motivational interviewing is a counseling style that was developed for use with alcoholics. The method is useful for interacting with patients who are ambivalent about changing their diet or physical activity behaviors. The strategies used focus on resolving this ambivalence by having patients explore reasons why they want to change and reasons why they find their current behavior more comfortable. The method grows out of the idea that motivation cannot be created, but that for many patients the motivation is already there, it simply needs to be identified and redirected.

25. Discuss the role of diet in the treatment of the obese patient.

The mainstays of dietary modification in weight loss therapy have been diets low in fat and reduced in calories. Compelling evidence in favor of this approach comes from the Diabetes Prevention Project and other related trials in individuals at high risk for the development of diabetes. Whatever changes the person makes must be sustained to be beneficial. The clinician should assess the current diet with a good nutritional history, which may involve a verbal 24- or 72-hour intake recall. Alternatively, the patient may keep a written 3- to 7-day food diary. Assessing meal pattern is important, because many people skip breakfast and eat lunch erratically. Attention should be paid to how often the person eats out, especially fast food. Many patients are able to identify key foods that are a problem for their weight loss efforts. Small, gradual changes may be more successful than drastic ones.

26. Should patients be encouraged to attend a commercial weight loss program?

Yes. Most people know what they should eat. The problem is that they either do not pay attention to what they eat or do not find a "healthy diet" palatable. The use of commercial programs, such as Weight Watchers, can provide reasonable nutritional counseling along with social support that often cannot be provided in the context of a busy office practice. Many patients are surprised at the cost of these programs, which may be a deterrent to their continued use. However, this kind of program involves no risk and may be cheaper in the long term than pharmacologic treatment. The scientific literature supports the notion that for many people, commercial weight loss programs are a reasonable option.

27. Are meal replacements useful in a weight loss program?

For some people, it is difficult to control calories through self-selected meals. Time may not be available for food preparation, and convenience may override health concerns. For such people, meal replacements—calorie, nutritionally complete meal—are a reasonable option with scientifically proven effectiveness if used as a long-term strategy. In fact, this approach was used in the NIH-funded Look Ahead Trial, and participants who were in the highest quartile of meal replacement use were four times as likely to meet their weight loss goals.

28. What are low-calorie and very-low-calorie diets? When should their use be considered?

A very-low-calorie diet (VLCD) is a nutritionally complete diet of 800 kcal/day that produces rapid weight loss. A low-calorie diet (LCD) contains between 800 and 1000 kcal/day. Commercially available products typically consist of liquid meals that have been supplemented with essential amino acids, essential fatty acids, vitamins, and micronutrients taken four or five times per day. Supplementing the commercial product with fruits and vegetables converts a VLCD to an LCD and may make the diet more tolerable to patients. Data suggest that VLCDs and LCDs may produce a degree of weight loss that is better than those with traditional dietary approaches and closer to what is seen with bariatric surgery. Such diets may also be useful for the patient who needs short-term weight loss for a diagnostic or surgical procedure. Gallstone formation is a recognized complication of VLCDs and LCDs.

29. What is the Atkins Diet? Does it work?

The Atkins Diet is a severely carbohydrate-restricted (< 20 g/day during the induction phase) diet. The severe carbohydrate restriction produces what Dr. Robert Atkins calls "benign dietary ketosis," which he argues suppresses appetite. The diet has few other restrictions. Several studies support the idea that the Atkins Diet produces more weight loss than a low-fat diet over 6 months but that long-term weight loss is comparable to that seen with diets that are higher in carbohydrate and lower in fat. These studies have shown no adverse effects on blood lipid levels. The Atkins Diet can be difficult for people to adhere to long term.

KEY POINTS 1: OBESITY

1. Obesity is defined as a body mass index greater than 30 kg/m^2.
2. A 5% to 10% weight loss is a good goal with known health benefits.
3. A number of randomized controlled clinical trials show that over 6 to 12 months, there are no adverse effects on lipids from the Atkins Diet plan.
4. Orlistat, phentermine, and lorcaserin are the only medications currently approved by the U.S. Food and Drug Administration to help overweight and obese patients lose weight.
5. The average weight loss following gastric bypass surgery is 30%.

30. What drugs are available to treat obesity?

- Phentermine (Adipex-P, Fastin, Ionamin)
- Orlistat (Xenical, Alli)
- Lorcaserin (Belviq)
- Phentermine plus topiramate (Qsymia)

31. Are phentermine and amphetamine related?

Yes. Phentermine is chemically related to amphetamine and works predominantly on the neurotransmitter norepinephrine to reduce appetite. The addictive effects of amphetamine are thought to be due to its actions on the neurotransmitter dopamine. Phentermine has substantially fewer dopaminergic effects than amphetamine and thus has minimal potential for addiction.

32. Is phentermine effective? What is the usual dose?

Compared with placebo, phentermine produces roughly a 5% weight loss in 50% to 60% of those who take it. The dose used ranges from 15 to 37.5 mg/day. It is the most widely prescribed weight loss medication.

33. Discuss the side effects of phentermine.

Phentermine is a central stimulant and can cause hypertension, tachycardia, nervousness, headache, difficulty sleeping, and tremor in some people. It should not be used in people with uncontrolled hypertension. Blood pressure should be monitored closely after initiation of this medicine. There is no evidence that, when used alone (in contrast to the combination of phentermine with fenfluramine), it is associated with cardiac valvular or pulmonary vascular toxicity. Phentermine is approved by the U.S. Food and Drug Administration (FDA) only for 3-month use. However, it is often prescribed "off label" for longer than 3 months. Evidence of the safety of phentermine comes from the fact that has been widely prescribed longer than any other weight loss agent, and there has been no evidence of serious long-term side effects.

34. How does orlistat work? What is the usual dose?

Orlistat is a pancreatic lipase inhibitor. At prescription strength, 120 mg three times a day with meals, it reduces the absorption of dietary fat by roughly 30% by inhibiting the enzyme responsible for fat

digestion. The average weight loss seen is about 5% to 8%. This medication may be preferred in people with mood disorders, heart disease, or poorly controlled hypertension. A 60-mg form is approved by the FDA and available over the counter. This strength is less effective than the prescription strength, giving roughly a 2% to 4% weight loss.

35. What are the side effects of orlistat?

The main side effects of orlistat are due to the malabsorption of fat that it causes. Patients using the agent who eat a high-fat meal experience greasy stools and may even have problems with incontinence of stool. If the patient chooses to skip the medication, he or she can eat a high-fat meal without side effects and without the benefit that the medication would otherwise provide. The FDA has approved orlistat for long-term use, and there is no specific mention in the package insert of when it should be stopped. Because of the potential to cause fat-soluble vitamin deficiencies, patients should be instructed to take a multiple vitamin daily. Orlistat should be used with caution in those taking warfarin (Coumadin) and is contraindicated in those undergoing cyclosporin therapy.

36. Discuss the use of lorcaserin.

Lorcaserin is the most recently FDA-approved weight loss medication. It is a selective 5-HT2C receptor agonist that modifies serotonin signaling to reduce food intake. Lorcaserin is indicated as an adjunct to a reduced-calorie diet and increased physical activity for long-term weight management in adults with an initial BMI of 30 kg/m^2 or greater or with an initial BMI 27 kg/m^2 or greater and at least one weight-related comorbid condition. Average weight loss with lorcaserin was approximately 4% to 6% in clinical trials.

37. Discuss the role of bupropion in the treatment of obesity.

A number of studies demonstrate that bupropion can produce gradual weight loss over as long as 1 year in many people. This medication is not approved by the FDA for weight loss. Bupropion may be useful in obese patients with depression severe enough to warrant pharmacotherapy.

38. Discuss the use of phentermine plus topiramate in obesity treatment.

Phentermine plus topiramate is the most recently FDA-approved medication for weight loss. Topiramate is indicated for the treatment of seizure disorder and migraine. In clinical trials, individuals taking phentermine plus topiramate had a mean weight loss of 8% to 10%. The recommended dose is phentermine 7.5 mg plus topiramate extended release 46 mg. The higher dosage of phentermine 15 mg plus topiramate 92 mg can also be prescribed. The combination medication cannot be used during pregnancy because data have shown that fetuses exposed to topiramate during the first trimester were at increased risk of oral clefts (cleft lip with or without cleft palate). Females of reproductive age should have a negative pregnancy test result before starting the medication, should use effective contraception, and should have pregnancy tests every month while taking the medication. Additionally, the medication cannot be used in patients with glaucoma or hyperthyroidism.

39. Are there any new weight loss drugs on the horizon?

A number of weight loss medications have been reviewed by the FDA over the past several years. Several glucagon-like peptide-1 (GLP-1) agonists are available for the treatment of diabetes. Exenatide and liraglutide are being evaluated with the intent to seek FDA approval for a weight loss indication. A bupropion-naltrexone combination is also being evaluated but has not yet received FDA approval.

40. How long will a weight loss medication need to be taken?

Medications used to promote weight loss will work only as long as they are taken. If a patient loses weight while taking a medication and then stops using it, he or she is likely to regain the lost weight. If a physician and a patient decide to try a weight loss medication, it should be taken for a minimum of 1 to 3 months to determine whether the patient will experience a weight loss benefit. Then some form of long-term use should be considered, given the available information about the risks and potential benefits of the medication. There are also data supporting the intermittent use of weight loss medications.

41. Discuss the role of exercise in a weight loss program.

Increased physical activity appears to be a central part of a successful weight loss program. Although exercise does not produce much added weight loss over diet alone in the short run, it appears to be extremely important in maintaining the reduced state. The National Weight Control Registry is a group of 3000 people who were identified because they successfully lost 30 lb and kept it off for at least 1 year. They self-report 2000 kcal/week of planned physical activity (60-80 min/day on most days of the week). A discussion of physical activity with a patient should begin with a physical activity history. Ask about the frequency of engaging in planned physical activity. Then ask about hours per day of television viewing, computer time, and other sedentary activities. Finally, discuss activities of daily living, including work-related activities. Assess the individual's readiness to change his or her physical activity level.

42. How much physical activity is necessary to prevent weight gain as opposed to maintaining a reduced weight?

In 2008, the U.S. government published physical activity guidelines for Americans. These guidelines suggest that all adults should do 2 hours and 30 minutes a week of moderate-intensity or 1 hour and 15 minutes per week of vigorous-intensity aerobic physical activity. In addition, they advise that muscle-strengthening activities involving all major muscle groups be performed on 2 or more days per week. This level of activity is designed to prevent weight gain. It appears that 60 to 90 minutes per day of moderate physical activity may be needed for maintenance of weight loss.

43. What are pedometers? How are they used?

Pedometers are small devices that clip to the waistbands of clothing. They can be used both to assess usual physical activity and to make and monitor physical activity goals. The usual number of steps taken by an average person is 6,000 per day. The recommended number of steps to prevent weight gain is 10,000 per day. People in the National Weight Control Registry using physical activity to maintain a reduced obese state average 12,000 steps/day.

44. What are the common types of weight loss surgery?

Restrictive surgery limits the amount of food the stomach can hold and slows the rate of gastric emptying. The most commonly performed restrictive operation is laparoscopic adjustable silicone gastric banding (LAP-BAND). A newer operation, the sleeve gastrectomy, markedly restricts gastric capacity in an irreversible manner and appears to be more effective than laparoscopic banding, although it also carries greater risks of complications. The restrictive-malabsorptive Roux-en-Y gastric bypass (RYGB) procedure combines gastric restriction with selective malabsorption and produces greater weight loss. This procedure may be performed through an open incision or laparoscopically. The less commonly performed biliopancreatic diversion–duodenal switch procedure produces even more malabsorption and greater weight loss. Although these malabsorptive procedures produce more rapid and profound weight loss, they also put patients at risk of complications, such as vitamin deficiencies and protein-energy malnutrition. Restrictive procedures are considered simpler and safer but may result in less long-term weight loss.

45. Who are good candidates for surgical treatment of obesity?

Eligible patients are those with a BMI greater than 40 kg/m^2 without comorbidities or a BMI greater than 35 kg/m^2 with comorbidities, such as diabetes, sleep apnea, reflux, hypertension, and degenerative joint disease (DJD); patients with a family history of comorbidities; patients for whom other forms of therapy have failed; and patients with no serious cardiac, pulmonary, or psychiatric disease. Bariatric surgery is increasingly being performed in adolescents who are severely obese, who have gone through puberty, and for whom other forms of treatment have failed.

46. What are the expected outcomes and health benefits of weight loss surgery?

Bariatric surgery is the most effective weight loss treatment available for those with clinically severe obesity. In one meta-analysis, the overall percentage of excess weight loss for all surgery types was

61.2% (see Buchwald et al, 2004). This translates into roughly a 30% overall loss compared with preoperative weight. Weight loss is greater after the combined restrictive-malabsorptive procedures than after the restrictive procedures. In the meta-analysis, diabetes completely resolved in 77% of patients and resolved or improved in 86% of patients following bariatric surgery. Two other series have reported resolution of diabetes in 83% and 86% of patients (see Schauer et al, 2003 and Sugarman et al, 2003). In the meta-analysis, hyperlipidemia improved in 70% or more of the patients, hypertension resolved in 62% and resolved or improved in 79% of patients, and obstructive sleep apnea resolved in 86%. Hypertension improves in many patients but is more resistant to improvement than diabetes or sleep apnea.

47. What is the mortality rate associated with bariatric surgery?

The surgical mortality rate associated with bariatric surgery is 0.1% to 2.0%. In the meta-analysis previously cited, mortality at 30 or fewer days was 0.1% for the purely restrictive procedures, 0.5% in patients undergoing gastric bypass procedures, and 1.1% in patients undergoing biliopancreatic diversion–duodenal switch procedures (see Buchwald et al, 2004). In a later prospective observational study, the 30-day rate of death among patients who underwent RYGB or laparoscopic adjustable gastric banding was 0.3%, and a total of 4.3% of patients had at least one major adverse outcome. Common causes of death among patients undergoing bariatric surgery included pulmonary embolism and anastomotic leaks. Factors that have been found to contribute to increased mortality include lack of experience on the part of the surgeon or the program, advanced patient age, male sex, severe obesity (BMI > 50 kg/m^2), and coexisting conditions. Risk is higher in low-volume programs.

48. What are the most common complications of bariatric surgery?

Nonfatal perioperative complications include venous thromboembolism, anastomotic leaks, wound infections, bleeding, incidental splenectomy, incisional and internal hernias, and early small bowel obstruction. Stomal stenosis or marginal ulcers (occurring in 5% to 15% of patients) present as prolonged nausea and vomiting after eating or inability to advance the diet to solid foods. These complications are treated by endoscopic balloon dilatation and acid suppression therapy, respectively. Abdominal and incisional hernias occur in roughly 30% of patients following open RYGB. Dumping syndrome following simple sugar intake, especially added sugars, has been reported in as many as 76% of RYGB patients. To prevent dumping syndrome, patients should be encouraged to consume frequent, small meals and to avoid fruit juices and added sugars.

49. What is a rare cause of hypoglycemia following RYGB?

Post–gastric bypass hyperinsulinemic hypoglycemia is increasingly being recognized. Some investigators have hypothesized that changes in gut hormones such as GLP-1 following gastric bypass may promote beta-cell hyperplasia and predispose to this condition. Unlike patients with insulinomas, these patients often experience severe hypoglycemia following the ingestion of carbohydrates. Initial descriptions emphasized the presence of nesidioblastosis, or beta-cell hyperplasia as a cause and demonstrated the value of partial pancreatectomy as a treatment in severe cases. More recently, studies have suggested that most patients with this syndrome can be treated by modifying the diet to include less carbohydrate and increasing the consumption of slowly absorbed (low glycemic index) carbohydrates in the context of mixed meals. While dietary carbohydrate restriction is the principal treatment for hypoglycemia following gastric bypass surgery, a number of medications have been found to be of use including acarbose, calcium channel blockers, diazoxide, and octreotide.

50. What vitamin and micronutrient deficiencies are patients at risk for following bariatric surgery?

By bypassing the stomach, duodenum, and varying portions of the jejunum and ileum, malabsorption of thiamine, iron, folate, vitamin B12, calcium, and vitamin D may occur. In general, the greater the degree of malabsorption, the higher the risk of nutritional deficiencies. To prevent deficiencies, patients should routinely be discharged from the hospital with daily vitamin and mineral supplementation that contains between 1.5 and 1.8 mg thiamine, 28 and 40 mg elemental iron, 500 μg oral B12, 400 μg folate, 1200 to 1500 mg calcium, and 800 to 1200 IU vitamin D.

51. What laboratory tests should be performed to follow up on a patient who has had weight loss surgery?

The following laboratory tests should be performed preoperatively and at 6-month intervals for the first 2 years, followed by annual assessments thereafter: complete blood count, comprehensive metabolic panel, lipid panel, and measurements of hemoglobin A_{1C} (for diabetic patients), ferritin, folate, vitamin B12, 25-hydroxy vitamin D, and parathyroid hormone. With more extensive procedures, such as biliopancreatic diversion, protein malnutrition and deficiencies of the fat-soluble vitamins (A, D, E, and K) may occur. Some patients in whom iron deficiency anemia develops following weight loss surgery require treatment with parenteral iron. With judicious monitoring and adequate supplementation, all of these deficiencies are largely avoidable and treatable.

WEBSITES

1. Weight Control Information Network Overweight and Obesity Statistics. http://www.win.niddk.nih.gov/statistics/index.htm.
2. American College of Sports Medicine. http://www.acsm.org.
3. Motivational interviewing. http://www.motivationalinterview.org
4. National Institute of Diabetes and Digestive and Kidney Diseases. http://www.niddk.nih.gov/health/nutrit/nutrit.htm.
5. U.S. Department of Human Services Physical Activity guidelines for Americans. http://www.health.gov/paguidelines/factsheetprof.aspx.

BIBLIOGRAPHY

Buchwald H, Avidor Y, Braunwald E, et al: Bariatric surgery: a systematic review and meta-analysis, *JAMA* 292:1724–1728, 2004.

Dansinger ML, Gleason JA, Griffith JL, et al: Comparison of the Atkins, Ornish, Weight Watchers, and Zone diets for weight loss and heart disease risk reduction: a randomized trial, *JAMA* 293:43–53, 2005.

Fidler MC, Sanchez M, Anderson CM, et al: BLOSSOM Clinical Trial Group. A one-year randomized trial of lorcaserin for weight loss in obese and overweight adults: the BLOSSOM trial, *J Clin Endocrinol Metab* 96:3067–3077, 2011.

Finkelstein EA, Trogdon JG, Cohen JW, et al: Annual medical spending attributable to obesity: payer- and service-specific estimates, *Health Affairs* 28:822–831, 2009.

Flegal KM, Carroll MD, Kit BK, et al: Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999–2010, *JAMA* 307:491–497, 2012.

Foster GD, Wyatt HR, Hill JO, et al: A randomized trial of a low-carbohydrate diet for obesity, *N Engl J Med* 348:2082–2090, 2003.

Hession M, Rolland C, Kulkarni U, et al: Systematic review of randomized controlled trials of low-carbohydrate vs. low-fat/low-calorie diets in the management of obesity and its comorbidities, *Obes Rev* 10(1):36–50, 2009.

Heymsfield SB, Van Mierlo CA, Van Der Knapp HC, et al: Weight management using a meal replacement strategy: meta and pooling analysis, *Int J Obesity Relat Metab Disord* 27:537–549, 2003.

Knowler WC, Barrett-Conner E, Fowler SE, et al: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin, *N Engl J Med* 346:393–403, 2002.

Kral JG, Naslund E: Surgical treatment of obesity, *Nat Clin Pract Endocrinol Metab* 3:574–583, 2007.

Kushner RF: Obesity management, *Gastroenterol Clin North Am* 36:191–210, 2007.

Kushner RF, Bessesen DH: *Treatment of the obese patient*, Totowa, NJ, 2007, Humana Press.

Lauderdale DS, Liu K, et al: Cross-sectional and longitudinal associations between objectively measured sleep duration and body mass index: the CARDIA Sleep Study, *Am J Epidemiol* 170:805–813, 2009.

Li Z, Maglione M, Tu W, et al: Meta-analysis: pharmacologic treatment of obesity, *Ann Intern Med* 142:532–546, 2005.

Longitudinal Assessment of Bariatric Surgery (LABS) Consortium, Flum DR, Belle SH, King WC, et al: Perioperative safety in the longitudinal assessment of bariatric surgery, *N Engl J Med* 361:445–454, 2009.

Maggard MA, Shugarman LR, Suttorp M, et al: Meta-analysis: surgical treatment of obesity, *Ann Intern Med* 142:547–559, 2005.

Maria EJ: Bariatric surgery for morbid obesity, *N Engl J Med* 356:2176–2183, 2007.

McTigue KM, Harris R, Hemphill B, et al: Screening and interventions for obesity in adults: summary of the evidence for the U.S. Preventive Services Task Force, Med 139:933–1049, 2003.

Mechanick JI, Kushner RF, Sugerman HJ, et al: American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic & Bariatric Surgery medical guidelines for clinical practice for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient, *Obesity (Silver Spring)* 17:S1–70, 2009.

National Institutes of Health: The practical guide to the identification, evaluation and treatment of overweight and obesity in adults, *Obesity Res* 6:(Suppl 12), 1998.

Ogden CL, Carroll MD, Kit BK, et al: Prevalence of obesity and trends in body mass index among US children and adolescents, 1999–2010, *JAMA* 307(5):483–490, 2012.

Ramachandrappa S, Farooqi IS: Genetic approaches to understanding human obesity. *J Clin Invest* 121(6) 2080. 6, 2011.

Samaha FF, Iqbal N, Seshadri P, et al: A low-carbohydrate as compared with a low-fat diet in severe obesity, *N Engl J Med* 348:2074–2081, 2003.

Schauer PR, Burguera B, Ikramuddin S, et al: Effect of laparoscopic Roux-en Y gastric bypass on type 2 diabetes mellitus, *Ann Surg* 238:467–484, 2003.

Service GJ, Thompson GB, Service FJ, et al: Hyperinsulinemic hypoglycemia with nesidioblastosis after gastric-bypass surgery, *N Engl J Med* 353:249–254, 2005.

Shah M, Simha V, Garg A: Long-term impact of bariatric surgery on body weight, comorbidities, and nutritional status, *J Clin Endocrinol Metab* 91:4223–4231, 2006.

Snow V, Barry P, Fitterman N, et al: Pharmacologic and surgical management of obesity in primary care: a clinical practice guideline from the American College of Physicians, *Ann Intern Med* 142:525–531, 2005.

Sugarman HJ, Wolfe LG, Sica DA, et al: Diabetes and hypertension in severe obesity and effects of gastric bypass-induced weight loss, *Ann Surg* 237:751–756, 2003.

Tsai AG, Wadden TA: Systematic review: an evaluation of major commercial weight loss programs in the United States, *Ann Intern Med* 142:56–66, 2005.

Tuomilehto J, Lindstrom J, Eriksson JG, et al: Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance, *N Engl J Med* 344:1343–1350, 2001.

Wadden TA, West DS, Neiberg RH, et al: One-year weight losses in the Look AHEAD study: factors associated with success, *Obesity (Silver Spring)* 17(4):713–722, 2009.

CHAPTER 8

OSTEOPOROSIS

Michael T. McDermott

1. What is osteoporosis?

Osteoporosis is a skeletal disorder characterized by compromised bone strength, which predisposes to the development of fragility fractures. Bone strength is determined by both bone mass and bone quality. The diagnosis of osteoporosis is established by the presence of a true fragility or, in patients who have never sustained a fragility fracture, by measurement of bone mineral density (BMD).

2. What are fragility fractures?

Fragility fractures are fractures that occur spontaneously or following minimal trauma, defined as falling from a standing height or less. Fractures of the vertebrae, hips, and distal radius (Colles fracture) are the most characteristic fragility fractures, but patients with osteoporosis are prone to all types of fractures. Osteoporosis accounts for approximately 1.5 million fractures in the United States each year.

3. What are the complications of osteoporotic fractures?

Vertebral fractures cause loss of height, anterior kyphosis (dowager's hump), reduced pulmonary function, and an increased mortality rate. Approximately one third of all vertebral fractures are painful, but two thirds are asymptomatic. Hip fractures are associated with permanent disability in nearly 50% of patients and with a 20% higher mortality rate than in the age-matched population without fractures.

4. What factors contribute most to the risk of an osteoporotic fracture?

- Low BMD (twofold increased risk for every one standard deviation [SD] decrease of BMD)
- Age (twofold increased risk for every decade of age above 60 years)
- Previous fragility fracture (fivefold increased risk for a previous fracture)
- Frequent falls

5. What are the currently accepted indications for BMD measurement?

- Age $\geq$ 65 years
- Estrogen deficiency plus one risk factor for osteoporosis
- Vertebral deformity, fracture, or radiographic evidence of osteopenia
- Primary hyperparathyroidism
- Glucocorticoid therapy, $\geq$ 5 mg/day of prednisone for $\geq$ 3 months
- Monitoring the response to an osteoporosis medication approved by the U.S. Food and Drug Administration (FDA)

6. How is BMD currently measured?

Dual-energy x-ray absorptiometry (DXA) is the most accurate and widely used method in current practice. BMD can also be measured by computed tomography (CT) and ultrasound (US). Central densitometry measurements (spine and hip) are the best predictors of fracture risk and have the best precision for longitudinal monitoring. Peripheral densitometry measurements (heel, radius, hands) are more widely available and less expensive.

7. How do you read a bone densitometry report?

- *T-score:* The number of SDs the patient's value is below or above the mean value for young normal subjects (peak bone mass). The T-score is a good predictor of the fracture risk.
- *Z-score:* The number of SDs the patient's value is below or above the mean value for age-matched normal subjects. The Z-score indicates whether or not the BMD is appropriate for age.
- *Absolute BMD:* The actual BMD expressed in g/cm^2. This is the value that should be used to calculate changes in BMD during longitudinal follow-up.

8. How is the diagnosis of osteoporosis made?

Osteoporosis should be diagnosed in any patient who sustains a fragility fracture. In a patient without fractures, the diagnosis can be made on the basis of the BMD T-score at the lowest skeletal site, using the following criteria:

- T-score ≥ -1 = Normal
- T-score between -1 and -2.5 = Osteopenia
- T-score ≤ -2.5 = Osteoporosis

9. What are the major risk factors for the development of osteoporosis?

Non-modifiable risk factors	Age
	Race (Caucasian, Asian)
	Female gender
	Early menopause
	Slender build
	Positive family history
Modifiable risk factors	Low calcium intake
	Low vitamin D intake
	Estrogen deficiency
	Sedentary lifestyle
	Cigarette smoking
	Alcohol excess ($>$ 2 drinks/day)
	Caffeine excess ($>$ 2 servings/day)

10. What other conditions must be considered as causes of low BMD?

- Osteomalacia
- Celiac disease
- Osteogenesis imperfecta
- Inflammatory bowel disease
- Hyperparathyroidism
- Primary biliary cirrhosis
- Hyperthyroidism
- Multiple myeloma
- Hyperprolactinemia
- Rheumatoid arthritis
- Hypogonadism
- Renal failure
- Cushing's syndrome
- Renal tubular acidosis
- Eating/exercise disorders
- Idiopathic hypercalciuria
- Systemic mastocytosis
- High-risk medications*

*Well-established risk: glucocorticoids, excess thyroid hormone, anticonvulsants. Probable/possible risk: thiazolidinediones, selective serotonin reuptake inhibitors, proton pump inhibitors (PPIs).

11. Outline a cost-effective evaluation to rule out other causes of low bone mass.

- Calcium
- Creatinine (estimated glomerular filtration rate)

- Alkaline phosphatase
- 25-hydroxyvitamin D (25-OHD)
- Testosterone (men)
- Thyroid-stimulating hormone (TSH)
- Celiac disease antibody testing
- Urine (24-hour) calcium, sodium, creatinine

In approximately one third of women and two thirds of men, an abnormality will be detected with this evaluation.

12. How do you determine whether a patient has had a previous vertebral fracture?

Back pain and tenderness are helpful clues but may be absent because two thirds of vertebral fractures are asymptomatic. Height loss of 2 inches or more and dorsal kyphosis are highly suggestive clinical findings. Lateral spine films and dual-energy x-ray absorptiometry vertebral fracture assessment (VFA) are the most accurate ways to detect existing vertebral fractures.

13. What are the most significant risk factors for frequent falls?

- Use of sedatives
- Visual impairment
- Cognitive impairment
- Lower extremity disability
- Obstacles to ambulation in the home

14. What non-pharmacologic measures help to prevent and treat osteoporosis?

- Adequate calcium intake (diet plus supplements): 1000-1200 mg/day for premenopausal women and men; 1200-1500 mg/day for postmenopausal women and men 65 years or older
- Adequate vitamin D intake: 800-1200 U/day (D_3 preferred)
- Regular exercise: aerobic and resistance
- Limitation of alcohol consumption to fewer than 2 drinks/day
- Limitation of caffeine consumption to fewer than 2 servings/day
- Smoking cessation
- Fall prevention

15. How can dietary calcium intake be accurately assessed?

The major bioavailable sources are dairy products and calcium-fortified fruit drinks. The following approximate calcium contents should be assigned for dairy product intake:

- Milk/yogurt: 300 mg/cup
- Cheese: 300 mg/oz
- Fruit juice with calcium: 300 mg/cup

Add 300 mg for the general nondairy diet for a reasonable estimate of daily intake.

16. How do you ensure adequate intake of calcium?

Low-fat dairy products are the best source of calcium. Calcium supplements should be added when the desired goals cannot be reached with dietary sources. Calcium carbonate and calcium citrate are both well absorbed when taken with meals. Gastric acid is needed for normal calcium absorption; calcium carbonate absorption may be significantly reduced in patients who have achlorhydria or who use a PPI. Calcium citrate absorption is less likely to be affected by PPI use.

17. What are the best ways achieve adequate vitamin D intake?

There are two natural forms of vitamin D: cholecalciferol (vitamin D_3) and ergocalciferol (vitamin D_2). Fatty fish (D_3) and some fortified milk and cereal products (D_2 and D_3) are good dietary sources. Vitamin D_2 and D_3 supplements are available over the counter in multiple doses, and 50,000-unit vitamin D_2 supplements can be given by prescription. Sunlight exposure raises vitamin D levels but

often must be limited for many reasons; therefore, oral vitamin D is the major source for most people. The optimal vitamin D intake is 800 to 1200 units daily.

18. How do you treat patients with vitamin D deficiency?

The serum 25-OHD goal level is 30 to 100 ng/mL. In general, 1000 units (U) daily of vitamin D will raise the serum level by 10 ng/mL. I recommend the following:

25-OHD LEVEL (NG/ML)	MANAGEMENT
20-30	2000 U D_3 daily
10-20	50,000 U D_2 weekly for 3 months, then 2000 U D_3 daily
< 10	50,000 U D_2 twice weekly for 3 months, then 2000 U D_3 daily

19. When should pharmacologic therapy be initiated for osteoporosis?

Pharmacologic therapy should be advised for anyone who has had a vertebral or hip fracture or who has a T-score less than -2.5. The FRAX tool, developed by the World Health Organization (WHO), is recommended for making treatment decisions in drug-naïve patients with osteopenia (for information, go to www.shef.ac.uk/FRAX). Treatment is advised for those who have a 10-year risk of 3% or higher for hip fracture or 20% or higher for other major osteoporotic fractures.

20. Describe bone remodeling.

Bone remodeling is the process that removes old bone and replaces it with new bone (Fig. 8-1). Osteoclasts attach to bone surfaces and secrete acid and enzymes that dissolve away underlying bone. Osteoblasts then migrate into these resorption pits and secrete osteoid, which becomes mineralized with calcium phosphate crystals (hydroxyapatite). Osteocytes serve as the mechanoreceptors that sense skeletal stress and send signals to orchestrate the process of bone remodeling in areas of bone that need renewal.

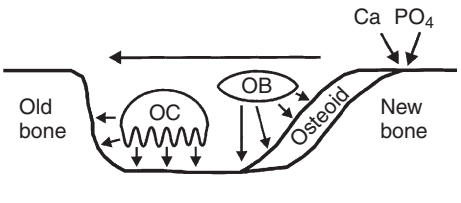


Figure 8-1. Bone remodeling. Ca, calcium; OB, osteoblast; OC, osteoclast; PO_4, phosphate.

21. What are RANK, RANK-L, and Osteoprotegerin?

RANK (receptor activator of nuclear factor κ) is a specific receptor on osteoclasts. RANK-L (RANK ligand) binds to RANK to stimulate osteoclastic bone resorption. Osteoprotegerin is a soluble decoy receptor that binds to RANK-L, preventing it from binding to RANK. Bone resorption is driven by RANK-L and inhibited by osteoprotegerin.

22. How do the pharmacologic agents for osteoporosis work?

Osteoporosis medications are classified into two main categories: antiresorptive agents and anabolic agents. Antiresorptive medications include the bisphosphonates, denosumab (monoclonal antibody against RANK-L), raloxifene, calcitonin, and estrogens. The only currently available anabolic agent is teriparatide.

23. What pharmacologic agents are FDA approved and how are they used?

MECHANISM	ROUTE	DOSE	FREQUENCY
Antiresorptive Agents			
Bisphosphonates			
Alendronate (Fosamax)	Oral	10 mg	Daily
		70 mg	Weekly
Risedronate (Actonel)	Oral	5 mg	Daily
		35 mg	Weekly
		150 mg	Monthly
Ibandronate (Boniva)	Oral	150 mg	Monthly
	Intravenous (IV)	3 mg	3 Months
Zoledronic acid (Reclast)	IV	5 mg	Yearly
Non-bisphosphonates			
Denosumab (Prolia)	Subcutaneous (SC)	60 mg	6 Months
Raloxifene (Evista)	Oral	60 mg	Daily
Calcitonin (Miacalcin)	Nasal	200 U	Daily
	SC	100 U	Daily
Estrogen therapy (multiple preparations and regimens)			
Anabolic Agent			
Teriparatide (Forteo)	SC	20 μg	Daily

24. How could teriparatide be an anabolic agent for treating osteoporosis?

Persistently elevated serum parathyroid hormone (PTH) levels (primary hyperparathyroidism) promote osteoclastic bone resorption and bone loss. In contrast, intermittent daily pulses of exogenous PTH actually stimulate osteoblastic bone formation and increase bone mass. Teriparatide is a 34–amino acid fragment of intact PTH that retains the ability to bind to and activate PTH receptors on osteoblasts.

25. Have all of these medications been shown to prevent fractures?

All of the FDA-approved medications listed in the previous table have been demonstrated in randomized controlled trials (RCTs) to significantly reduce vertebral fractures in women with postmenopausal osteoporosis. Hip fractures have also been reduced by alendronate, risedronate, zoledronic acid, and denosumab. Nonvertebral fracture reduction has been reported with alendronate, risedronate, zoledronic acid, denosumab, and teriparatide.

26. Are medication combinations more effective than single agents?

Combinations of antiresorptive agents increase bone mass more than single agents alone, but fracture data are not yet available for such regimens. Furthermore, there are concerns that oversuppression of bone resorption may be harmful. Combinations of anabolic and antiresorptive agents used concurrently have disappointingly shown no greater effects than single agents alone. Studies investigating sequential rather than concurrent use of various agents are currently in progress.

27. Is osteonecrosis of the jaw (ONJ) related to bisphosphonate therapy?

ONJ manifests as persistently exposed bone following an invasive dental procedure. It occurs most often during high-dose IV bisphosphonate therapy for multiple myeloma or bone metastases. ONJ has also been identified in some patients taking bisphosphonates for osteoporosis. Good oral hygiene and regular dental care are the best preventive measures. Temporarily stopping bisphosphonates for invasive dental procedures is a common and reasonable practice but has not been shown to prevent ONJ.

28. What about atypical femoral fractures with bisphosphonate use?

Atypical femoral fractures have been reported in some patients undergoing long-term bisphosphonate therapy (> 5 years). It is not clear whether the fractures resulted from bisphosphonate use or the underlying osteoporosis. Currently, no data exist regarding preventive measures. After 5 years of bisphosphonate use, many providers recommend a 1- to 2-year bisphosphonate "drug holiday" for patients who have osteopenia and a temporary switch to anabolic therapy or other non-bisphosphonate agent for those with previous fractures or very low BMD.

29. How should BMD be used to monitor the response to osteoporosis therapy?

BMD testing to monitor therapy responses is most often repeated after 2 years of treatment. To accurately interpret serial changes, the least significant change (LSC) for the specific instrument must be known. The LSC is a precision estimate that informs the user about the minimum BMD change that should be considered significant. Standard procedures for performing the LSC assessment are available on the International Society for Clinical Densitometry's Website (www.iscd.org).

30. How do you interpret BMD changes in patients taking osteoporosis medications?

BMD CHANGE	INTERPRETATION	RECOMMENDED ACTION
Increase ≥ LSC	Good response	Continue therapy
No change or < LSC	Adequate response	Continue therapy
Decrease ≥ LSC	Treatment failure	Evaluate; consider therapy change

31. What markers are available to assess bone remodeling, and how are they used?

Markers of bone formation	Serum alkaline phosphatase
	Serum osteocalcin
Markers of bone resorption	Urine or serum *N*-telopeptides
	Serum *C*-telopeptides

Elevation of biomarkers predicts future bone loss. A 30% reduction of biomarkers after therapy is initiated verifies compliance and predicts an increase in bone mass. However, great variability in biomarker measurement limits the utility of this tool.

32. What do you do when BMD falls significantly during osteoporosis therapy?

The common causes of BMD loss on treatment and their management are as follows:

CAUSE	MANAGEMENT
Nonadherence	Encourage adherence
Calcium deficiency	Ensure adequate calcium intake
Vitamin D deficiency	Ensure adequate vitamin D intake
Secondary bone loss	Treat the cause
Treatment failure	Change medication

33. How does osteoporosis differ in men?

Approximately 1 to 2 million men in the United States have osteoporosis. The diagnostic criteria are the same in men as in women (fragility fracture or T-score ≤ -2.5). Nearly two thirds of osteoporotic men have an identifiable secondary cause of bone loss, most often alcohol abuse, glucocorticoid use, or hypogonadism, including that due to use of a gonadotropin-releasing hormone (GnRH) analog for prostate cancer. Treatment is generally the same as in women although testosterone replacement in hypogonadal men can be an effective adjunctive strategy.

34. How can falls be prevented?

1. Minimize or discontinue sedatives.
2. Correct visual impairment.
3. Prescribe ambulatory aids when appropriate.
4. Make a "fall-proof" home: adequate lighting, carpeting, handrails, non-slip bathroom surfaces, removal of clutter and obstacles to walking.

35. Outline an efficient and effective management strategy for a patient with osteoporosis.

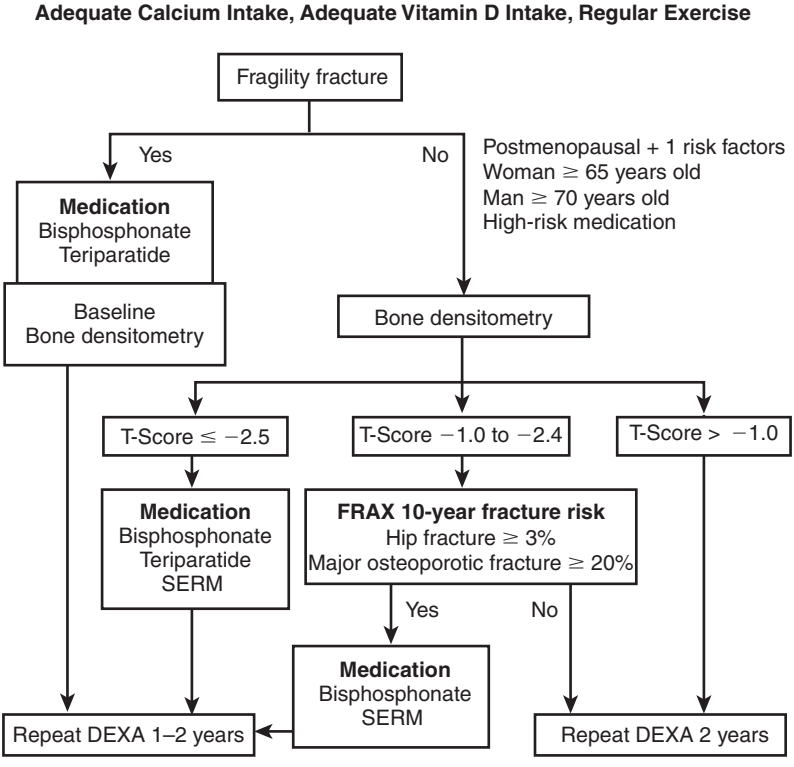


Figure 8-2. Osteoporosis management algorithm.

KEY POINTS 1: OSTEOPOROSIS

1. In the United States, osteoporosis affects nearly 10 million women and men, who have a significantly increased risk for fragility fractures.
2. The major risk factors for fragility fractures are low bone mass, advancing age, previous fragility fractures, and the propensity to fall.
3. Disorders causing secondary bone loss are present in approximately one third of women and two thirds of men who have osteoporosis.
4. Patients with osteoporosis should undergo a complete history, complete physical examination, and key, cost-effective laboratory testing to identify any underlying responsible disorders.
5. Nonpharmacologic measures that are effective for prevention and treatment of osteoporosis include adequate calcium and vitamin D nutrition, regular exercise, fall prevention, smoking cessation, and limitation of alcohol and caffeine intake.
6. Pharmacologic therapy should be initiated in patients who have had a fragility fracture, a BMD T-score ≤ -2.5, or a FRAX-derived 10-year risk of $\geq 3\%$ for hip fractures and $\geq 20\%$ for other major osteoporotic fractures.
7. There are two primary categories of effective medications for treating osteoporosis, antiresorptive agents and anabolic agents.
8. All FDA-approved medications for osteoporosis have been shown to significantly reduce the risk of vertebral fractures. Some have also been demonstrated to have efficacy in preventing hip fractures and nonvertebral fractures.
9. Osteonecrosis of the jaw and atypical femoral fractures have been reported in some patients using bisphosphonates; prevention strategies are currently being investigated.
10. BMD loss during osteoporosis therapy is most often due to therapy nonadherence, but affected patients should also be evaluated for other causes of bone loss.

BIBLIOGRAPHY

Abrahamsen B, Eiken P, Eastell R: Subtrochanteric and diaphyseal femur fractures in patients treated with alendronate: a register-based national cohort study, *J Bone Miner Res* 24:1095–1102, 2009.

Black DM, Cummings SR, Karpf DB, et al: Randomized trial of effect of alendronate on risk of fracture in women with existing vertebral fractures, *Lancet* 348:1535–1541 (FIT 1), 1996.

Black DM, Delmas PD, Eastell R, et al: Once yearly zoledronic acid for treatment of postmenopausal osteoporosis, *N Engl J Med* 356:1809–1822, 2004.

Black DM, Kelly MP, Genant HK, et al: Bisphosphonates and fractures of the subtrochanteric or diaphyseal femur, *N Engl J Med* 362:1761–1771, 2010.

Black DM, Schwartz AV, Ensrud KE, et al: Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long Term Extension (FLEX), a randomized trial, *JAMA* 296:2927–2938, 2006.

Bonnick S, Johnston CC, Kleerekoper M, et al: Importance of precision in bone density measurements, *J Clin Densitom* 4:1–6, 2001.

Canalis E, Giustina A, Bilezikian JP: Mechanisms of anabolic therapies for osteoporosis, *N Engl J Med* 357:905–916, 2007.

Chesnut CH, Silverman S, Andriano K, et al: A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the Prevent Recurrence of Osteoporotic Fractures Study, *Am J Med* 109:267–276 (PROOF), 2000.

Cummings SR, Palermo L, Browner W, et al: Monitoring osteoporosis therapy with bone densitometry, *JAMA* 283:1318–1321, 2000.

Cummings SR, San Martin J, McClung MR, et al: Denosumab for prevention of fractures in postmenopausal women with osteoporosis, *N Engl J Med* 361:756–764, 2009.

Dawson-Hughes B, Bischoff-Ferrari HA: Therapy of osteoporosis with calcium and vitamin D, *J Bone Min Res* 22:V59–63, 2007.

Delmas PD, Recker RR, Chesnut CH, et al: Daily and intermittent oral ibandronate normalize bone turnover and provide significant reduction in vertebral fracture risk: results from the BONE study, *Osteoporosis Int* 15:792–798, 2004.
Ettinger B, Black DM, Mitlak BH, et al: Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene, *JAMA* 282:637–645 (MORE), 1999.
Fauvus MJ: Bisphosphonates for osteoporosis, *N Engl J Med* 363:2027–2035, 2010.
Harris ST, Watts NB, Genant HK, et al: Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis. A randomized controlled trial, *JAMA* 282:1344–1352 (VERT-NA), 1999.
Heaney RP, Recker RR, Weaver CM: Absorbability of calcium sources: the limited role of solubility, *Calcif Tissue Int* 46: 300–304, 1990.
Heaney RP: Vitamin D endocrine physiology, *J Bone Min Res* 22:V25–27, 2007.
Holick MF: Vitamin D deficiency, *N Engl J Med* 357:266–281, 2007.
Jones G, Horst R, Carter G, et al: Contemporary diagnosis and treatment of vitamin D related disorders, *J Bone Min Res* 22:V11–15, 2007.
Khosla S, Burr D, Cauley J, et al: Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research, *J Bone Min Res* 22:1479–1491, 2007.
Khosla S, Melton LJ: Osteopenia, *N Engl J Med* 356:2293–2300, 2007.
Lewiecki EM: Nonresponders to osteoporosis therapy, *J Clin Densitom* 6:307–314, 2003.
Lindsay R, Silverman SL, Cooper C, et al: Risk of new vertebral fracture in the year following a fracture, *JAMA* 285: 320–323, 2001.
Lyles KW, Colon-Emeric CS, Magaziner JS, et al: Zoledronic acid and clinical fractures and mortality after hip fracture, *N Engl J Med* 357:1799–1809, 2007.
McClung MR, Geusens P, Miller PD, et al: Effect of risedronate on the risk of hip fracture in elderly women, *N Engl J Med* 344:333–340 (HIP), 2001.
McClung MR, Lewiecki EM, Cohen SB, et al: Denosumab in postmenopausal women with low bone mineral density, *N Engl J Med* 354:821–831, 2006.
Neer RM, Arnaud CD, Zanchetta JR, et al: Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis, *N Engl J Med* 344:1434–1441, 2001.
Neviaser AS, Lane JM, Lenart BA, et al: Low-energy femoral shaft fractures associated with alendronate use, *J Orthop Trauma* 22:346–350, 2008.
Orwoll E, Ettinger M, Weiss S, et al: Alendronate for the treatment of osteoporosis in men. *N Engl J Med* 343:604–610, 2000.
Orwoll E, Scheele WH, Paul S, et al: The effect of teriparatide [human parathyroid hormone (1-34)] therapy on bone density in men with osteoporosis, *J Bone Miner Res* 18:9–17, 2003.
Orwoll ES: Osteoporosis in men, *Osteoporosis* 27:349–367, 1998.
Painter SE, Kleerekoper M, Camacho PM: Secondary osteoporosis: a review of the recent evidence, *Endocr Pract* 12: 436–445, 2006.
Recker RR: Calcium absorption and achlorhydria, *N Engl J Med* 313:70–73, 1985.
Rittmaster RS, Bolognese M, Ettinger MP, et al: Enhancement of bone mass in osteoporotic women with parathyroid hormone followed by alendronate, *J Clin Endocrinol Metab* 85:2129–2134, 2000.
Shoback D: Update in osteoporosis and metabolic bone disorders, *J Clin Endocrinol Metab* 92:747–753, 2007.
Targownik LE, Lix LM, Tetge CJ, et al: Use of proton pump inhibitors and risk of osteoporosis-related fractures, *CMAJ* 179:319–326, 2008.
Visekruna M, Wilson D, McKierman FE: Severely suppressed bone turnover and atypical skeletal fragility, *J Clin Endocrinol Metab* 93:2948–2952, 2008.
Woo SB, Hellstein JW, Kalmar JR: Systemic review: bisphosphonates and osteonecrosis of the jaws, *Ann Intern Med* 144:753–761, 2006.
Writing Group for the Women's Health Initiative Investigators: Risk and benefits of estrogen plus progestin in healthy postmenopausal women. Principal results from the Women's Health Initiative randomized controlled trial, *JAMA* 288: 321–333, 2002.
Yang YX, Lewis JD, Epstein S, et al: Long-term proton pump inhibitor therapy and risk of hip fractures, *JAMA* 296: 2947–2953, 2006.

GLUCOCORTICOID-INDUCED OSTEOPOROSIS

CHAPTER 9

Michael T. McDermott

1. How common is glucocorticoid-induced osteoporosis (GIOP)?

Glucocorticoid-induced osteoporosis (GIOP) is the most common cause of secondary osteoporosis. Significant bone loss and skeletal fractures may occur within 6 months of starting glucocorticoid therapy, and up to 50% of people undergoing long-term glucocorticoid treatment have osteoporotic fractures.

2. What are the important determinants of bone loss with glucocorticoid therapy?

Bone loss is related mainly to the dose and the duration of glucocorticoid therapy. Prednisone doses of 7.5 mg or higher (or equivalent doses of other glucocorticoids) are associated with the greatest risk. However, a large cohort study showed a significantly increased fracture risk even in those whose median prednisolone doses had been as low as 2.5 mg daily. Decreased bone mass and increased fracture risk have also been demonstrated with inhaled glucocorticoids.

3. Explain the pathogenesis of GIOP.

Glucocorticoids adversely affect three phases of bone remodeling. Bone formation is impaired by apoptosis (cell death) of existing osteoblasts and decreased recruitment of new osteoblasts. Glucocorticoids also promote apoptosis of osteocytes, the mechanoreceptors that normally maintain bone strength by coordinating bone remodeling so that older, weaker bone is continuously replaced by newer, stronger bone. Finally, bone resorption is initially increased through various mechanisms, including decreased production of sex steroids and osteoprotegerin, an endogenous inhibitor of bone resorption (Fig. 9-1).

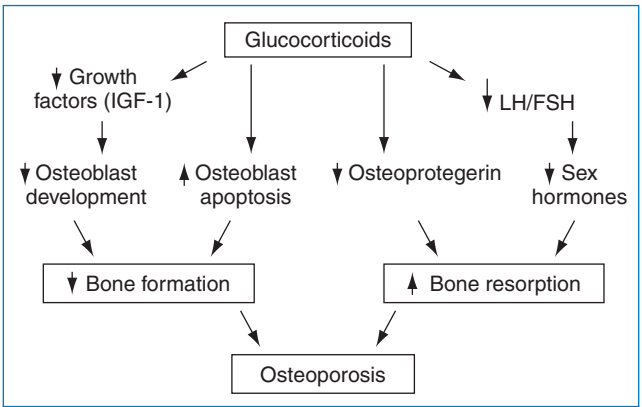


Figure 9-1. Pathophysiology of glucocorticoid-induced osteoporosis. FSH, follicle-stimulating hormone; IGF, insulin-like growth factor; LH, luteinizing hormone.

4. What are the BMD criteria for a diagnosis of GIOP?

The ideal bone mineral density (BMD) criteria for the diagnosis of GIOP are still being debated, but the best existing evidence suggests that the fracture risk per BMD decrement is higher in GIOP than in primary osteoporosis. The same BMD criteria are currently used to diagnose osteoporosis in patients taking glucocorticoids as in those who are not taking glucocorticoids, but active treatment should be considered at an earlier stage (T-score ≤ -1.0) because of the rapidity of bone loss in GIOP.

5. In which patients taking glucocorticoids should BMD be tested?

Patients who are starting glucocorticoid therapy (prednisone dose $\geq$ 5-7.5 mg/day or equivalent) with planned treatment duration of 3 months or longer or who have been receiving treatment for 3 months or longer.

6. When should BMD be tested?

- BMD (spine and hip) should be measured at the initiation of glucocorticoid therapy or as soon as possible thereafter.
- BMD should be repeated every 6 to 12 months as long as glucocorticoid therapy is continued.

7. What measures should be instituted in all patients taking glucocorticoids?

All glucocorticoid-treated patients should be advised to consume adequate calcium (1200-1500 mg daily; combination of dietary intake plus supplements) and vitamin D (800-1200 U/day), to exercise regularly (aerobic and resistance), to stop smoking, and to limit alcohol and caffeine consumption.

8. Who should be considered for pharmacologic therapy?

The American College of Rheumatology (ACR) recommends pharmacologic therapy for anyone who will receive or has received $\geq$ 7.5 mg/day of prednisone (or equivalent) for at least 3 months but recommends therapy for high-risk patients undergoing glucocorticoid therapy of any dose or duration. The National Osteoporosis Foundation recommends therapy for anyone who will receive or has received $\geq$ 5 mg/day of prednisone (or equivalent) for at least 3 months.

9. Which medications are effective in preventing and treating GIOP?

Bisphosphonates increase bone mass and prevent fractures in patients with GIOP. Alendronate, risedronate, and zoledronic acid are all approved by the U.S. Food and Drug Administration (FDA) for this disorder. In a randomized controlled trial, teriparatide was reported to increase bone density more than alendronate and to reduce fractures by 90% in patients with GIOP. The ACR currently recommends bisphosphonates as first-line therapy, with teriparatide reserved for those at highest risk or in whom bisphosphonate therapy fails. Denosumab is a potentially effective option but is not yet approved by the FDA for this condition. The dose regimens for these agents are discussed in the chapter on osteoporosis (see Chapter 8).

10. When should gonadal steroids be considered?

Gonadal steroids may be considered, usually in combination with other agents, in postmenopausal women and hypogonadal men (men with low serum testosterone).

KEY POINTS 1: PREVALENCE AND PATHOPHYSIOLOGY OF GIOP

1. Glucocorticoid-induced osteoporosis is the most common type of secondary osteoporosis.
2. High doses and prolonged use of glucocorticoids produce greater risk, but all doses of oral glucocorticoids and even inhaled steroids increase the risk of osteoporotic fractures.
3. Glucocorticoid-induced osteoporosis results from suppressed bone formation, impaired osteocyte function, and enhanced bone resorption, accounting for the rapid bone loss and disproportionately low bone strength seen in glucocorticoid-treated patients.

KEY POINTS 2: PREVENTION AND TREATMENT OF GIOP

1. Bone mineral density (BMD) testing is recommended before initiation of glucocorticoid therapy in patients who will receive $\geq$ 5 to 7.5 mg/day of prednisone (or equivalent) for $\geq$ 3 months, duration and every 6 to 12 months thereafter as long as glucocorticoid therapy is continued.
2. The American College of Rheumatology recommends treatment for all patients who will be treated or have been treated with $\geq$ 7.5 mg/day of prednisone (or equivalent) for $\geq$ 3 months. The National Osteoporosis Foundation recommends treatment at $\geq$ 5 mg daily of prednisone.
3. Bisphosphonates are recommended as first-line agents for GIOP, and teriparatide is usually reserved for the highest risk patients or those in whom bisphosphonate therapy fails.

BIBLIOGRAPHY

Adachi JD, Olszynski WP, Hanley DA, et al: Management of corticosteroid-induced osteoporosis, *Semin Arthritis Rheum* 29:228–251, 2000.

Amin S, LaValley MP, Simms RW, et al: The comparative efficacy of drug therapies used for the management of corticosteroid-induced osteoporosis: a meta-regression, *J Bone Miner Res* 17:1512–1526, 2002.

Canalis E: Glucocorticoid-induced osteoporosis, *Curr Opin Endocrinol Diabetes* 7:320–324, 2000.

Devogelaer JP: Glucocorticoid-induced osteoporosis: mechanisms and therapeutic approach, *Rheum Dis Clin North Am* 32:733–756, 2006.

Gourlay M, Franceschini N, Sheyn Y: Prevention and treatment strategies for glucocorticoid induced osteoporotic fractures, *Clin Rheumatol* 26:144–153, 2007.

Grossman JM, Gordon R, Ranganath VK, et al: American College of Rheumatology 2010. Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis, *Arthritis Care Res (Hoboken)* 62:1515–1526, 2010.

Hanson KE, Wilson HA, Zapalowski C, et al: Uncertainties in the prevention and treatment of glucocorticoid-induced osteoporosis, *J Bone Min Res* 26:1989–1996, 2011.

Isreal E, Banerjee TR, Fitzmaurice GM, et al: Effects of inhaled glucocorticoids on bone density in premenopausal women, *N Engl J Med* 345:941–947, 2001.

Rubin MR, Bilezikian JP: The role of parathyroid hormone in the pathogenesis of glucocorticoid-induced osteoporosis: a re-examination of the evidence, *J Clin Endocrinol Metab* 87:4033–4041, 2002.

Saag KG, Shane E, Boonen S, et al: Teriparatide or alendronate in glucocorticoid-induced osteoporosis, *N Engl J Med* 357:2028–2039, 2007.

Sambrook PN: How to prevent steroid induced osteoporosis, *Ann Rheum Dis* 64:176–178, 2007.

Van Staa TP, Leufkens HGM, Abenhaim L, et al: Use of oral corticosteroids and risk of fractures, *J Bone Miner Res* 15:993–1000, 2000.

Van Staa TP, Leufkens HGM, Cooper C: Use of inhaled corticosteroids and risk of fractures, *J Bone Miner Res* 16:581–588, 2001.

Weinstein RS: Glucocorticoid induced bone loss, *N Engl J Med* 365:62–70, 2011.

CHAPTER 10

MEASUREMENT OF BONE MASS

William E. Duncan

1. Why measure bone mass?

Bone mass, measured by bone mineral densitometry, is used to establish the diagnosis of osteoporosis, to predict the risk of subsequent fractures, and to monitor changes in bone mass during therapy for osteoporosis. No clinical finding, laboratory test, or other radiographic examination is able to reliably identify individuals with osteoporosis. Conventional radiographic techniques are not sensitive enough to diagnose osteoporosis as they do not reliably detect bone loss until 30% to 40% of bone mineral is lost. Although bone densitometry may determine low bone mass, it cannot identify the etiology of the bone loss. Thus, bone densitometry must be used with a complete clinical evaluation, laboratory testing, and other diagnostic studies to determine the cause of and the most appropriate treatment for osteoporosis.

2. Is bone mass the only parameter that determines whether a bone will fracture?

Although decreased bone mass is the primary determinant of whether a bone will fracture, bone architecture and geometry are also important factors contributing to bone strength. The relationship between bone mass and fracture risk is more powerful than the relationship between serum cholesterol concentration and coronary artery disease. A decrease in bone mass of one standard deviation (SD) doubles the risk of fracture. In comparison, a decrease in the cholesterol concentration of 1 SD increases the risk of coronary artery disease by only 20% to 30%.

3. How does bone densitometry measure bone mass?

All bone densitometry techniques determine the amount of calcium present in bone by utilizing an ionizing radiation source (either from a radionuclide or from an x-ray tube) and a radiation detector. Bone densitometry is based on the principle that bone absorbs radiation in proportion to its bone mineral content. The bone mineral content of the bone (or a region of interest within a bone) is then divided by the measured area. The result is the bone mineral density (BMD), expressed in grams per unit area (g/cm^2). This BMD is not a true volumetric density (g/cm^3) but rather an areal density. In this chapter, bone mass and BMD are used interchangeably.

4. What techniques are available to measure bone mass?

The techniques available to measure bone mass include dual-energy x-ray absorptiometry (DXA) and quantitative computed tomography (QCT). Central DXA measures bone mass of the hip, spine, and whole skeleton, whereas peripheral DXA measures bone mass of the forearm only. Another technique, quantitative ultrasound (QUS), transmits ultrasound waves through the bone. The more complex and denser the bone structure, the greater will be the attenuation of the ultrasound wave. Thus, QUS may determine both density and structure of the bone. Table 10-1 compares these bone mass measurement techniques.

5. What is the preferred method for measuring bone mass?

DXA is the preferred method for measuring bone mass. It has the best correlation with fracture risk, requires relatively short scanning times ($<$ 5 minutes), determines bone mass in all areas of the skeleton with high accuracy and reproducibility (precision), and is associated with a small radiation exposure. DXA does not require replacement of the radiation source. Drawbacks of DXA are the cost of the

TABLE 10-1. COMPARISON OF BONE MASS MEASUREMENT TECHNIQUES

CHARACTERISTIC	CENTRAL DXA	PERIPHERAL DXA	QCT	QUS
Diagnosis: Use with WHO classification	Yes	Limited	No	No
Fracture prediction	Yes	Yes	Yes	Yes
Use with FRAX	Yes	No	No	No
Monitoring	Yes	No	Yes	No
Ionizing radiation	Yes	Yes	Yes	No
Good precision	Yes	Yes	Yes	No
Cost	Moderate	Low	High	Low
Portable	No	Yes	No	Yes
Reference range database	Large	Limited	Limited	Limited

DXA, dual-energy x-ray absorptiometry; QCT, quantitative computed tomography; QUS, quantitative ultrasound; WHO, World Health Organization.

equipment, exposure of patients to ionizing radiation (no matter how small a dose), and cost of the test (in comparison with some other methods).

6. What are the indications for the measurement of bone mass?

Widespread BMD screening for osteoporosis is not recommended at this time. The United States Preventive Services Task Force (USPSTF) has recommended screening for osteoporosis of women of all racial and ethnic groups age 65 or greater and in women 50 to 65 years of age whose 10-year risk for any osteoporotic fracture is 9.3% or greater (determined by the FRAX fracture assessment tool; see later). The USPSTF concluded that for men, evidence of the benefits of screening for osteoporosis is lacking and the balance of benefits and harms cannot be determined.

The National Osteoporosis Foundation (NOF) recommends BMD testing for the following:

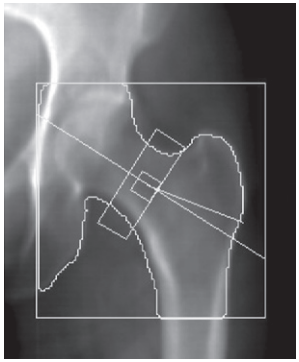
- Women age 65 and older and men age 70 and older regardless of clinical risk factors
- Younger postmenopausal women and men age 50 to 69 for whom there is concern about the patient's clinical risk factor profile
- Women in the menopausal transition if there is a specific risk factor associated with increased fracture risk, such as low body weight, prior low-trauma fracture, or high-risk medication
- Adults who have a fracture after age 50
- Adults who have a condition (e.g., rheumatoid arthritis) or are taking a medication (e.g., glucocorticoids in a daily dose $\geq$ 5 mg prednisone or equivalent for $\geq$ 3 months) associated with low bone mass or bone loss
- Anyone being considered for pharmacologic therapy for osteoporosis
- Anyone being treated for osteoporosis, to monitor treatment effect
- Anyone not receiving therapy in whom evidence of bone loss would lead to treatment

Postmenopausal women who are discontinuing estrogen should be considered for bone density testing.

In addition, DXA is also being increasingly used to study bone status in pediatric and adolescent patients, to perform vertebral fracture assessment, and to determine body composition.

7. What do bone mass measurements mean?

The bone densitometry report gives the absolute bone mass measurements (in g/cm^2), which do not provide clinically useful information unless these values are compared with those of reference populations. To do this, the BMD report provides additional pieces of information: a T-score and a Z-score (Fig. 10-1).



98 x 101
Neck: 48 x 15
HAL: 96 mm

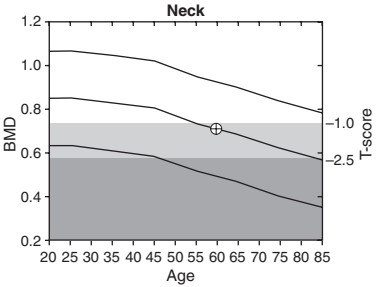
Scan Information:

Scan Date: September 14, 2008 ID: A09140803
Scan Type: x Left Hip
Analysis: November 30, 2008 12:20 Version 13.0 Left Hip
Operator:
Model: Discovery A (S/N 83709)
Comment

DXA Results Summary:

Region	Area (cm^2)	BMC (g)	BMD (g/cm^2)	T–score	PR (%)	Z–score	AM (%)
Neck	**4.85**	**3.46**	**0.715**	**–1.2**	**84**	**0.1**	**101**
Total	30.87	27.30	0.884	–0.5	94	0.5	107

Total BMD CV 1.0%
WHO Classification: Osteopenia



FRAX® WHO Fracture Risk Assessment Tool

10–year Fracture Risk[1]

Major Osteoporotic Fracture	**20%**
Hip Fracture	**1.8%**

Reported Risk Factors:
US (Caucasian), Neck BMD=0.715, BMI:22.1, parental fracture, smoking, rheumatoid arthritis, alcohol use

[1]FRAX® Version 3.05. Fracture probability calculated for an untreated patient. Fracture probability may be lower if the patient has received treatment.

Comment:
All treatment decisions require clinical judgement and consideration of individual patient factors, including patient preferences, comorbidities, previous drug use and risk factors not captured in the FRAX model (e.g. frailty, falls, vitamin D deficiency, increased bone turnover, interval significant decline in BMD).

HOLOGIC®

Figure 10-1. Printout of dual-energy x-ray absorptiometry scan of the hip (personal data deleted).

8. What are T-scores?

The T-score is the number of SDs that the patient's BMD is above or below the mean BMD of a normal young adult gender-matched population. This population represents the optimal or peak BMD for the patient. A patient whose BMD is 1 SD below that of the young reference population has a T-score of −1.0. At the spine, 1 SD represents about 10% of the bone mass. Thus, someone with a T-score of −1.0 has lost about 10% of his or her bone mass or has fallen short by 10% of achieving an optimal peak bone mass. Because the T-score is a good predictor of future fractures, it is used to diagnose osteoporosis.

9. What do Z-scores tell us about the patient?

The Z-score is the number of SDs that the patient's BMD is above or below the mean BMD of an age- and gender-matched population. The Z-score compares a patient's BMD with that of other individuals of the same age. A Z-score less than expected for a given individual (e.g., less than −2.0) indicates that the individual has lower BMD than is normal for his/her age. This finding should prompt a search for associated medical or lifestyle conditions (current or in the past) that may have accelerated bone loss or prevented the patient from reaching peak bone mass.

10. What are the diagnostic classifications for bone mass?

In 1994, the World Health Organization (WHO) developed criteria for the diagnosis of osteoporosis and osteopenia in postmenopausal white women and older men using T-scores calculated from DXA BMD measurements from the spine, hip, or forearm. A T-score greater than −1.0 defines normal BMD, a T-score between −1.0 and −2.5 defines low BMD (or osteopenia), and a T-score less than −2.5 defines osteoporosis. Established (or severe) osteoporosis is defined as a T-score less than −2.5 and the presence of one or more osteoporotic fractures.

11. How should the WHO criteria be used?

The WHO classification criteria were derived from data from white postmenopausal women. Thus, these definitions should be applied to other ethnic groups or to men with caution. The WHO criteria were not intended to apply to premenopausal women, men younger than 50 years, or children. Also, these criteria were developed from studies using DXA. Therefore, applying the WHO criteria to bone mass measurements obtained with other technologies (such as QCT and QUS) may be misleading. Finally, the WHO definitions for osteopenia and osteoporosis were developed as general guidelines for diagnosis and were not intended to require or restrict therapy for individual patients.

12. How are bone density measurements interpreted in men and non-Caucasians?

The criteria by which a densitometric diagnosis of osteoporosis can be made in males and in non-Caucasians is extremely controversial because it is unclear whether fractures occur at the same BMD values in men and non-Caucasians as in Caucasian women. Pending additional studies, the International Society for Clinical Densitometry (ISCD) has recommended that osteoporosis in these groups be diagnosed at or below a T-score of −2.5 using a gender-adjusted but not a race-adjusted normative database. The database is programmed into the densitometer. The clinician needs to understand which database is being used to generate the T- and Z-scores.

13. Can bone densitometry determine vertebral fractures?

Vertebral fractures are the most common of all osteoporotic fractures, occurring in 15% of women 50 to 59 years of age and in 50% of women 85 years or older. The majority of these vertebral fractures are classified as mild, with a reduction in height of not more than 20% to 25%. They may be asymptomatic, often occur in the absence of specific trauma, and frequently do not come to clinical attention or are underreported when radiographic studies are performed. The presence of these mild fractures increases the risk of subsequent fractures. The image generated by routine spine DXA should not be used to diagnose vertebral fractures. Some DXA machines have a special program (Vertebral Fracture Assessment [VFA]) to image the thoracic and lumbar spine for the purpose of detecting these morphometric vertebral fracture deformities. The identification of a previously

unrecognized vertebral fracture may change diagnostic classification, assessment of fracture risk, and treatment decisions. Appropriate candidates for VFA include postmenopausal women or men with low bone mass (osteopenia) and at least one risk factor (see the ISCD website for a list of specific risk factors for men and women), women or men receiving long-term glucocorticoid therapy (equivalent to 5 mg or more of prednisone daily for 3 months or longer), and postmenopausal women or men with osteoporosis, if documentation of one or more vertebral fractures will alter clinical management.

14. How is fracture risk determined?

The WHO has developed the FRAX fracture risk assessment tool to determine the 10-year probability of a major osteoporotic fracture and the 10-year probability of hip fracture in men and women. This tool utilizes clinical risk factors and BMD at the femoral neck (or total hip BMD) when available. Treatment guidelines that rely exclusively or predominantly on a densitometric diagnosis of osteoporosis to select patients for treatment will miss many patients with T-scores greater than −2.5 who are at high risk for fracture and might benefit from pharmacologic therapy. Therefore, it is recommended that this tool be used for untreated postmenopausal women or men older than 50 years who have T-scores between −1.0 and −2.5, with no history of hip or vertebral fracture, and with a DXA-evaluable hip. The FRAX assessment tool is available at www.shef.ac.uk/FRAX and should be available soon on newer DXA scanners.

FRAX is intended for determining fracture risk for postmenopausal women and men age 50 and older. It should not be used in younger adults or children. The tool has not been validated in patients currently or previously treated with medications for osteoporosis. In such patients, clinical judgment must be exercised in interpreting FRAX scores. In the absence of femoral neck BMD, total hip BMD may be substituted. However, use of BMD from non-hip sites in the algorithm is not recommended because such use has not been validated.

15. Discuss how bone mass measurements are used to determine the need for treatment of osteoporosis.

The health-care provider should use information from bone mass testing in conjunction with knowledge of a patient's specific medical and personal history to determine the most appropriate treatment. BMD results should not be used as the sole determinant for treatment decisions. The National Osteoporosis Foundation recommends treatment of postmenopausal women and men age 50 and older with all of the following features:

- A hip or vertebral (clinical or morphometric) fracture
- A T-score ≤ -2.5 at the femoral neck or spine after appropriate evaluation to exclude secondary causes
- Low bone mass (T-score between −1.0 and −2.5 at the femoral neck or spine) and a 10-year probability of a hip fracture $\geq$ 3% or a 10-year probability of a major osteoporosis-related fracture $\geq$ 20% based on the U.S.-adapted FRAX assessment tool

Clinicians should use clinical judgment to treat patients at lower FRAX risk levels if additional risk factors are present.

16. Which bone(s) should be selected for measurement of bone mass?

It is possible to measure bone mass at several sites (Fig. 10-2). Measurement of bone mass at any skeletal site has value in predicting fracture risk. However, the bone density of the hip is the best predictor of hip fractures (the osteoporotic fracture with the greatest mortality and morbidity). The bone mass of the hip also predicts fractures at other sites, as well as do bone mass measurements at those sites. Hip bone mass measurements are the only ones used by the FRAX assessment tool. For these reasons, the hip is the preferred site for measurement. Although there is significant concordance between skeletal sites in predicting bone mass, there is still enough discordance in bone mass at various sites that single bone mass measurements should not be relied on to diagnose osteoporosis. Thus, bone mass should be measured at both the hip and the spine, and the diagnosis of osteoporosis should be based on the lowest T-score.

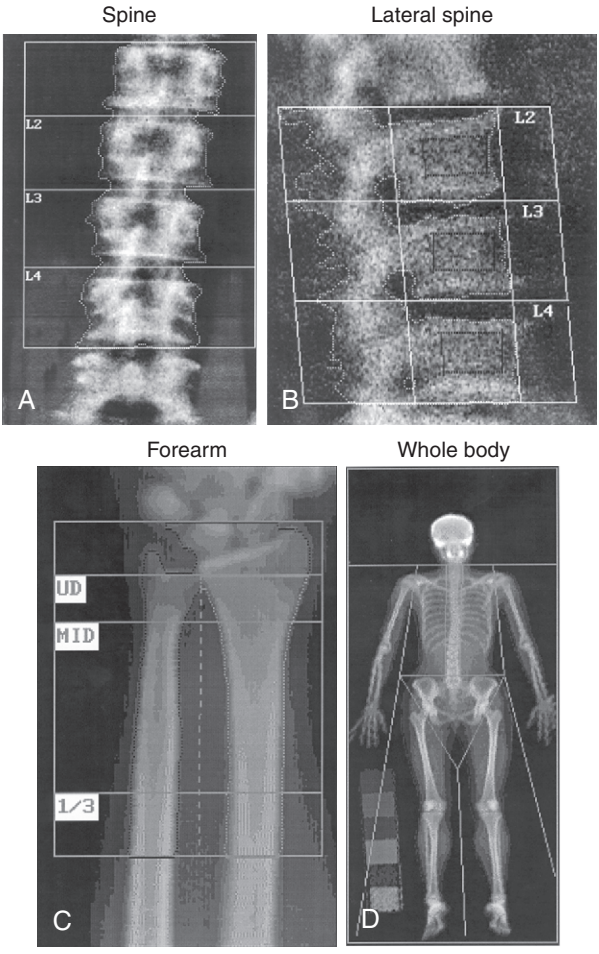


Figure 10-2. Images of several skeletal sites scanned by a dual-energy x-ray absorptiometry bone densitometer. (See Figure 10-1 for image of the hip.)

17. What is the role of bone mass measurements of the forearm?

Measurement of peripheral bone mass (e.g., the forearm) generally adds little to the evaluation of an individual with postmenopausal osteoporosis. However, the forearm appears to be the best site to assess the effects on bone of excess parathyroid hormone associated with primary hyperparathyroidism. In addition, measurement of forearm bone mass should be performed when the hip and spine cannot be accurately measured or when a patient is over the weight limit for the DXA table. The weight limit for most DXA machines is 300 pounds, although some newer machines can measure bone density in people who weigh up to 400 pounds. Peripheral bone mass measurements have not been shown to be useful for monitoring the effects of therapy for osteoporosis because changes in bone density occur very slowly at this site.

18. How often should bone mass measurements be repeated?

The frequency of bone density measurements is determined, in part, by the precision error (or reproducibility) of the technique. The precision of BMD measurements by DXA is approximately 1.0% for spine and 1% to 2% for the femoral neck. This means that the smallest difference between two BMD measurements that is significant is a change of 2.83% at the spine and 5.66% at the femoral neck. In contrast, the average amount of early postmenopausal bone loss from the spine is 1% to 2% per year. Therefore, to obtain statistically meaningful BMD results, postmenopausal women should not undergo routine DXA measurements of the spine more often than once every 2 years unless accelerated bone loss is suspected. Measurement of BMD every 6 months is recommended for patients in whom glucocorticoid therapy is being initiated for this reason. One study has indicated that the interval for repeat BMD measurements to screen for osteoporosis may be considerably longer than 2 years for older women with normal or near-normal bone mass on initial screening.

19. What conditions limit the accuracy of bone mass measurements?

Degenerative changes, oral contrast agents used for other radiographic studies, and osteophytes all falsely elevate the measured spine bone density. Anatomic distortions such as lumbar disc disease, compression fractures, scoliosis, prior surgical intervention, and vascular calcifications in the overlying aorta also affect the accuracy of spine measurements. Likewise, previous surgery on the hip may alter bone mass at this site.

20. Interpret the BMD results from the four patients whose BMD scores are shown in the table. Each patient is a white postmenopausal woman.

Patient 1	T-score = −0.9	Z-score = +0.2
Patient 2	T-score = −2.0	Z-score = −0.9
Patient 3	T-score = −3.0	Z-score = −1.4
Patient 4	T-score = −3.0	Z-score = −2.5

Interpretation:

- Patient 1 has a normal bone mass.
- Patient 2 has a low bone mass (osteopenia) that is appropriate for her age because her Z-score is greater than −2.0.
- Patient 3 has osteoporosis, and this bone loss is appropriate for her age.
- Patient 4 has osteoporosis with bone loss that is greater than expected for her age. This bone density finding should prompt a thorough evaluation to rule out secondary causes of osteoporosis (such as hyperthyroidism, malabsorption, Cushing's syndrome, hypogonadism, vitamin D deficiency, excessive alcohol consumption, celiac disease, and use of certain drugs).

KEY POINTS 1: MEASUREMENT OF BONE MASS

1. Direct measurement of bone mass is the only method to diagnose osteoporosis. No clinical finding, laboratory test, or other radiographic examination can reliably identify people with low bone mass.
2. The preferred technique for diagnosis of osteoporosis is DXA of the spine and hip.
3. The diagnosis of osteoporosis is made using the WHO criteria of a T-score less than or equal to −2.5.
4. Assessment of the probability for fracture using the FRAX® tool is necessary to identify those patients with osteopenia who might benefit from treatment.
5. BMD measurement of the forearm is the study of choice for patients with hyperparathyroidism.

WEBSITES

1. National Osteoporosis Foundation: http://www.nof.org, accessed 8-29-12.
2. International Society for Clinical Densitometry: http://www.iscd.org, accessed 8-29-12.
3. The FRAX® Fracture Assessment tool: www.shef.ac.uk/FRAX, accessed 8-29-12.

BIBLIOGRAPHY

Binkley N, Schmeer P, Wasnich R, et al: What are the criteria by which a densitometric diagnosis of osteoporosis can be made in males and noncaucasians? *J Clin Densitom* 5(Suppl):S19, 2002.

Binkovitz LA, Sparke P, Henwood MJ: Pediatric DXA: clinical applications, *Pediatr Radiol* 37:625, 2007.

Blake G, Fogelman I: Dual energy x-ray absorptiometry and its clinical applications, *Semin Musculoskelet Radiol* 6:207, 2002.

Blake GM, Fogelman I: The clinical role of dual energy X-ray absorptiometry, *Eur J Radiol* 71:406, 2009.

Cummings SR, Bates D, Black D: Clinical use of bone densitometry: scientific review, *JAMA* 288:1889, 2002.

Dasher LG, Newton CD, Lenchik L: Dual x-ray absorptiometry in today's clinical practice, *Radiol Clin N Am* 48:541, 2010.

Diacinti D, Guglielmi G: Vertebral morphometry, *Radiol Clin N Am* 48:561, 2010.

Gourlay ML, Fine JP, Preisser JS, et al: Bone-density testing interval and transition to osteoporosis in older women, *N Engl J Med* 364:248, 2012.

Hamdy R, Petak S, Lenchik L: Which central dual x-ray absorptiometry skeletal sites and regions of interest should be used to determine the diagnosis of osteoporosis? *J Clin Densitrom* 5(Suppl):S11, 2002.

Kanis JA, Hans D, Cooper C: Interpretation and use of FRAX in clinical practice, *Osteoporos Int* 22:2395, 2011.

Lenchik L, Kiebzak G, Blunt B: What is the role of serial bone mineral density measurements in patient management? *J Clin Densitom* 5(Suppl):S29, 2002.

Lewiecki EM: Bone densitometry and vertebral fracture assessment, *Curr Osteoporos Rep* 8:123, 2010.

Lewiecki EM, Laster AJ: Clinical applications of vertebral fracture assessment by dual-energy x-ray absorptiometry, *J Clin Endocrinol Metab* 91:4215, 2006.

Miller P: Bone mineral density—clinical use and application, *Endocrinol Metab Clin North Am* 32:159, 2003.

Miller PD, Leonard MB: Clinical use of bone mass measurements in adults for the assessment and management of osteoporosis. In Favus MJ, editor: *Primer on the metabolic bone diseases and disorders of mineral metabolism*, New York, 2006, Raven Press, p 150.

Miller PD, Zapalowski C, Kulak CA, et al: Bone densitometry: the best way to detect osteoporosis and to monitor therapy, *J Clin Endocrinol Metab* 84:1867, 1999.

Shagam J: Bone densitometry: an update, *Radiol Technol* 74:321, 2003.

Siris ES, Baim S, Nattiv A: Primary care use of FRAX®: absolute fracture risk assessment in postmenopausal women and older men, *Postgrad Med* 122:82, 2010.

U.S. Preventive Services Task Force: Screening for Osteoporosis: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med* 154:356, 2011.

WHO Study Group: Assessment of fracture risk and its application to screening for postmenopausal osteoporosis, *WHO Tech Rep Ser 843*, 1994. World Health Organization: Geneva.

CHAPTER 11

OSTEOMALACIA, RICKETS, AND VITAMIN D INSUFFICIENCY

William E. Duncan

1. What are osteomalacia and rickets?

Osteomalacia and rickets are terms that describe the clinical, histologic, and radiologic abnormalities of bone that are associated with more than 50 diseases and conditions. Osteomalacia is a disorder of mature (adult) bone, whereas rickets occurs in growing bone. Although rickets and osteomalacia were initially viewed as distinct clinical entities, the same pathologic processes may result in either disorder. In both conditions, mineralization of newly formed osteoid (the bone protein matrix) is inadequate or delayed. In individuals with rickets, defective mineralization occurs in both bones and cartilage of the epiphyseal growth plates and is associated with growth retardation and skeletal deformities that are not typically seen in adults with osteomalacia.

2. Why is it important to know about osteomalacia and rickets?

In the United States at the beginning of the 20th century, rickets due to a deficiency of vitamin D was common in urban areas. In the 1920s, rickets was virtually eliminated by an appreciation of the antirachitic properties of sunlight and the use of cod liver oil (which contains vitamin D). However, with the development of effective treatments for previously fatal diseases that affect vitamin D metabolism (such as chronic renal failure) and with an improved understanding of both vitamin D and mineral metabolism, many additional syndromes with osteomalacia or rickets as a feature have emerged. Many later studies have demonstrated that undiagnosed vitamin D deficiency or insufficiency is common in the United States, and for a significant number of adult women with osteoporosis, vitamin D insufficiency may be an unsuspected component of their bone loss.

3. List the causes of osteomalacia and rickets

The primary abnormality of bone in patients with either osteomalacia or rickets is defective mineralization of the bone matrix. The major mineral in bone is hydroxyapatite—$Ca_{10}(PO_4)_6(OH)_2$. Thus, any disease that results in decreased availability to bone of either calcium or phosphorus may result in osteomalacia or rickets (Table 11-1). Causes of osteomalacia and rickets fall into three categories: (1) disorders associated with abnormalities of vitamin D metabolism or action that limit the availability of calcium for mineralization of bone, (2) disorders associated with abnormalities of phosphorus metabolism, and (3) a small group of disorders in which there is normal vitamin D and mineral metabolism.

4. Describe how vitamin D is synthesized and metabolized.

Serum vitamin D comes from two sources: dietary intake and conversion by ultraviolet (UV) irradiation of 7-dehydrocholesterol or ergosterol in the skin. Vitamin D is then transported through the blood to the liver, where it is converted to 25-hydroxyvitamin D (25-OHD) by the hepatic 25-hydroxylase enzyme. The 25-OHD is then converted in the kidney to the active hormone, 1,25-dihydroxyvitamin D, by the renal 1α-hydroxylase enzyme. This active vitamin D metabolite has effects in many tissues, including the intestine (increases calcium absorption), the kidney (increases calcium reabsorption), the parathyroid glands (decreases parathyroid hormone [PTH] secretion), and bone (stimulates osteoblast maturation and bone matrix synthesis) (Fig. 11-1). Studies have now suggested possible other roles for vitamin D in cardiovascular and neurologic diseases, insulin resistance and diabetes, malignancies, autoimmune conditions, and infections. From an understanding of how vitamin D is metabolized, it is apparent that even when dietary intake and UV-mediated vitamin D synthesis are normal, vitamin D deficiency may occur in association with severe malabsorptive, renal, or liver disease.

TABLE 11-1. CONDITIONS ASSOCIATED WITH OSTEOMALACIA AND RICKETS

CONDITION	PRIMARY MECHANISM*
Abnormal Vitamin D Metabolism or Action	
Nutritional deficiency	Vitamin D deficiency
Malabsorption	Vitamin D deficiency
Primary biliary cirrhosis	Malabsorption of vitamin D
Chronic renal disease	Impaired 1α-hydroxylation of 25-hydroxyvitamin D
Chronic liver disease	Impaired 25-hydroxylation of vitamin D
Vitamin D–dependent rickets (VDDR) type I	1α-hydroxylase deficiency
VDDR type II	Mutation of the vitamin D receptor gene
Drugs (phenytoin, barbiturates, cholestyramine)	Increased catabolism and/or excretion of vitamin D
Phosphate Deficiency or Renal Phosphate Wasting	
Diminished phosphate intake	Phosphate deficiency
Excessive aluminum hydroxide intake	Increased binding of intestinal phosphate
X-linked hypophosphatemic rickets	PHEX mutation causing phosphate wasting
Tumor-induced osteomalacia	Urinary phosphate wasting caused by fibroblast growth factor-23
Miscellaneous renal tubular defects (renal tubular acidosis, Fanconi's syndrome)	Renal phosphate transport defect
Normal Vitamin D and Phosphate Metabolism	
Hypophosphatasia	Alkaline phosphatase deficiency
Drugs (fluoride, aluminum, high-dose etidronate)	Inhibition of mineralization or stimulation of matrix synthesis
Osteogenesis imperfecta	Abnormal bone collagen
Fibrogenesis imperfecta ossium	Defective bone matrix

*Although only one mechanism for osteomalacia or rickets is given, other mechanisms also may contribute to the bone disease.

5. Discuss the disease processes that interfere with the metabolism of vitamin D.

Clinically apparent vitamin D deficiency is rarely seen in the United States except when exposure to sunlight and intake of vitamin D–fortified milk and other dairy products are limited. However, many elderly Americans are at risk for occult vitamin D deficiency or insufficiency because of sun avoidance, sunscreen use, an age-related decrease in dermal vitamin D synthesis, impaired hepatic and renal vitamin D hydroxylation, and diminished intestinal responsiveness to 1,25-dihydroxyvitamin D. Celiac disease or sprue, regional enteritis, intestinal bypass surgery, partial gastrectomy, chronic liver disease, primary biliary cirrhosis, pancreatic insufficiency, chronic renal failure, and certain medications have also been associated with the development of osteomalacia.

6. List genetic disorders that interfere with vitamin D synthesis or action.

Two extremely rare genetic syndromes are also associated with rickets. Vitamin D–dependent rickets (VDDR) type I (also called pseudovitamin D deficiency rickets) is caused by an almost complete absence of renal 25-hydroxyvitamin D–1α-hydroxylase activity. VDDR type II results from a mutation of the vitamin D receptor gene that causes end-organ resistance to 1,25-dihydroxyvitamin D and lack of vitamin D action.

7. What conditions associated with abnormalities of phosphate metabolism result in osteomalacia or rickets?

Nutritional phosphate deficiency, decreased intestinal phosphate absorption due to ingestion of phosphate binders (such as aluminum hydroxide), or renal phosphate wasting may result in osteomalacia

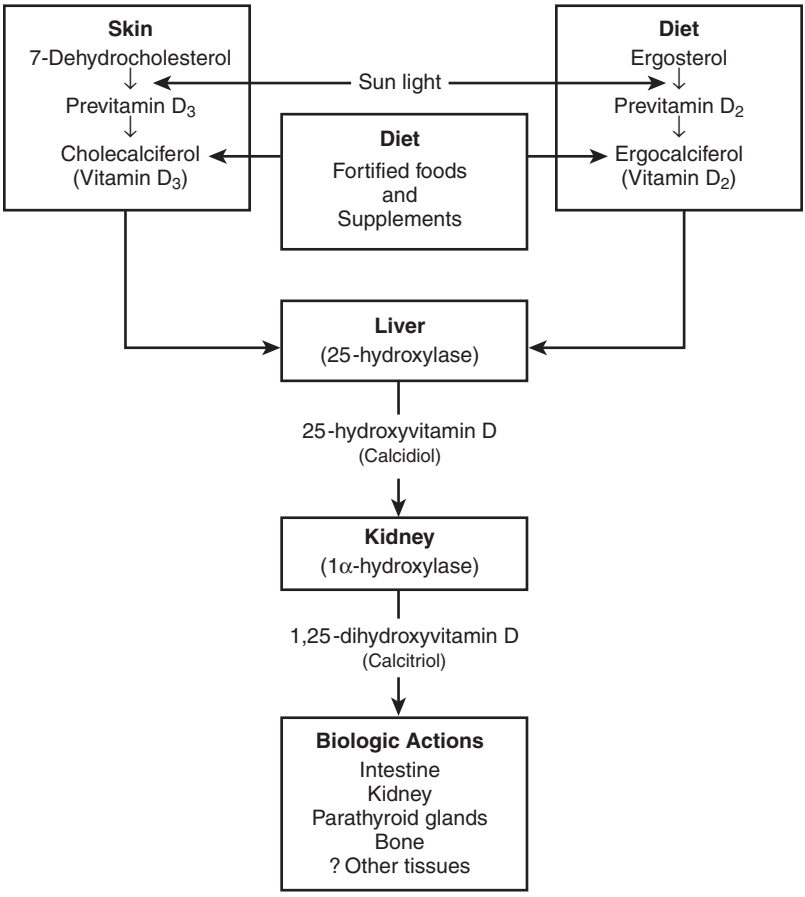


Figure 11-1. Synthesis and metabolism of Vitamin D.

or rickets. Hypophosphatemic rickets (also called vitamin D–resistant rickets) is a syndrome of renal phosphate wasting and decreased renal synthesis of 1,25-dihydroxyvitamin D. Hypophosphatemic rickets, which is transmitted as an X-linked dominant trait, is the most common inherited form of rickets. Another syndrome, tumor-induced osteomalacia, is observed when usually benign neoplasms of mesenchymal origin secrete fibroblast growth factor-23 (FGF-23), which promotes renal phosphate wasting and produces osteomalacia.

8. Does chronic renal failure cause osteomalacia and rickets?

Chronic renal failure is associated with several bone diseases: osteomalacia or rickets, adynamic bone, osteitis fibrosa cystica (due to long-standing secondary hyperparathyroidism), and a combination of both osteomalacia and osteitis fibrosa cystica (termed *mixed renal osteodystrophy*). Rickets or osteomalacia is usually a late finding in the course of the kidney disease and is rarely seen before patients begin dialysis. Rickets or osteomalacia associated with chronic renal failure is caused by decreased circulating concentrations of 1,25-dihydroxyvitamin D, by aluminum

intoxication from aluminum-containing antacids used as phosphate binders or an aluminum-contaminated dialysate, and possibly by the chronic metabolic acidosis associated with the renal failure.

9. What signs and symptoms are associated with osteomalacia?

In adults, osteomalacia may be asymptomatic. When symptomatic, osteomalacia may manifest as diffuse skeletal pain (often aggravated by physical activity or palpation), muscle weakness, and sometimes muscle wasting. The muscle weakness often involves the proximal muscles of the lower extremities and may result in a waddling gait and difficulties rising from a chair or climbing stairs. The bone pain is described as dull and aching and is usually located in the back, hips, knees, and legs and at sites of fractures. Fractures may result from only minor trauma.

10. Describe the clinical findings in rickets.

Because of impaired calcification of cartilage at the growth plates in children with rickets, the clinical manifestations of rickets are significantly different from those of osteomalacia. Widening of the metaphyses (the growth zones between the epiphysis and diaphysis), slowed growth, and various skeletal deformities are prominent in this condition. The effects of rickets are greatest at sites where bone growth is most rapid. Because the rate of skeletal growth varies with age, the manifestations of rickets likewise vary. One of the earliest signs of rickets in infants is craniotabes (abnormal softness of the skull). In older infants and younger children, thickening of the forearm at the wrist and of the costochondral junctions (also known as the rachitic rosary) and Harrison's groove, a lateral indentation of the chest wall at the sites of attachment of the diaphragm, may be present. In older children, bowing of the tibia and fibula may be observed. At any age, if rickets (or osteomalacia) is associated with hypocalcemia, paresthesias of the hands and around the mouth, muscle cramps, presence of Chvostek and Trousseau signs, tetany, and seizures may be evident.

11. What are the biochemical abnormalities seen with osteomalacia and rickets caused by vitamin D deficiency?

The laboratory abnormalities encountered with osteomalacia or rickets depend on the underlying defect or process causing the bone disease. To understand the biochemical abnormalities observed in conditions associated with abnormal vitamin D metabolism, an understanding of the body's response to hypocalcemia and knowledge of the vitamin D metabolic pathway are necessary. Thus, in patients with nutritional vitamin D deficiency or malabsorption, low vitamin D levels result in low or low-normal serum calcium concentrations, which stimulate increased PTH secretion (secondary hyperparathyroidism). This hyperparathyroid state, in turn, causes increased renal phosphate excretion, decreased serum phosphate, elevated serum alkaline phosphatase values, and reduced urinary calcium excretion.

12. What are the vitamin D metabolite concentrations associated with the diseases that interfere with vitamin D metabolism or action?

Depending on the abnormality of vitamin D metabolism, different vitamin D metabolite patterns may be observed. In nutritional vitamin D deficiency, 25-OHD levels are low. In VDDR type I, which results from a deficiency of the renal 25-hydroxyvitamin D-1α-hydroxylase enzyme, normal or increased serum 25-OHD and low or undetectable serum 1,25-dihydroxyvitamin D levels are observed. In contrast, in VDDR type II, which causes resistance of target organs to 1,25-dihydroxyvitamin D, the values of both 25-OHD and 1,25-dihydroxyvitamin D are elevated.

13. What radiographic findings are associated with osteomalacia and rickets?

The biochemical abnormalities associated with rickets and osteomalacia are usually evident before radiographic abnormalities are observed. The most common radiographic change in patients with osteomalacia is a reduction in bone mass. Pseudofractures (also called Looser's zones or Milkman's fractures) or complete fractures also may be observed. Pseudofractures are transverse radiolucent bands ranging from a few millimeters to several centimeters in length, usually perpendicular to the

surfaces of the bones. They are most often bilateral and are particularly common in the femur, pelvis, and small bones of the hands and feet. Patients with osteomalacia may have additional findings due to secondary hyperparathyroidism. Such findings include subperiosteal resorption of the phalanges, loss of the lamina dura of the teeth, widening of the spaces at the symphysis pubis and sacroiliac joints, and presence of brown tumors or bone cysts.

Certain radiographic abnormalities are observed primarily in children with rickets. These include fraying of the metaphyses of the long bones, widening of the unmineralized epiphyseal growth plates, and bowing of the legs. These skeletal deformities may persist into adulthood.

14. Discuss the histologic features of osteomalacia.

The two diagnostic histologic findings in osteomalacia are the presence of widened osteoid seams and increased mineralization lag time (the time necessary for newly deposited matrix to mineralize). The mineralization lag time is assessed clinically by administering two short courses of oral tetracycline several weeks apart before the bone biopsy is performed. Because tetracycline is deposited at the mineralization front in newly formed bone, the lag time may be determined by measuring the distance between the two fluorescent tetracycline bands in the biopsy specimen. Depending on the cause of the osteomalacia, hyperparathyroid bone changes may also be seen. Because of the varied clinical signs and symptoms, radiographic findings, and biochemical abnormalities associated with osteomalacia and rickets, none of these tests or findings is pathognomonic. The bone biopsy remains the gold standard in establishing the diagnosis of rickets and osteomalacia. The bone biopsy specimen must be evaluated by personnel specially trained in the interpretation of bone histology.

15. Describe the therapy for vitamin D deficiency.

The goal of therapy for patients with osteomalacia and rickets due to an abnormality of vitamin D metabolism is to correct the hypocalcemia and the deficiency of active vitamin D metabolites through the administration of calcium salts and vitamin D preparations. In the United States, vitamin D_2 (ergocalciferol), vitamin D_3 (cholecalciferol), 1,25-dihydroxyvitamin D (calcitriol), and calcitriol analogs are available. Each of these preparations has a different half-life and potency. The choice and dose of vitamin D preparation are determined by the underlying pathologic defect of vitamin D metabolism. For patients with vitamin D deficiency, treatment with ergocalciferol along with elemental calcium is often sufficient to heal the osteomalacia.

16. What are the treatments for osteomalacia and rickets not due to vitamin D deficiency?

Osteomalacia associated with VDDR type II, which involves profound resistance to the effects of vitamin D, must be treated with the most potent vitamin D metabolite, 1,25-dihydroxyvitamin D, in extraordinarily high doses, along with large doses of oral calcium. In severe cases, high-dose intravenous calcium infusions are required to heal the rickets. VDDR type I is also treated with calcitriol, but physiologic doses are usually sufficient. For treatment of hypophosphatemic rickets, both phosphate supplements and calcitriol are necessary to heal the bone disease. Tumor removal or irradiation is required to treat tumor-induced osteomalacia. In chronic renal failure with aluminum-induced osteomalacia, aluminum can be removed from affected bone with the chelating agent deferoxamine. The bone disease can then be treated with calcium and calcitriol. Osteomalacia associated with renal tubular acidosis is treated with vitamin D and bicarbonate to correct the acidosis.

17. Why is vitamin D insufficiency important, and how is it diagnosed?

The association of vitamin D insufficiency with low bone mass and an increased risk of hip fracture has only been recently appreciated. It is generally agreed that the optimal circulating 25-OHD concentration is at least 30 ng/mL (75 nmol/L). Various writers and medical organizations have defined vitamin D deficiency as a 25-OHD concentration of either 10 or 20 ng/mL (25 or 50 nmol/L). The 25-OHD level in vitamin D insufficiency falls between these deficient and sufficient levels. Inadequate vitamin D status is a common problem. Data from the National Health and Nutrition Examination Survey (2001-2004) population demonstrated that only 23% had circulating concentrations of 25-OHD

above 30 ng/mL, and 6% had values less than 10 ng/mL. As circulating 25-OHD concentrations decrease from sufficient levels, there is a growing negative impact on skeletal health. It therefore seems prudent to provide vitamin D supplementation to individuals with circulating 25-OHD levels less than 30 ng/mL.

18. What are the complications of treatment with vitamin D_2 or vitamin D metabolites?

When high doses of vitamin D_2 or one of the potent vitamin D metabolites are used, it is important to monitor carefully for the development of hypercalcemia. Mild hypercalcemia may be asymptomatic. However, severely hypercalcemic patients may complain of anorexia, nausea, vomiting, weight loss, headache, constipation, polyuria, polydipsia, and altered mental status. Impaired renal function, nephrocalcinosis, nephrolithiasis, and even death may eventually ensue. If vitamin D intoxication occurs, all calcium supplements and vitamin D preparations must be discontinued immediately, and therapy for hypercalcemia instituted.

KEY POINTS 1: OSTEOMALACIA, RICKETS, AND VITAMIN D INSUFFICIENCY

1. Osteomalacia and rickets are disorders resulting in inadequate or delayed mineralization of bone.
2. Osteomalacia occurs in mature bone, whereas rickets occurs in growing bone. Thus the clinical and radiographic findings of these two conditions differ.
3. The causes of osteomalacia and rickets fall into three categories: (1) disorders associated with abnormal vitamin D metabolism or action, (2) disorders associated with abnormal phosphate metabolism, and (3) a small group of disorders with normal vitamin D and mineral metabolism.
4. Vitamin D insufficiency is common in the United States and has a negative impact on skeletal health.

BIBLIOGRAPHY

Adams JS, Hewison M: Update in vitamin D, *J Clin Endocrinol Metab* 95:471, 2010.

Berry JL, Davies M, Mee AP: Vitamin D metabolism, rickets, and osteomalacia, *Semin Musculoskelet Radiol* 6:173, 2002.

Carpenter TO: The expanding family of hypophosphatemic syndromes, *J Bone Miner Metab,* 30:1, 2012.

Demay MB: Rickets caused by impaired vitamin D activation and hormone resistance: pseudovitamin D deficiency rickets and hereditary vitamin D resistant rickets. In Favus MJ, editor: *Primer on the metabolic bone diseases and disorders of mineral metabolism*, 6, Washington, DC, 2006, American Society for Bone and Mineral Research, p 338.

Ginde AA, Liu MC, Camargo Jr CA: Demographic differences and trends of vitamin D insufficiency in the US population, 1988-2004, *Arch Intern Med* 169:626, 2009.

Holick MF, Brinkley NC, Bischoff-Ferrari HA, et al: Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline, *J Clin Endocrinol Metab* 96:1911, 2011.

Holick MF, Garabedian M: Vitamin D: photobiology, metabolism, mechanism of action and clinical applications. In: Favus MJ, editor: *Primer on the metabolic bone diseases and disorders of mineral metabolism*, ed 6, Washington, DC, 2006, American Society for Bone and Mineral Research, p 106.

Holick MF: Resurrection of vitamin D deficiency and rickets, *J Clin Invest* 116:2062, 2006.

Holick MF: Vitamin D deficiency, *N Engl J Med* 357:266, 2007.

Jan de Beur SM, Tumor-induced osteomalacia. In Favus MJ, editor: *Primer on the metabolic bone diseases and disorders of mineral metabolism*, ed 6, Washington, DC, 2006, American Society for Bone and Mineral Research, p 345.

Malloy PJ, Feldman D: Genetic disorders and defects in vitamin D action, *Endocrinol Metab Clin North Am* 39:333, 2010.

Pettifor JM: Nutritional and drug-induced rickets and osteomalacia. In Favus MJ, editor: *Primer on the metabolic bone diseases and disorders of mineral metabolism*, ed 6, Washington, DC, 2006, American Society for Bone and Mineral Research, p 330.

Rosen CJ: Vitamin D insufficiency, *N Engl J Med* 364:248, 2011.

Thacher TD, Clarke BL: Vitamin D insufficiency, *Mayo Clin Proc* 86:50, 2011.

Wolinsky-Friedland M: Drug-induced metabolic bone disease, *Endocrinol Metab Clin North Am* 24:395, 1995.

CHAPTER 12

PAGET'S DISEASE OF BONE

William E. Duncan

1. What is Paget's disease of bone?

Paget's disease affects approximately 1.5 million people in the United States. It is characterized by abnormal bone architecture resulting from an imbalance between osteoblastic bone formation and osteoclastic bone resorption. Skeletal remains indicate that Paget's disease first appeared in Western European populations during the Roman period. Sir James Paget first described this disease in 1876, and he called the condition osteitis deformans. We now know that Paget's disease of bone is not an inflammation of bone (osteitis) and only rarely results in deformity.

2. Discuss how Paget's disease is diagnosed.

The diagnosis of Paget's disease is generally based on a combination of clinical manifestations, radiographic signs, and characteristic biochemical changes. Although histologic examination of pagetic bone is diagnostic, a bone biopsy is often unnecessary. Bone biopsy should be performed when the diagnosis of Paget's disease is unclear or when osteogenic sarcoma or metastatic carcinoma must be excluded.

3. What are the clinical manifestations of Paget's disease?

Most patients (70%-80%) with Paget's disease are asymptomatic. This disorder is often suspected from radiographs performed for other reasons or from an unexpected elevation of the serum alkaline phosphatase concentration. The most common symptom of Paget's disease is bone or joint pain. The pain is often described as dull and aching. Other manifestations of Paget's disease, such as headache, bone deformity, skull enlargement, fracture, change in skin temperature over an involved bone, high-output congestive heart failure, and entrapment neuropathies that may cause hearing loss or other neurologic deficits, are much less common (Box 12-1). Neurologic deficits may arise from bony impingement on the brain or cranial nerves exiting from the skull, spinal nerve entrapment, or direct pressure of pagetic

BOX 12–1. COMPLICATIONS ASSOCIATED WITH PAGET'S DISEASE OF BONE

- Bone pain
- Bone deformity and enlargement
- Secondary osteoarthritis adjacent to pagetic bone
- Neurologic abnormalities:
  - Spinal stenosis
  - Hearing loss and other cranial nerve palsies
  - Radiculopathy
- Obstructive hydrocephalus
- Cardiovascular complications:
  - High-output cardiac failure
  - Vascular and aortic valve calcifications
- Fracture
- Malignant transformation
- Immobilization hypercalcemia

vertebrae on the spinal cord. Bone deformity is usually seen in patients with long-standing Paget's disease. Most commonly, the skull, clavicles, and long bones are deformed and exhibit both an increase in size and an abnormal contour. There is speculation that Ludwig van Beethoven's hearing loss, headaches, and progressive hyperostosis frontalis were the results of advanced Paget's disease of bone.

4. What disorders are associated with Paget's disease of bone?

Several disorders are more prevalent in patients with Paget's disease than in unaffected individuals. They include arthritis, fractures, primary hyperparathyroidism, osteoporosis, thyroid disease, and kidney stones.

5. What are the three phases of Paget's disease of bone?

Paget's disease progresses through three distinct phases. The initial phase is an osteolytic phase characterized by predominantly osteoclastic bone resorption. Approximately 1% to 2% of patients exhibit this purely lytic phase. The osteolytic phase evolves into one marked by both osteoclastic and osteoblastic overactivity. This mixed phase is followed by a phase characterized by less active bone remodeling and marked sclerosis. In this final phase, excessive osteoblastic bone deposition predominates. Most patients who come to medical attention exhibit findings compatible with this phase.

6. Describe the radiographic findings associated with the osteolytic phase of Paget's disease.

The characteristic radiographic finding in patients in the initial osteolytic phase of Paget's disease of bone is an advancing wedge-shaped resorption front at either end of long tubular bones. In the skull, this phase is manifested by large circumscribed osteolytic lesions (termed *osteoporosis circumscripta*).

7. What are the radiographic findings most commonly found in the osteoblastic phase of the disease?

Evolution of osteolytic lesions into the osteoblastic phase may require years or even decades, during which the affected bone may become sclerotic and enlarged and may demonstrate bowing deformities, incomplete transverse fractures (pseudofractures), and even complete fractures. When the skull is involved in the osteoblastic phase, thickening of the calvarium and a patchy increase in bone density may give the skull a "cotton-wool" appearance. In this phase, the sclerotic bone changes may be so extensive that they may be confused with metastatic disease. Both metastatic cancer and Paget's disease are common in the elderly and may coexist in the same patient. Thus, clinicians caring for patients with Paget's disease must be alert for evidence of metastatic disease to bone.

8. What is the best radiographic evaluation to determine the extent of Paget's disease?

The metabolic activity of osteoblastic pagetic bone lesions is most easily assessed by radionuclide scanning because these lesions avidly take up the technetium-labeled bisphosphonate. Although bone scans are diagnostically less specific than radiographic studies, they identify approximately 15% to 30% of pagetic lesions not visualized on radiographs. Conversely, when radiographs demonstrate pagetic involvement but the serum alkaline phosphatase concentration is normal and the bone scan reveals little isotope uptake at those sites, the diagnosis of relatively inactive or "burned out" Paget's disease is most likely. Predominantly lytic bone lesions (such as osteoporosis circumscripta) may not be detected on bone scan. Computed tomography (CT) and magnetic resonance imaging (MRI) add little to the workup of patients with uncomplicated Paget's disease.

9. Which bones are involved in Paget's disease?

Paget's disease is monostotic (i.e., involves only one bone) in about 20% of patients. Polyostotic Paget's disease involves more than one area of the skeleton. Common sites of pagetic involvement are the pelvis, hip, spine, skull, tibia, and humerus. Less common sites of involvement ($<$ 20% of cases) include the forearm, clavicles, scapulae, and ribs.

10. Discuss the laboratory abnormalities associated with Paget's disease.

The abnormal laboratory values associated with Paget's disease reflect either increased bone formation or increased bone resorption. Unless a patient with widespread Paget's disease is immobilized, serum calcium and phosphate concentrations should be normal. An elevated serum alkaline phosphatase concentration reflects increased osteoblastic function. Measurement of serum osteocalcin, another marker of bone formation, provides little additional information to that given by measurement of alkaline phosphatase. The serum bone-specific alkaline phosphatase is a more sensitive marker of bone formation than the total alkaline phosphatase concentration and thus may be a useful parameter to follow in the management of monostotic disease. Measurement of urinary pyridinium collagen crosslinks (pyridinoline) is a better indicator of increased bone resorption than measurement of urinary hydroxyproline.

11. Which laboratory test should be used to monitor patients with Paget's disease?

When the Paget's disease is primarily lytic, the alkaline phosphatase concentration may be normal. Otherwise, the serum alkaline phosphatase activity generally parallels other chemical indices of bone resorption. Thus, the total serum alkaline phosphatase concentration is the simplest and least expensive laboratory value for following the course and the response to treatment in most cases of Paget's disease. Of interest, a markedly elevated alkaline phosphatase concentration (e.g., 10 times the upper limit of normal) is usually associated with pagetic involvement of the skull, whereas widespread disease in the rest of the skeleton without involvement of the skull may be associated with more modest elevations of serum alkaline phosphatase. In patients with increased total alkaline phosphatase concentrations, liver disease should be excluded, because this enzyme is abundant in both liver and bone. If liver-specific measurements, such as of 5′-nucleotidase, gamma-glutamyl transpeptidase, or the liver alkaline phosphatase isoenzyme, are normal, it is likely that the elevated alkaline phosphatase value originates from bone.

12. What are the histologic findings in bone affected by Paget's disease?

The early lesions of Paget's disease are characterized by increased numbers of large multinucleated osteoclasts, some containing up to 100 nuclei. In the mixed osteolytic-osteoblastic phase, large numbers of active osteoblasts are seen forming bone at sites of prior osteoclastic bone resorption. In areas of intense osteoblastic activity, bone is deposited in a chaotic fashion (in a mosaic or woven pattern) rather than in the orderly lamellar pattern of normal bone. The woven bone of Paget's disease is structurally weaker than normal lamellar bone and explains the propensity for pagetic bone to fracture or deform.

13. Which patients are most likely to have Paget's disease?

The incidence of Paget's disease varies with age, gender, and geographic location. Although Paget's disease may manifest in younger individuals, this disease is most common in patients older than 50 years. Men are more commonly affected than women (the male-to-female ratio is approximately 3:2). Although there is no definite hereditary pattern, between 15% and 40% of affected patients have a first-degree relative with Paget's disease. The disease is more common in the populations of eastern and northern Europe and in areas where Europeans have immigrated (such as the United States, Australia, New Zealand, and South Africa). Paget's disease is uncommon in Scandinavia, Asia, and Africa, as well as in African American populations.

14. What is the cause of Paget's disease?

Although the cause of Paget's disease is unknown, both genetic and nongenetic factors have been implicated in its pathogenesis. Several Paget's disease–associated polymorphisms have been identified. The SQSTM1 mutation is present in up to 50% of patients with familial disease and 10% to 20% of sporadic cases. Patients carrying this mutation have more extensive disease than noncarriers. However, the finding of monostotic disease, the variable penetrance of Paget's disease in families with a genetic disposition, and the observation that the incidence of Paget's disease has been decreasing over the past 25 years support a role for environmental factors in the etiology of this

disease. Reports of structures resembling paramyxovirus nucleocapsids in the osteoclasts of active pagetic bone suggest a viral etiology. The measles virus, respiratory syncytial virus, and canine distemper virus have been suggested as etiologic agents, although to date no virus has ever been cultured from pagetic osteoclasts or osteoclast precursors.

15. What medications are available to treat Paget's disease?

Although there is no cure for Paget's disease, several medications are available to control the accelerated osteoclastic bone resorption seen in this disease. The medications used for the treatment of Paget's bone disease include bisphosphonates and calcitonin (Calcimar, Miacalcin injection). At present, five bisphosphonates are approved and available for the treatment of Paget's disease of bone in the United States: etidronate (Didronel), alendronate (Fosamax), risedronate (Actonel), pamidronate (Aredia), and zoledronic acid (Reclast, Aclasta). Another bisphosphonate, ibandronate (Boniva), has been used for the treatment of Paget's disease in research studies. However, this drug has not been approved for the treatment of Paget's disease. Salmon calcitonin is a parenteral preparation requiring daily or three-times-a-week intramuscular or subcutaneous injections for 6 months. Calcitonin nasal spray (Miacalcin, Fortical) is not effective for treating Paget's disease because of low drug bioavailability.

16. Which agents are the drugs of choice for Paget's disease of bone?

Bisphosphonates are the agents of choice for the treatment of Paget's disease. Treatment with bisphosphonates often results in suppression of disease activity for prolonged periods, sometimes several years, whereas the response to calcitonin is generally short-lived after treatment is discontinued. Etidronate and calcitonin are rarely used because of the availability of more potent medications. One study has compared a 15-minute infusion of zoledronic acid with 60 days of oral risedronate in patients with Paget's disease. The single infusion of zoledronic acid produced a more rapid, complete, and sustained response than daily treatments with risedronate. Thus, intravenous bisphosphonate therapy may be more appropriate for extensive active disease or for disease that is unresponsive to oral bisphosphonate therapy. Treatment of symptomatic patients should also include other therapeutic modalities, such as analgesics, nonsteroidal antiinflammatory drugs, canes, orthotics, hearing aids, and surgery.

17. Does resistance to therapy for Paget's disease of bone occur?

Resistance to both bisphosphonates and calcitonin does occur. Resistance to treatment of Paget's disease with salmon calcitonin is usually associated with the production of neutralizing antibodies. Development of resistance after therapy with some of the bisphosphonates has also been reported. However, studies suggest that resistance to one bisphosphonate does not preclude a good response to a second bisphosphonate.

18. What is osteonecrosis of the jaw, and do patients with Paget's disease treated with bisphosphonates get this disorder?

Osteonecrosis of the jaw (ONJ) is a rare finding in which an area of exposed bone in the maxillofacial area persists for more than 6 weeks. This condition usually occurs following dental surgery. The symptoms vary from painless exposed bone to severe jaw pain. ONJ has also been described in patients receiving prolonged intravenous bisphosphonates for cancer, although there have been a few reports of this condition occurring in patients with Paget's disease. Thus the risk of ONJ should not preclude the use of bisphosphonates for the treatment of Paget's disease. However, it is recommended that treatment with bisphosphonates be delayed until after planned extensive dental work or oral surgery is completed. All patients treated with bisphosphonates should receive routine dental examinations and oral care.

19. What are the indications for treatment of Paget's disease?

The primary indication for treatment is the presence of symptoms. However, not all symptoms respond to treatment. Bone pain usually responds, as do certain neurologic compression syndromes. In contrast, hearing loss, bony deformities, and mechanically dysfunctional joints are not likely to

BOX 12-2. INDICATIONS FOR TREATMENT OF PAGET'S DISEASE OF BONE

- Symptoms (bone pain, headache, and some neurologic abnormalities)
- Osteolytic bone disease
- Active asymptomatic disease in weight-bearing bones, areas adjacent to major joints, vertebral bodies, and the skull
- Disease in a young patient
- Planned orthopedic surgery on pagetic bone
- Immobilization hypercalcemia

improve with therapy. Additional indications for treatment of Paget's disease are the prevention of local progression, planned surgery at a pagetic site, widespread pagetic involvement in patients in whom prolonged immobilization is anticipated (to decrease the risk of hypercalcemia), and possible prevention of future complications. Treatment of asymptomatic patients with Paget's disease is controversial. However, untreated Paget's disease appears to be progressive with time, and not all asymptomatic patients remain so. Thus, many physicians treat patients with osteolytic Paget's disease or asymptomatic patients with active disease involving weight-bearing bones, vertebral bodies, the skull, or areas adjacent to major joints (Box 12-2).

20. What is the most serious complication of Paget's disease of bone?

The most serious complication of Paget's disease is the development of malignant sarcoma in pagetic bone. Such tumors are usually isolated, but 20% may be multicentric. Fortunately, this is a rare complication of Paget's disease, occurring in less than 1% of patients with clinically apparent disease. This tumor is extremely aggressive, and patients with Paget's sarcoma generally survive less than a year. The pelvis and long bones (humerus, femur, and tibia) are the most common sites for sarcomatous transformation. The tumor is usually an osteogenic sarcoma, but fibrosarcomas and chondrosarcomas have also been reported in bone affected by Paget's disease. A biopsy of the involved bone is usually diagnostic. Other bone neoplasms, such as benign giant cell tumors, are also associated with Paget's disease, but these tumors do not carry such a grave prognosis.

21. When should malignant sarcoma in a pagetic bone lesion be suspected?

Malignant transformation within pagetic bone is usually heralded by the onset of new or worsening bone pain and/or soft tissue swelling. Usually, progressive destruction of pagetic bone is found on radiographs. Less commonly, increasing sclerosis or masses of dense amorphous deposits in bone are suggestive of malignant change. The serum concentration of alkaline phosphatase may rise rapidly in an otherwise previously stable patient. Bone scans usually demonstrate decreased uptake of radionuclide in the area of the tumor. Gallium scans also show increased uptake in the involved area(s).

KEY POINTS 1: PAGET'S DISEASE OF BONE

1. Paget's disease is the second most common metabolic bone disease, affecting up to 5% of the Caucasian population over age 50 years.
2. Paget's disease is characterized by abnormal bone architecture resulting from an imbalance between osteoblastic bone formation and osteoclastic bone resorption.
3. Bisphosphonates are the most effective treatment for Paget's disease of bone.

WEBSITE

The Paget Foundation: http://www.paget.org.

BIBLIOGRAPHY

Cundy T, Reid IR: Paget's disease of bone, *Clin Biochem* 45:43, 2012.

Drake WM, Kendler DL, Brown JP: Consensus statement on the modern therapy of Paget's disease of bone from a Western Osteoporosis Alliance Symposium, *Clin Ther* 23:620, 2001.

Falchetti A, Masi L, Brandi ML, Paget's disease of bone: there's more than the affected skeletal—a clinical review and suggestions for the clinical practice, *Curr Opin Rheumatol* 22:410, 2010.

Hadjipavlou A, Lander P, Srolovitz H, Enker IP: Malignant transformation in Paget's disease of bone, *Cancer* 70:2802, 1992.

Hain SF, Fogelman I: Nuclear medicine studies in metabolic bone disease, *Semin Musculoskelet Radiol* 6:323, 2002.

Joshua F, Epstein M, Major G: Bisphosphonate resistance in Paget's disease of bone, *Arthritis Rheum* 48:2321, 2003.

Michou L, Brown JP: Emerging strategies and therapies for treatment of Paget's disease of bone, *Drug Des Devel Ther* 5:225, 2011.

Mills BG: Etiology and pathophysiology of Paget's disease–update, *Endocrinologist* 7:222, 1997.

Naot D: Paget's disease of bone: an update, *Curr Opin Endocrinol Diabetes Obes* 18:352, 2011.

Proceedings of the Third International Symposium on Paget's Disease: *J Bone Mineral Res* 14(Suppl 2): 1999.

Ralston SH, Albagha OME: Genetic determinants of Paget's disease of bone, *Ann NY Acad Sci* 1240:53, 2011.

Reid IR, Hosking DJ: Bisphosphonates in Paget's disease, *Bone* 49:89, 2011.

Reid IR, Miller P, Lyles K, et al: Comparison of a single infusion of zoledronic acid with risedronate for Paget's disease, *N Engl J Med* 353:9, 2005.

Roodman GD, Windle JJ: Paget disease of bone, *J Clin Invest* 115:200, 2005.

Roodman GD: Insights into the pathogenesis of Paget's disease, *Ann NY Acad Sci* 1192:176, 2010.

Sawin CT: Historical note: Sir James Paget and osteitis deformans, *Endocrinologist* 7:205, 1997. (Also see page 255 in the same issue for a reproduction of one of James Paget's original articles on osteitis deformans.)

Sellars SL: Beethoven's deafness, *S Afr Med J* 48:1585, 1974.

Siris ES, Lyles KW, Singer FR, Meunier PJ: Medical management of Paget's disease of bone: indications for treatment and review of current therapies, *J Bone Miner Res* 21(Suppl 2):94, 2006.

Siris ES, Roodman GD: Paget's disease of bone. In Favus MJ, editor: *Primer on the metabolic bone diseases and disorders of mineral metabolism*, ed 6, New York, 2006, Raven Press, p 320.

Whyte MP: Paget's disease of bone, *N Engl J Med* 355:593, 2006.

Wimalawansa SJ, Gunasekera RD: Pamidronate is effective for Paget's disease of bone refractory to conventional therapy, *Calcif Tissue Int* 53:237, 1993.

CHAPTER 13

HYPERCALCEMIA

Leonard R. Sanders

1. What is hypercalcemia? How does protein binding affect the calcium level?

Hypercalcemia is a corrected total serum calcium value above the upper limit of the normal range or an elevated ionized calcium value. Calcium is 50% free (ionized), 40% protein-bound, and 10% complexed to phosphate, citrate, bicarbonate, sulfate, and lactate. Only elevations in the free calcium are associated with symptoms and signs. Of the protein-bound calcium, about 80% is bound to albumin and 20% to globulins. A decrease or increase in serum albumin of 1 g/dL from 4 g/dL decreases or increases the serum calcium by 0.8 mg/dL. An increase or decrease in serum globulin by 1 g/dL increases or decreases serum calcium by 0.16 mg/dL. Such protein changes do not affect free calcium and do not cause calcium-related symptoms.

2. How common are hypercalcemia and its main associated conditions?

Hypercalcemia affects 0.5% to 1% of the general population. The incidence may increase to 3% among postmenopausal women. Primary hyperparathyroidism (PHPT) causes 70% of outpatient and 20% of inpatient cases of hypercalcemia. Cancer causes 50% of inpatient cases of hypercalcemia. Ten percent of patients with malignancy experience hypercalcemia. Hyperparathyroidism and cancer cause 90% of all hypercalcemia. About 10% of patients with hyperparathyroidism experience nephrolithiasis. Although calcium oxalate stones are usually the most common stone type, calcium phosphate stones are more common in hyperparathyroidism.

3. How would you classify mild, moderate, and severe hypercalcemia?

First, consider the patient's general health, hypercalcemic symptoms, and the normal upper limit for calcium in your laboratory. For example, a patient with renal failure and a serum phosphorus value of 8.5 mg/dL may have metastatic calcification with a serum calcium level of 10.5 mg/dL. Then the serum calcium (Ca) is corrected for the albumin concentration, as follows:

$$Ca_{corrected} = Ca_{observed} + [(4.0 - albumin) \times 0.8]$$

With this in mind, a serum calcium value 1.5 to 3.5 mg/dL above the upper normal limit defines moderate hypercalcemia. Mild hypercalcemia occurs below this range and severe hypercalcemia above. Thus if the upper normal limit for calcium is 10.5 mg/dL, a serum calcium value of 12 to 14 mg/dL indicates moderate hypercalcemia. A serum calcium value less than 12 mg/dL indicates mild hypercalcemia and a level greater than 14 mg/dL severe hypercalcemia.

4. Discuss the signs and symptoms of hypercalcemia.

No symptoms are usually present with mild hypercalcemia ($<$ 12 mg/dL). Moderate or severe hypercalcemia and rapidly developing mild hypercalcemia may cause symptoms and signs. Common symptoms and signs involve (1) the central nervous system (lethargy, stupor, coma, mental changes, psychosis), (2) the gastrointestinal tract (anorexia, nausea, constipation, acid peptic disease, pancreatitis), (3) the kidneys (polyuria, nephrolithiasis), (4) the musculoskeletal system (arthralgias, myalgias, weakness), and (5) the vascular system (hypertension). The classic electrocardiographic (ECG) change associated with hypercalcemia is a short QT interval. Occasionally, severe hypercalcemia also causes dysrhythmias, sinus arrest, disturbances in atrioventricular (AV) conduction, and ST segment elevation mimicking myocardial infarction.

5. What are the sources of serum calcium?

Bone calcium approximates 1 kg and 99% of body calcium. A normal serum calcium level is maintained by integrated regulation of calcium absorption, resorption, and reabsorption; these processes occur, respectively, in the gut, bone, and kidney. Of the 1000 mg/day of dietary calcium intake, the gut absorbs 300 mg/day, secretes 100 mg/day, and excretes 800 mg/day. Net absorption averages 200 mg/day. Calcium absorption is usually about 30% of dietary calcium; however, absorption may increase to more than 50% when people also take large doses of $1,25(OH)_2D$. The kidney reabsorbs 98% of filtered calcium and excretes 200 mg/day. Bone exchanges about 500 mg of calcium per day with serum (Fig. 13-1).

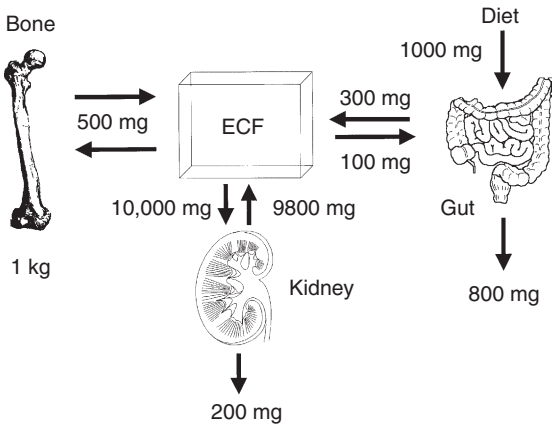


Figure 13-1. Normal calcium balance. ECF, extracellular fluid.

6. What are the major anatomic and physiologic determinants of vitamin D?

Diet, skin, liver, and kidney control the amount, synthesis, and secretion of vitamin D. Dietary sources of vitamin D include liver, fish oils, egg yolks, vitamin D–fortified foods, and vitamin D supplements. Skin exposure to ultraviolet sunlight activates 7-dehydrocholesterol to pre–vitamin D, which subsequently rearranges to form vitamin D. Hepatic 25-hydroxylase then converts vitamin D to 25-hydroxyvitamin D (25-OHD). 25-OHD circulates and interacts with two renal mitochondrial hydroxylases. High parathyroid hormone (PTH), low phosphate, and low calcium levels stimulate 1α-hydroxylase activity to increase conversion of 25-OHD to $1,25(OH)_2D$ (calcitriol)—the most potent metabolite of vitamin D. Low PTH, high phosphate, and high calcium levels suppress 1α-hydroxylase activity and stimulate 24-hydroxylase activity. This process inhibits calcitriol production and, through 24-hydroxylase, converts 25-OHD to 24,25-dihydroxyvitamin D $[24,25(OH)_2D]$, which promotes antiresorptive effects on bone and positive calcium balance. This same sequence occurs less intensely with normal levels of PTH, PO_4 (phosphate), and calcium. Calcitriol feeds back negatively on its own synthesis by suppressing 1α-hydroxylase activity, stimulating 24-hydroxylase activity, decreasing PTH, and increasing calcium and phosphate. Calcitriol is also degraded primarily through the enzyme 24-hydroxylase. The activity of 1α-hydroxylase is classically thought of as occurring only in the kidneys, but this enzyme is also present in bone, brain, pancreas, heart, intestines, lymph nodes, adrenal gland, prostate, and other tissues (Fig. 13-2). Fibroblast growth factor-23 (FGF-23) also has an important role in calcium and vitamin D metabolism.

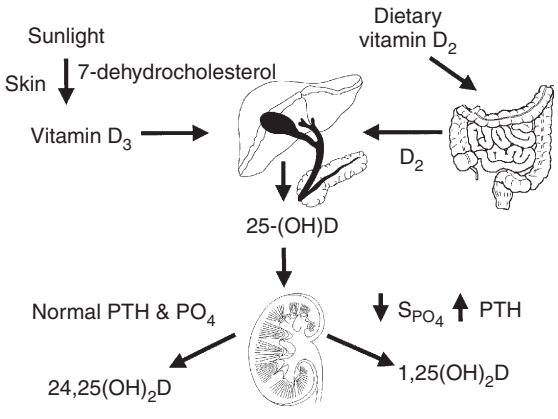


Figure 13-2. Vitamin D metabolism. PO_4, phosphate; PTH, parathyroid hormone.

7. What is fibroblast growth factor-23 and what role does it play in calcium, phosphate, and vitamin D metabolism?

FGF-23 is a newly discovered phosphaturic hormone that is produced by osteocytes in response to increases in serum levels of phosphate, $1,25(OH)_2D$, and PTH. FGF-23 then decreases phosphate, $1,25(OH)_2D$, and PTH by reducing proximal renal tubular phosphate reabsorption, stimulating 24-hydroxylase, inhibiting 1α-hydroxylase, and variably inhibiting PTH synthesis and secretion by the parathyroid glands. FGF-23 accumulates to very high levels in chronic kidney disease (CKD) and is associated with increased mortality in CKD.

8. What are the classical and nonclassical effects of vitamin D and what is the role of the vitamin D receptor?

Calcitriol acts classically on intestine, bone, kidneys, and parathyroid glands to help regulate calcium and phosphate metabolism. When calcitriol activates the parathyroid vitamin D receptor (VDR), it decreases PTH messenger RNA (mRNA) synthesis by inhibiting the pre-pro-PTH gene at the vitamin D response element. This inhibition decreases PTH synthesis within the chief cell of the parathyroid gland and ultimately lowers PTH levels. Additionally, calcitriol increases intestinal calcium and phosphate absorption, increases bone calcium and phosphate resorption, enhances bone turnover, and enhances renal calcium and phosphate reabsorption. The VDR is a nuclear hormone receptor that is also regulated by calcium and PTH. Many proteins are downregulated and upregulated by the activated VDR. Downregulated proteins include PTH, 1α-hydroxylase, bone matrix protein, bone sialoprotein, type I collagen, interferons, interleukins, tumor necrosis factor (TNF), epidermal growth factor receptors, renin, and peroxisome proliferator-activated receptor (PPAR) gamma-2. Upregulated proteins include osteopontin, matrix Gla protein, type IV collagen, interleukins, VDR, calcium-sensing receptor (CaSR), and 24-hydroxylase. Through activation of the VDR, calcitriol has many (nonclassical) effects other than those related to calcium and phosphorus metabolism. VDR activation may ameliorate arterial calcification, retard neuronal degeneration, enhance host defenses against bacterial infection and tumor growth, enhance Sertoli cell function and spermatogenesis, enhance insulin synthesis and secretion from pancreatic beta cells, and assist with glycogen and transferrin synthesis in liver parenchymal cells. Additionally, calcitriol has antiproliferative and prodifferentiating effects on myeloid cell precursors, cardiac and smooth muscle cells, and a variety of skin cells, including keratinocytes, fibroblasts, hair follicles, and melanocytes.

9. What is the CaSR, and what role does it play in calcium metabolism?

The CaSR is a membrane-bound calcium sensor-receptor. The most important locations of the CaSRs are the parathyroid glands and the renal tubular cells but the receptors are located in many other tissues, including at low levels in pancreatic beta cells and thyroid C cells. The major function of the CaSR is to maintain extracellular calcium concentrations in the normal range and prevent hypercalcemia. In the parathyroid chief cells, the CaSR has a large extracellular domain of 700 amino acids (primary calcium binding site), a seven-segment transmembrane portion (primary calcimimetic binding site), and a cytoplasmic carboxyl-terminal component of about 200 amino acids (primary effector site for metabolic changes). The CaSR belongs to subfamily C of the G protein–coupled receptor family. The CaSR senses the minutest change in ionized calcium (0.1 mg/dL) and regulates PTH secretion in order to maintain steady-state calcium levels within a narrow optimal range. These changes center on a set point for calcium-regulated PTH release that is unique for each individual. Cinacalcet, a calcimimetic drug, binds to the transmembrane portion of the CaSR, making it markedly more responsive to any level of ambient calcium. After activation by calcium, the CaSR activates phospholipase C, inhibits adenylate cyclase, and opens nonselective cation channels. This effect increases cytoplasmic calcium by mobilizing calcium from thapsigargin-sensitive intracellular stores and enhancing calcium influx through voltage-insensitive cation channels. These CaSR-induced changes in intracellular calcium act on the calcium response element of the pre-pro-PTH gene to decrease chief cell PTH messenger RNA synthesis, reduce PTH secretion, and decrease parathyroid gland hyperplasia. The parathyroid glands secrete both intact PTH (iPTH) and carboxy-terminal PTH fragments (CPTH). Intact PTH acts directly on bone PTH receptors. CPTH remains in the circulation much longer and at higher concentrations than iPTH and, although it was previously thought to be inactive, data now suggest that CPTH fragments can exert direct effects on bone cells through a novel class of CPTH receptors. CPTH fragments accumulate in renal failure. PTH functions to keep calcium in the normal range and helps prevent hypocalcemia.

10. What is the function of the CaSR in the kidneys?

In the kidney, as in the parathyroid glands, the CaSR functions to prevent hypercalcemia. Activation of the CaSR located on the basolateral membrane in the thick ascending limb of Henle's loop decreases tubular reabsorption of calcium and increases excretion. Activation of the renal CaSR generates an arachidonic acid metabolite that inhibits the luminal potassium channel and the sodium-potassium adenosine triphosphatase (ATPase) pump on the basolateral membrane. This diminishes the lumen-positive electrical gradient needed for passive calcium and magnesium reabsorption. Thus there is less reabsorption and more excretion of calcium. Because PTH is decreased by the CaSR activated in the parathyroid gland, there is less PTH-mediated distal tubular reabsorption of calcium, net calcium loss, and lower plasma calcium.

11. What are the overall effects of PTH, vitamin D, and FGF-23 on calcium metabolism?

Plasma calcium must be maintained within a narrow concentration range because of the key role it plays in a diverse array of physiologic processes, including intracellular signal transduction, muscle contraction, blood clotting, and neuronal transmission. Indeed, calcium in a given person is so tightly regulated that the average daily ionized calcium level does not deviate more than 0.3 mg/dL. Regulation of plasma calcium depends on normal amounts of PTH and calcitriol. Both hormones are also necessary for normal bone health. PTH and calcitriol provide the main control of serum calcium. Both PTH and calcitriol increase bone resorption by increasing osteoclast activity. At physiologic levels, PTH and calcitriol also increase bone formation. Because osteoclasts have no known receptors for either hormone, PTH and calcitriol stimulate osteoclast activity indirectly. Both hormones promote normal bone formation by direct action on the osteoblast line of cells. PTH enhances the activity of osteoblasts, which secrete factors such as interleukin-6 (IL-6) that stimulate osteoclastic bone resorption. PTH and calcitriol promote osteoclast differentiation from promonocytes to monocytes to macrophages to pre-osteoclasts and finally to osteoclasts. This is accompanied by an increase in osteoclast number and activity and decreased collagen synthesis. In addition, calcitriol increases

calcium transport from bone to blood and maintains a favorable calcium-phosphate product necessary for normal bone mineralization. Both PTH and calcitriol stimulate osteoblast production of receptor activator of nuclear factor kappa B ligand (RANKL). RANKL binds to its membrane-bound receptor (RANK) on pre-osteoclasts and osteoclasts. This action stimulates osteoclast differentiation and osteoclast attachment to the bone via integrins and, ultimately, bone resorption. Both PTH and calcitriol also control osteoblast production and secretion of osteoprotegerin (OPG), which blocks the effects of excess RANKL and promotes normal bone metabolism. This process depends on the concentration of PTH and calcitriol. Higher PTH and calcitriol levels increase bone resorption abnormally and may cause hypercalcemia and loss of bone mass. Denosumab is a monoclonal antibody to RANKL that in clinical trials has decreased hypercalcemia but is not yet approved for hypercalcemia treatment. Bone resorption is the major mechanism of most occurrences of hypercalcemia (see Table 13-3). However, PTH and calcitriol also act on the kidney to increase Ca reabsorption. PTH increases renal phosphate excretion, and calcitriol increases its reabsorption. PTH has no direct effect on the intestine, but calcitriol increases absorption of both calcium and phosphate. The higher calcium and calcitriol levels provide negative feedback on PTH secretion, whereas higher phosphate levels provide positive feedback. The net effect is normal bone function and plasma calcium at physiologic levels of PTH and calcitriol and loss of bone mineral and hypercalcemia at high levels. FGF-23 counters the effects of excess PTH and calcitriol by inhibiting synthesis of both hormones and increasing renal phosphate excretion.

12. How do calcium and phosphate interact with calcium-regulating hormones?

Table 13-1 summarizes the main factors controlling serum calcium. The arrows show direct actions of factors in the left column on factors in the top row, whereas the plus (+) and minus (−) signs show indirect actions. As a rule, the direct effects predominate as the net effect. Table 13-2 outlines the specific effects of each of these factors.

TABLE 13-1. INTERACTION OF FACTORS CONTROLLING SERUM CALCIUM

	PTH	$1,25(OH)_2D$	CALCITONIN	CALCIUM	PO_4
Parathyroid hormone (PTH)	—	↑+	+	↑+	↓↑+
$1,25(OH)_2D$	↓−	↓−	+	↑	↑
Calcitonin	+	+	—	↓	↓
Calcium	↓	↓	↑	—	↓
Phosphate (PO_4)	↑+	↓	—	↓	—
Fibroblast growth factor-23 (FGF-23)	↓+	↓+	—	− +	↓−

Arrows (↑, increase; ↓, decrease) indicate direct effects; + and − indicate indirect effects; —, no effect.

TABLE 13-2. SUMMARY OF CALCIUM AND PHOSPHATE CONTROL

VARIABLE	DIRECT ACTION(S)
Parathyroid hormone (PTH)	Increased bone resorption of calcium and phosphate Increased distal renal tubular calcium reabsorption Decreased renal tubular phosphate reabsorption Increased renal production of $1,25(OH)_2D$ Net effect: increased serum calcium and decreased phosphate

TABLE 13-2. SUMMARY OF CALCIUM AND PHOSPHATE CONTROL—cont'd

VARIABLE	DIRECT ACTION(S)
$1,25(OH)_2D$	Increased bone resorption of calcium and phosphate Increased renal reabsorption of calcium and phosphate Increased gut absorption of calcium and phosphate Decreased parathyroid production of PTH Decreased renal production of $1,25(OH)_2D$ Net effect: increased serum calcium and phosphate
Calcitonin	Decreased bone resorption of calcium and phosphate Decreased renal reabsorption of calcium and phosphate Decreased gut absorption of calcium and phosphate Net effect: decreased serum calcium and phosphate
Calcium	Decreased PTH synthesis and secretion Decreased $1,25(OH)_2D$ production in the kidney Increased calcitonin release from the thyroid C cells Decreased phosphate
Phosphate	Decreased $1,25(OH)_2D$ production in the kidney Decreased calcium Increased PTH synthesis in parathyroid chief cells
Fibroblast growth factor-23 (FGF-23)	Decreased $1,25(OH)_2D$ production in the kidney Decreased renal tubular phosphate reabsorption Decreased parathyroid production of PTH

BOX 13-1. MNEMONIC FOR CAUSES OF HYPERCALCEMIA

V = Vitamins
I = Immobilization
T = Thyrotoxicosis
A = Addison's disease
M = Milk-alkali syndrome
I = Inflammatory disorders
N = Neoplasm-related disease
S = Sarcoidosis
T = Thiazide diuretics (drugs)
R = Rhabdomyolysis
A = Acquired immunodeficiency syndrome
P = Paget's disease, parenteral nutrition, pheochromocytoma, parathyroid disease

13. List the main causes of hypercalcemia.

The mnemonic VITAMINS TRAP (see Pont, 1989) includes most causes of hypercalcemia (Box 13-1).

14. How do various causes of hypercalcemia increase the serum calcium level?

True hypercalcemia results from altered bone resorption, renal tubular reabsorption, and gut absorption of calcium. Although the bone (resorption and formation), kidney (reabsorption and excretion), and gut (absorption and secretion) each have two major processes involved with mineral metabolism, only resorption, reabsorption, and absorption play a significant role in hypercalcemia. An exception to this rule occurs when decreased renal function from renal or prerenal disease impairs calcium filtration and excretion. In Figure 13-3, *solid arrows* represent potential causes of increased calcium, and *dashed arrows* represent potential causes of decreased calcium.

15. What are the mechanisms and causes of hypercalcemia?

From the preceding discussions, one can appreciate that mechanisms of hypercalcemia are usually multifactorial. However, most hypercalcemic syndromes have a primary or predominant mechanism, as outlined in Table 13-3. Most resorptive hypercalcemia is humoral (PTH, PTH-related peptide

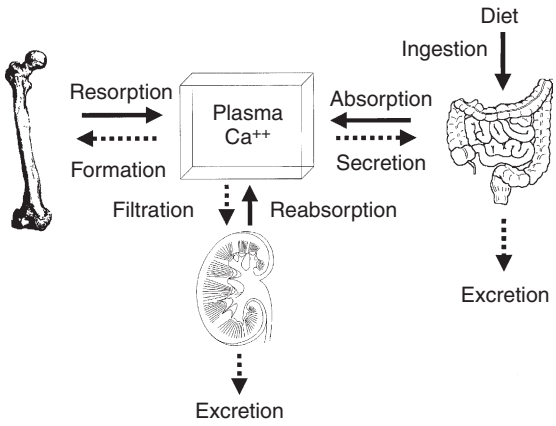


Figure 13-3. Calcium (Ca^{++}) metabolism. *Solid arrows* represent potential causes of increased calcium, and *dashed arrows* represent potential causes of decreased calcium.

TABLE 13-3. MECHANISMS AND CAUSES OF HYPERCALCEMIA

PRIMARY MECHANISM	CAUSE(S) OF HYPERCALCEMIA
Increased bone resorption	Hyperparathyroidism
	Local osteolytic hypercalcemia
	Humoral hypercalcemia of malignancy
	Thyrotoxicosis
	Pheochromocytoma
	Excessive vitamin A (usually > 25,000 IU/day)
	Lithium carbonate
	Immobilization
	Addison's disease
Increased renal reabsorption or decreased excretion	Milk-alkali syndrome
	Rhabdomyolysis
	Thiazide diuretics
	Familial hypocalciuric hypercalcemia
	Renal failure
	Lithium carbonate
	Addison's disease
Increased gut absorption	Excessive vitamin D (usually > 10,000 IU/day)
	Berylliosis
	Candidiasis, coccidioidomycosis
	Eosinophilic granuloma
	Histoplasmosis
	Sarcoidosis
	Silicone implants
	Tuberculosis
	Inflammatory disorders
	Acquired immunodeficiency syndrome
	Lymphomas

[PTHrP], transforming growth factor-α [TGF-α], TNF) or local osteolytic hypercalcemia (PTHrP, interleukins, prostaglandins). Increased calcium absorption usually occurs because of high $1,25(OH)_2D$ levels either from excess vitamin D ingestion or produced by tumors or granulomas. Ninety percent of hypercalcemia cases result from hyperparathyroidism or cancer.

KEY POINTS 1: HYPERCALCEMIA

1. Therapy for hypercalcemia should be directed at the underlying etiology, including excess bone resorption, renal tubular reabsorption, and gut absorption.
2. Although there are more than 30 different causes of hypercalcemia, hyperparathyroidism and hypercalcemia of malignancy account for more than 90% of cases.
3. Most patients with severe hypercalcemia require normal saline hydration and multiple-drug therapy, but most therapies for hypercalcemia inhibit bone resorption.
4. Zoledronic acid is the most potent bisphosphonate approved for treatment of hypercalcemia and has the advantage over pamidronate of a shorter infusion time and a longer duration of action.
5. Cinacalcet is a calcimimetic that lowers parathyroid hormone (PTH), calcium, and phosphorus levels. It is approved for treatment of secondary hyperparathyroidism (HPT) and parathyroid carcinoma. It is now approved for treating primary HPT in patients with clinically significant hypercalcemia when parathyroidectomy is not clinically appropriate or is contraindicated. Although not approved for such situations, cinacalcet also lowers PTH and calcium in kidney transplant recipients who have persistently elevated PTH.

16. What is the relative frequency of skeletal lesions in patients with advanced cancer?

The relative frequency is as follows: myeloma 95% to 100%, breast and prostate 70%, thyroid 60%, bladder 40%, lung 35%, renal 25%, and melanoma 14% to 45%. Common sites of bone metastases are ribs, spine, pelvis, and proximal extremities.

17. What is the incidence of hypercalcemia in patients with cancer?

Hypercalcemia affects 10% to 20% of patients with cancer. It is most common in squamous cell carcinoma of the lung, head, and neck, renal cell carcinoma, breast cancer, multiple myeloma, and lymphoma.

18. What are the multiple endocrine neoplasia syndromes?

Multiple endocrine neoplasia (MEN) is associated with three familial syndromes, two of which manifest as hypercalcemia due to hyperparathyroidism. MEN 1, or Wermer's syndrome, includes the three Ps: pituitary, parathyroid, and pancreatic tumors. Hypercalcemia due to hyperparathyroidism is usually the first feature of this syndrome to appear. MEN 2 has two variants. Patients with MEN 2A, or Sipple's syndrome, have medullary carcinoma of the thyroid (MCT), pheochromocytoma, and hyperparathyroidism. Patients with MEN 2B have MCT, pheochromocytoma, multiple mucosal neuromas, and marfanoid habitus; they usually do not have hyperparathyroidism. In comparison with sporadic hyperparathyroidism, parathyroid tumors in the MEN syndromes are more often bilateral, hyperplastic, and malignant.

19. How would you diagnose familial hypocalciuric hypercalcemia?

Familial hypocalciuric hypercalcemia (FHH), also called familial benign hypercalcemia, is due to autosomal dominant CaSR gene mutations, encoding inactive forms of the CaSR on parathyroid and renal tubular cell membranes. Important diagnostic features of FHH are the combination of

no symptoms, a family history of benign hypercalcemia, mild hypercalcemia, normal to high serum PTH levels, and decreased renal calcium clearance (fractional excretion of calcium [FECa] $<$ 1%). The clinical importance of FHH is to distinguish it from PHPT to avoid needless and ineffective parathyroidectomy. Patients with PHPT usually have an FECa value greater than 2%. In addition, patients with FHH usually have a 24-urinary calcium level lower than 100 mg, and those with HPT have values higher than 200 mg.

20. What is the likely cause of hypercalcemia in the following patient?

An 18-year-old man has had serum calcium values of 10.5 to 11.8 mg/dL for 2 years; his physical examination is normal, and he has a family history of hypercalcemia. Current laboratory values are as follows: calcium 11.5 mg/dL, intact PTH 70 pg/mL (normal NL $<$ 65), plasma creatinine (PCr) 1.0 mg/dL, random urine calcium (UCa) 5 mg/dL, and urine creatinine (UCr) 90 mg/dL. Because circulating proteins bind 40% of the calcium, the kidney filters only 60%. Plasma calcium (PCa) available for filtration is 0.6 $\times$ 11.5, or 6.9 mg/dL, as shown by the following calculations:

$$\text{FECa} = [\text{UCa/PCa}]/[\text{UCr/PCr}] = [\text{UCa/PCa}] \times [\text{PCr/UCr}]$$

$$\text{FECa} = [5\ \text{mg/dL}/6.9\ \text{mg/dL}] \times [1\ \text{mg/dL}/90\ \text{mg/dL}] \times 100\% = 0.8\%$$

The history, physical findings, laboratory values, and FECa $<$ 1% support the diagnosis of FHH.

21. What therapy is useful for hypercalcemia?

Most patients with severe hypercalcemia require treatment with multiple drugs. The lowest amount and least frequent dose that will achieve and maintain acceptable serum calcium levels should be given. The usual order of therapy is normal saline, calcitonin, zoledronic acid, and glucocorticoids, if indicated. Furosemide should be given only after good hydration, primarily to avoid volume overload and improve urinary volume. Gallium nitrate is rarely used for severe hypercalcemia of malignancy that is refractory to all other therapy. Consultation with nephrology should be sought, and dialysis considered, for acute management of severe and refractory hypercalcemia and hypercalcemic crisis (Table 13-4).

22. Describe the mechanisms of action of drug therapies for hypercalcemia.

See Table 13-5.

23. How might calcimimetic drugs be useful in therapy for hypercalcemia?

On March 8, 2004, the U.S. Food and Drug Administration (FDA) approved cinacalcet, the first-in-class oral calcimimetic for clinical use. Calcimimetics are potentially the most useful drugs for the treatment of hypercalcemia caused by hyperparathyroidism. Cinacalcet remains the only calcimimetic available for patient care. It acts by increasing the sensitivity of the CaSR to calcium activation (see questions 8 and 9). The increased sensitivity shifts the PTH-calcium curve to the left, increasing parathyroid cell sensitivity to the PTH-suppressive effects of high extracellular calcium and decreasing its responsiveness to the PTH-stimulatory effects of low calcium. By increasing CaSR calcium sensitivity in Henle's loop, cinacalcet also increases renal calcium excretion. The net effect is a dose-dependent marked reduction in PTH secretion, an increase in urinary calcium excretion, and a drop in serum calcium. Cinacalcet is FDA approved for treatment of secondary HPT in patients with chronic kidney disease undergoing dialysis, of parathyroid carcinoma, and of severe hypercalcemia in patients with primary HPT who are unable to undergo parathyroidectomy. Although not approved for the following uses, cinacalcet has successfully improved persistent HPT after kidney transplantation, hypercalcemia due to FHH, and lithium-induced hypercalcemia (see question 24).

24. How does lithium cause hypercalcemia?

Lithium decreases urinary calcium through competitive inhibition of the CaSR in the thick ascending limb of Henle's loop, causing increased calcium reabsorption, decreased calcium excretion, and

TABLE 13-4. THERAPY FOR HYPERCALCEMIA

THERAPY	DOSE	ROUTE	MONITOR/COMMENT
Saline	250-1000 mL/h	IV	Cardiopulmonary function with examination, central venous pressure/ pulmonary capillary wedge pressure and chest radiograph
Furosemide	20-80 mg every 2-4 h or 40 mg/h CI	IV	Serum and urine electrolytes. Replace K, Mg, and PO_4 based on serum levels and urinary losses.
Salmon calcitonin	4-8 IU/kg every 6-12 h	IM, SC	Allergic reaction. Give a skin test of 1 IU intradermally before treatment. Effective only during first 48-72 h.
Prednisone/ methylprednisolone	20 mg 2-3 times a day	PO/IV	Possible adjunct to calcitonin. Effective in $1,25(OH)_2D$ associated hypercalcemia.
Zoledronic acid	4 mg IV over 15 min every 2-4 weeks PRN	IV	Drug of choice for malignancy-associated hypercalcemia. Caution with chronic kidney disease and myeloma.
Pamidronate	30-90 mg over 2-24 h every 1-3 weeks PRN	IV	Infuse over at least 4 hours in severe renal failure (glomerular filtrating rate $<$ 30 mL/ min).
Cinacalcet	30-90 mg b.i.d.-q.i.d.	PO	Take with meals. Monitor parathyroid hormone, Ca, and PO_4 at least 12 h after dose.
Gallium nitrate	200 mg/m^2/day CI over 4 h PRN for 5 days	IV	Avoid in renal failure. Monitor creatinine, PO_4, and complete blood count.
Dialysis	Low or no calcium dialysate	Hemodialysis/ peritoneal dialysis Continuous venovenous hemodialysis	Hypercalcemic crisis or refractory hypercalcemia. Useful in renal failure. May require PO_4 addition to dialysate. Nephrologic consultation.

b.i.d., twice daily; CI, continuous infusion; IM, intramuscularly; IV, intravenously; K, potassium; Mg, magnesium; Na, sodium; PO, orally; PO_4, phosphate; PRN, as needed; q.i.d., four times daily; SC, subcutaneously.

hypercalcemia. Urinary calcium may be low in lithium-treated patients as it is in patients with FHH. Lithium also decreases the sensitivity of the parathyroid CaSR to calcium and shifts the PTH-calcium curve in the parathyroids to the right. Thus, for any given calcium level, there is less suppression of PTH secretion and synthesis and higher PTH levels. Unlike in hyperparathyroidism, serum phosphate tends to be normal and magnesium higher in lithium-treated patients. Because hypercalcemia and elevated PTH may persist after lithium is discontinued, therapy other than just discontinuing lithium may be indicated if the hypercalcemia is symptomatic. Cinacalcet has successfully corrected or ameliorated PTH and serum Ca levels in such patients. This effect is expected because cinacalcet sensitizes the CaSR to calcium and shifts the PTH-calcium curve to the left.

TABLE 13–5. MECHANISMS OF ACTION OF HYPERCALCEMIC THERAPY

DRUG	MECHANISM(S) OF ACTION
Saline	Dilutes serum calcium by volume expansion and increases urinary flow and calcium excretion
Furosemide	Impairs renal sodium and calcium reabsorption in Henle's loop, increasing urinary flow and calcium excretion
Calcitonin	Binds to receptors on osteoclasts, inhibiting osteoclast activity and decreasing bone resorption; also decreases renal reabsorption
Glucocorticoids	Antagonism of vitamin D, causing decreased calcium absorption and reabsorption; in tumoral states, may be tumor lytic and may decrease production of osteoclast-activating factors and vitamin D
Bisphosphonates	Impair osteoclast differentiation, recruitment, motility, and attachment; incorporate into bone matrix, making the matrix resistant to hydrolysis; overall effect is decreased bone resorption
Cinacalcet	Calcimimetic that binds to the calcium sensing receptor, making it markedly more responsive to calcium activation
Gallium nitrate	Adsorbs to and decreases solubility of hydroxyapatite crystals, decreasing bone resorption
Dialysis	Direct removal of calcium from blood

Note: For long-term hypocalcemic effects, drug therapy for hypercalcemia must antagonize one of the three main causes of hypercalcemia: bone resorption, renal reabsorption, or gut absorption. All hypercalcemia results from some abnormality in one of the three. Thus one of these etiologies should be considered in the choice of drug therapy. As noted, most drug therapies for hypercalcemia impair bone resorption.

WEBSITES

1. American Academy of Family Physicians: Available at http://www.aafp.org/afp/20030501/1959.html.
2. National Cancer Institute: Available at http://www.meb.uni-bonn.de/cancer.gov/CDR0000062737.html.
3. Zometa International: Zoledronic acid review: Available at http://www.zometa.com/monographs.html.
4. Endoctext.org: http://www.endotext.org/parathyroid/parathyroid2/parathyroidframe2.htm.

BIBLIOGRAPHY

Bergua C, Torregrosa JV, Cofán F, et al: Cinacalcet for the treatment of hypercalcemia in renal transplanted patients with secondary hyperparathyroidism, *Transplant Proc* 39:2254–2255, 2007.

Body JJ: Current and future directions in medical therapy, hypercalcemia, *Cancer* 88(Suppl 12):3054–3058, 2000.

Bringhurst FR, Demay MB, Kronenberg HM: Hormones and disorders of mineral metabolism. In Melmed S, Polonsky KS, Larsen PR, et al, editors: *Williams Textbook of Endocrinology*, ed 12, Philadelphia, 2011, Elsevier Saunders, p 1237.

Carroll MF, Schade DS: A practical approach to hypercalcemia, *Am Fam Physician* 67:1959–1966, 2003.

Carroll R, Matfin G: Review: Endocrine and metabolic emergencies: hypercalcaemia, *Ther Adv Endocrinol Metab* 1(5): 225–234, 2010.

Festen-Spanjer B, Haring CM, Koster JB, et al: Correction of hypercalcaemia by cinacalcet in familial hypocalciuric hypercalcaemia, *Clin Endocrinol* 68:324–325, 2008.

Jacobs TP, Bilezikian JP: Clinical review: rare causes of hypercalcemia, *J Clin Endocrinol Metab* 90:6316–6322, 2005.

Kallas M, Green F, Hewison M, et al: Rare causes of calcitriol-mediated hypercalcemia: a case report and literature review, *J Clin Endocrinol Metab* 95(7):3111–3117, 2010.

Kaye TB: Hypercalcemia: how to pinpoint the cause and customize treatment, *Postgrad Med* 97:153–155, 159–160, 1995.

Maalouf NM: Calcium homeostasis. Kovacs WJ, Ojeda SR, editors: *Textbook of Endocrine Physiology,* ed 6, New York, 2012, Oxford University Press, p 381.

Major P: The use of zoledronic acid, a novel, highly potent bisphosphonate, for the treatment of hypercalcemia of malignancy, *Oncologist* 7:481–491, 2002.
Major PP, Coleman RE: Zoledronic acid in the treatment of hypercalcemia of malignancy: results of the International Clinical Development Program, *Semin Oncol* 28:17–24, 2001.
Martin A, David V, Quarles LD: Regulation and function of the FGF23/Klotho endocrine pathways, *Physiol Rev* 92(1):131–155, 2012.
Mihai R, Wass JAH, Sadler GP: Asymptomatic hyperparathyroidism—need for multicentre studies, *Clin Endocrinol* 68: 155–164, 2008.
Mundy GR, Edward JR: PTH-Related peptide in hypercalcemia, *J Am Soc Nephrol* 19:672–675, 2008.
Nishi SPE, Barbagelata NA, Atar S, et al: Hypercalcemia-induced ST-segment elevation mimicking acute myocardial infarction, *J Electrocardiol* 39:298–300, 2006.
Peacock M, Bilezikian JP, Bolognese MA, et al: Cinacalcet HCL reduces hypercalcemia in primary hyperparathyroidism across a wide spectrum of disease severity, *J Clin Endocrinol Metab* 96(1):E9–E18, 2011.
Pont A: Unusual causes of hypercalcemia, *Endocrinol Metab Clin North Am* 18:753–764, 1989.
Popovtzer MM: Disorders of calcium, phosphorus, vitamin D, and parathyroid hormone activity. In Schrier RW, editor: *Renal and Electrolytes Disorders*, ed 7, Philadelphia, 2010, Lippincott Williams & Wilkins, p 216.
Rabbani SA: Molecular mechanism of action of parathyroid hormone related peptide in hypercalcemia of malignancy: therapeutic strategies [review], *Int J Oncol* 16:197–206, 2000.
Silverberg SH, Rubin MR, Faiman C, et al: Cinacalcet hydrochloride reduces the serum calcium concentration in inoperable parathyroid carcinoma, *J Clin Endocrinol Metab* 92:3803–3808, 2007.
Sloand JA, Shelly MA: Normalization of lithium-induced hypercalcemia and hyperparathyroidism with cinacalcet hydrochloride, *Am J Kidney Dis* 48:832–837, 2006.
Thakker RV, Newey PJ, Walls GV, et al: Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1), *J Clin Endocrinol Metab* 97(9):2990–3011, 2012.
Varghese J, Rich T, Jimenez C: Benign familial hypocalciuric hypercalcemia, *Endocr Pract* 17(Suppl 1):13–17, 2011.

CHAPTER 14

HYPERPARATHYROIDISM

Leonard R. Sanders

1. What is hyperparathyroidism?

Hyperparathyroidism (HPT) is a clinical syndrome causing specific symptoms and signs that result from excessive parathyroid hormone (PTH) secretion, PTH-induced bone resorption, and hypercalcemia. The three types of HPT are primary, secondary, and tertiary.

2. How common is primary HPT?

The prevalence of primary HPT in the United States is 0.1% to 0.3% of the general population. The female-to-male ratio is 2:1 to 3:1. The incidence increases with age, and the incidence in postmenopausal women is five times higher than that in the general population.

3. What causes primary HPT?

Primary HPT is characterized by abnormal regulation of PTH secretion by calcium, resulting in excessive PTH secretion and hypercalcemia. Although the cause of primary HPT is not known, increased PTH secretion is due in part to elevation of the calcium-suppressible PTH secretion set point and a change in the slope of the calcium-PTH curve that causes relatively nonsuppressible PTH secretion. Expression of the calcium sensor-receptor (CaSR) is reduced in parathyroid adenomas and hyperplasia and may be partly responsible for this relative PTH nonsuppressibility.

4. What anatomic alterations occur in primary HPT?

Most patients with primary HPT have a single parathyroid adenoma (85%), whereas four-gland hyperplasia (10%) and multiple adenomas (5%) are less common, and parathyroid carcinomas are rare ($<$5%). More than 95% of those with parathyroid adenomas have a single adenoma and fewer than 5% have two or more adenomas. Normal parathyroid glands weigh less than 50 mg each. The average weight of parathyroid adenomas is 500 mg to 5 g; however, some may weigh more than 25 g. The largest reported tumor weighed 120 g, and the largest number of glands reported in one patient was eight.

5. How do you diagnose primary HPT?

Persistent hypercalcemia with increased or high-normal serum PTH levels confirms the diagnosis of primary HPT. Associated low or low-normal serum phosphate makes this diagnosis more likely. Primary HPT should be suspected whenever a patient has documented hypercalcemia, which is the most common cause of hypercalcemia. Because symptoms of primary HPT are nonspecific or absent (see question 12), one must base the diagnosis primarily on laboratory studies. Furthermore, most patients with mild primary HPT have no specific symptoms or signs. Most cases are suspected after an elevated serum calcium value is found on routine laboratory screening.

6. How does age complicate the diagnosis of HPT?

The laboratory reference range for intact PTH (10-65 pg/mL) and calcium (8.5-10.5 mg/dL) may be different in the elderly and young individuals. However, the PTH reference range is not usually adjusted for age. PTH levels normally increase with age. Why PTH increases with age is unclear, but the change may be related to age-related declines in renal function and vitamin D levels. Thus, PTH levels in the upper normal range are more likely to represent HPT in patients who are younger than in those older than 50 years. Although serum calcium levels decline with age, the decline is usually related to decreasing albumin and does not generally affect serum PTH levels.

7. How might you make the diagnosis of primary HPT more certain before recommending parathyroidectomy?

Obtain at least three fasting serum calcium levels, ideally with no venous occlusion, and two PTH measurements at least several weeks apart. Ensure that the patient has normal renal function. Discontinue any thiazide diuretics for at least 1 week before measurement. Discontinue lithium if safe to do so. Measure serum total calcium and calculate the correction for albumin and total protein levels; order an ionized calcium measurement if there is any doubt (see Chapter 13). If calcium is elevated and the PTH value is high or high-normal, primary HPT is usually present. If calcium is normal and PTH is high, measure the serum 25-hydroxyvitamin D (25-OHD) level, because vitamin D deficiency is a common cause of secondary HPT. To exclude vitamin D deficiency, the 25-OHD level should be higher than 30 ng/mL. The immunoradiometric assay (IRMA) for intact PTH is standard and sufficient for diagnosis. However, if there is concern about the IRMA results, immunochemiluminometric assay (ICMA), which also measures intact PTH (1-84), can be used.

8. When lab results are not specific for primary HPT, what other classic laboratory changes may help with the diagnosis?

Increased serum chloride (Cl), decreased phosphate (PO_4), a Cl/PO_4 ratio greater than 33, elevated urinary pH ($>$ 6.0), and increased alkaline phosphatase levels support the diagnosis of primary HPT but are not specific. If the PTH level is normal or low and the patient has suspected cancer, serum PTH-related peptide (PTHrP) should be measured. Ectopic PTH is rare and should be considered only if the patient has cancer or results of surgical neck exploration for HPT are negative.

9. What differentiates familial hypocalciuric hypercalcemia from primary HPT?

If there is a family history of hypercalcemia and/or the serum calcium and PTH are mildly elevated chronically, consider familial hypocalciuric hypercalcemia (FHH). Calculate the fractional excretion of calcium (FECa) (see Chapter 13). The FECa is less than 1% in FHH and more than 2% in primary HPT. If the FECa is low, test family members to confirm the diagnosis. If they test positive, FHH is probably present. Avoid neck exploration, which will have no effect on reversing hypercalcemia in this genetic condition.

10. How does chronic kidney disease (CKD) complicate the diagnosis of primary HPT?

Renal failure increases serum PO_4 and decreases serum $1,25(OH)_2D$ (calcitriol). Because PO_4 directly stimulates and calcitriol directly inhibits PTH secretion, serum PTH levels increase in renal failure (secondary HPT). High PO_4 and low calcitriol levels also directly decrease serum calcium. The resulting absolute or relative hypocalcemia further increases PTH secretion. Symptoms and signs of renal insufficiency, such as lethargy, depression, anorexia, nausea, constipation, and weakness, may be identical to those of primary HPT. Thus, unless it is overt, the diagnosis of primary HPT may be more difficult in renal failure. Before parathyroidectomy for presumed primary HPT, tissue localization with ultrasound and with a technetium 99m sestamibi scan may be appropriate.

11. What changes occur in renal failure that may complicate the PTH assay result?

In renal failure, PTH rises above normal because of the stimulatory effects of high PO_4 and low calcitriol levels. In addition, a molecular fragment of PTH (PTH 7-84), which has antagonistic actions to those of intact PTH, accumulates in renal failure and cross-reacts with intact PTH in the intact two-site assays. For this reason, measured levels of intact PTH in patients with renal failure may be more than 1.5 times those of normal subjects to maintain physiologic PTH concentrations.

12. What are the symptoms and signs of primary HPT?

More than 85% of patients with primary HPT are asymptomatic. However, vascular, musculoskeletal, gastrointestinal, and neurologic symptoms may occur in primary HPT. The classic phrase for many of these features is “stones, bones, abdominal groans, and psychic moans.” Because of earlier diagnosis today, the incidence of nephrolithiasis has decreased to less than 10% in patients with primary HPT.

TABLE 14-1. HYPERPARATHYROIDISM: SYMPTOMS AND SIGNS AND THEIR PROBABLE CAUSES

SYMPTOMS AND SIGNS	PROBABLE CAUSE(S)
Renal: hypercalciuria, nephrolithiasis, nephrocalcinosis, polyuria, polydipsia, renal insufficiency	Parathyroid hormone (PTH) stimulates bone resorption, hypercalcemia, bicarbonaturia, and phosphaturia, causing decreased tubular responsiveness to antidiuretic hormone (ADH), polyuria, calcium oxalate and phosphate crystallization, nephrocalcinosis, and renal insufficiency
Neuromuscular: weakness, myalgia	Prolonged excessive PTH arguably causes direct neuropathy with abnormal nerve conduction velocities (NCVs) and characteristic electromyographic changes and myopathic features on muscle biopsy
Neurologic and psychiatric: memory loss, depression, psychoses, neuroses, confusion, lethargy, fatigue, paresthesias	PTH and calcium cause peripheral neuropathy with abnormal NCVs and central nervous system damage with abnormal electroencephalographic changes
Skeletal: bone pain, osteitis fibrosa, osteoporosis, and subperiosteal skeletal resorption	PTH increases bone resorption and acidosis with subsequent bone buffering and bone loss of calcium and phosphate
Gastrointestinal: abdominal pain, nausea, peptic ulcer, constipation, and pancreatitis	Hypercalcemia stimulates gastrin secretion, decreases peristalsis, and increases the calcium-phosphate product with calcium-phosphate deposition in and obstruction of pancreatic ducts
Hypertension	Hypercalcemia causes vasoconstriction, and parathyroid hypertensive factor (PHF) may raise blood pressure
Arthralgia, synovitis, arthritis	HPT is associated with increased crystal deposition from calcium phosphate (para-articular calcification), calcium pyrophosphate (pseudogout), and uric acid/urate (gout)
Band keratopathy	Calcium-phosphate precipitation in medial and limbic margins of cornea
Anemia	Unknown

Proximal muscle weakness is also characteristic. Other characteristic symptoms and signs and their probable cause(s) are outlined in Table 14-1.

13. What is band keratopathy?

Band keratopathy is a classic but unusual sign of HPT characterized by an irregular region of calcium phosphate deposition at the medial and lateral limbic margins of the outer edges of the corneas. The location is believed to be a result of diffusion of carbon dioxide from air-exposed areas of the cornea, leaving an alkaline environment that favors precipitation of calcium phosphate crystals. Band keratopathy occurs only with a high calcium phosphate product. Diagnosis is made by ophthalmologic slit-lamp examination. The sign differs from arcus senilis, an age-related, linear, concentric gray crescent separated from the extreme periphery (limbus corneae) by a rim of clear cornea that with time completely encircles the cornea.

14. What are the classic radiographic findings in HPT?

Because most patients are diagnosed early, there are often no radiographic findings related to HPT. If HPT is prolonged, osteopenia or osteoporosis develops. However, the classic radiographic finding is subperiosteal bone resorption along the radial aspect of the middle and distal phalanges and distal clavicles. Salt-and-pepper skull is another classic finding. Because cortical bone loss is higher in HPT, bone densitometry of the distal radius is a good way to monitor for bone loss in patients who do not undergo parathyroidectomy.

15. What is the differential diagnosis of primary HPT?

Because the main abnormality in primary HPT is hypercalcemia, the differential diagnosis initially is that of hypercalcemia (see Chapter 13). A history and physical examination focused on symptoms and signs (question 12) may suggest one of the causes of hypercalcemia. If hypercalcemia is mild and the history and physical findings are nonspecific, primary HPT is likely. The two most common causes of hypercalcemia are primary HPT and malignancy. In humoral hypercalcemia of malignancy (HHM), the tumor usually produces a PTH-like hormone called PTH-related peptide.

16. What lab tests help to distinguish the three types of HPT?

See Table 14-2.

17. What pathophysiologic changes occur in primary HPT?

Primary HPT is idiopathic and results from excessive secretion of PTH from parathyroid adenomas, hyperplasia, or rarely carcinoma. The increased PTH causes hypercalcemia. The PTH level is inappropriately normal or high.

18. What pathophysiologic changes occur in secondary HPT?

Secondary HPT is excessive PTH secretion occurring as a compensatory response to absolute or relative hyperphosphatemia, hypocalcemia, or low calcitriol levels. Renal failure is the most common cause of secondary HPT, often producing PTH hypersecretion by means of all three of these stimuli. In renal failure, phosphorus increases because of decreased renal function. The increased phosphorous stimulates PTH secretion and decreases calcium and $1,25(OH)_2D$ levels. The lower calcium and vitamin D levels also increase PTH synthesis and secretion. Thus, controlling phosphorus levels with diet and phosphate binders and appropriate calcitriol supplementation may delay onset of the secondary HPT of renal failure. Other causes of hypocalcemia are renal calcium leak, dietary calcium malabsorption, and vitamin D deficiency. Secondary HPT is generally accompanied by parathyroid hyperplasia as the parathyroid glands enlarge to enhance their PTH-secretory capacity.

19. What pathophysiologic changes occur in tertiary HPT?

Tertiary HPT results from progression of secondary HPT. In tertiary HPT, prolonged hyperphosphatemia and/or hypocalcemia cause further parathyroid hyperplasia with eventual development of autonomous parathyroid function and hypercalcemia. Spontaneous change from low or normal calcium levels to hypercalcemia marks the transition from secondary HPT to tertiary HPT. In tertiary HPT, PTH levels are usually approximately 15 to 30 times normal. This finding most commonly occurs in chronic renal failure. These changes are associated with decreased parathyroid CaSR, vitamin D receptor, and fibroblast growth factor receptor function and numbers. PTH remains elevated despite vitamin D therapy and correction of hyperphosphatemia. Hypercalcemia remains despite discontinuation of vitamin D and calcium supplements. Tertiary HPT usually requires resection of at least three and one-half parathyroid glands to correct the hypercalcemia. However, discontinuing vitamin D and a trial of cinacalcet therapy may lower PTH and calcium levels toward acceptable ranges and delay or obviate surgery.

TABLE 14-2. PARATHYROID HORMONE (PTH) AND CALCIUM LEVELS IN HYPERPARATHYROIDISM

TYPE OF HYPERPARATHYROIDISM	PTH	CALCIUM
Primary	Normal ↑	↑
Secondary	↑	↓ Normal
Tertiary	↑↑	↑

↑ = high and ↑↑ = very high.

20. How is HHM distinguished from primary HPT?

The main distinguishing features of HHM are the levels of intact PTH and PTHrP. The classic and most common patterns of these hormones are shown in Table 14-3. The patient with primary HPT usually has elevated intact PTH; PTHrP, when measured, is low. Malignancy-associated hypercalcemia, in contrast, is associated with low intact PTH levels, but 80% of patients have increased PTHrP levels (PTHrP malignancy) and 20% have low PTHrP levels (non-PTHrP malignancy). Thus, measuring the two hormones distinguishes all three disorders (see question 21).

21. How do PTHrP and PTH differ?

PTHrP consists of three protein forms with 139, 141, and 173 amino acids. The first 139 amino acids are the same among the three forms. Eight of the first 13 *N*-terminal amino acids are identical to those of intact PTH (1-84), allowing PTHrP to bind to and stimulate the same receptors as PTH and to have similar hypercalcemic effects. But the two hormones have different effects on levels of $1,25(OH)_2D$, partly because of their different secretion patterns. Both PTH (in primary HPT) and PTHrP (in HHM) stimulate receptors that activate renal 1α-hydroxylase. However, although PTH secretion in primary HPT is intermittent, continuous secretion of PTHrP by malignant tumors probably downregulates these receptors, inhibiting 1α-hydroxylase activity and decreasing $1,25(OH)_2D$ production. A continuous infusion of PTH causes similar decreases in $1,25(OH)_2D$. Other mechanisms may further decrease $1,25(OH)_2D$ in PTHrP-associated HHM. HHM may have an associated five- to tenfold increase in the phosphaturic factor fibroblast growth factor-23 (FGF-23), which inhibits 1α-hydroxylase activity and decreases $1,25(OH)_2D$ levels. The higher calcium levels typically encountered in HHM may also decrease 1α-hydroxylase activity and $1,25(OH)_2D$ levels.

22. What hormonal and laboratory changes occur in primary HPT?

Secretion of PTH in primary HPT is intermittent; intermittent secretion avoids receptor downregulation and results in increased $1,25(OH)_2D$ formation. Serum calcium levels are higher in HHM than in HPT, and higher calcium levels decrease $1,25(OH)_2D$ production. Thus $1,25(OH)_2D$ levels tend to be high in HPT and low in HHM (see Table 14-3). Traditional associations with primary HPT include hypophosphatemia, hyperchloremia, an increased chloride/phosphate ratio, and mild renal tubular acidosis. Unfortunately, such associations are nonspecific and too insensitive to be of diagnostic use. However, the triad consisting of hypercalcemia, elevated or high-normal PTH, and hypophosphatemia make the diagnosis of primary HPT likely.

23. What PTH assay is most useful in the workup of hypercalcemia?

Intact PTH has 84 amino acids, is 70% metabolized by the liver, is 20% metabolized by the kidneys, and has a half-life of 2 minutes. Less than 1% of the secreted intact hormone remains to interact physiologically with PTH receptors. Although the first 34 amino acids of the *N*-terminus contain the full biologic activity of the hormone, intact PTH (1-84) is the active hormone in vivo. The preferred assays for measurement are the ICMA and IRMA for intact PTH; both are highly sensitive and specific. Because of availability, the IRMA is more commonly used. The IRMA also measures the 7-84–amino acid fragment of intact PTH (1-84). The PTH assay from Scantibodies

TABLE 14-3. HYPERCALCEMIA, PRIMARY HPT, AND MALIGNANCY

	SERUM LEVELS			
	INTACT PTH	PTHRP	$1,25(OH)_2D$	CALCIUM
Primary HPT	↑	↓	↑	↑
PTHrP malignancy	↓	↑	↓	↑
Non-PTHrP malignancy	↓	↓	↓	↑

HPT, hyperparathyroidism; PTHrP, parathyroid hormone–related protein; ↑, increased; ↓, decreased.

Laboratory Inc., Santee, CA, measures whole PTH (1-84) and is a measure of the true intact PTH hormone. This assay was initially believed to be potentially more useful in patients with renal failure; however, it has not proved clinically to be more useful than the IRMA or ICMA assays. Rapid PTH measurements are usually measures of intact PTH and are often performed both preoperatively and intraoperatively (10 minutes after parathyroidectomy). A reduction in PTH of at least 50% indicates a successful operation.

24. What methods best localize the parathyroid tumor in HPT?

Technetium 99m sestamibi single-proton emission computed tomography (SPECT) may be more than 85% to 90% sensitive, specific, and accurate and therefore is the procedure of choice. Sestamibi scanning is most accurate for localizing parathyroid adenomas but is much less useful for parathyroid hyperplasia. Ultrasonography is usually complementary to sestamibi scanning and, when combined with it, increases localization sensitivity to 95%. More frequent use is being made of combined sestamibi uptake and intraoperative gamma-probe localization (see next question). Less commonly, cervical computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), intravenous digital subtraction angiography (IVDSA), arteriography, and selective venous sampling are used.

KEY POINTS 1: HYPERPARATHYROIDISM

1. Primary hyperparathyroidism (HPT) is associated with hypercalcemia, osteoporosis, nephrolithiasis, and symptoms associated with these conditions.
2. The new recommendations for surgery in patients with asymptomatic HPT are as follows: serum calcium more than 1 mg/dL above the upper normal limit, decreased estimated GFR to less than 60 mL/min, reduced bone density with T-score less than –2.5, age less than 50 years, and calcium nephrolithiasis.
3. It is never wrong to recommend surgery for the treatment of asymptomatic HPT if the patient has no contraindications to surgery and has access to a skilled parathyroid surgeon.
4. Advantages of parathyroid surgery include cure of HPT and hypercalcemia in most cases with a single operation, no need for regular prolonged follow-up, decreased fracture rate, and increased bone mass in most patients.
5. Most surgeons prefer preoperative localization studies before minimally invasive parathyroidectomy, before reoperative parathyroid surgery, and for suspected bilateral disease.

25. When should you use preoperative localization of a parathyroid adenoma?

More than 90% to 95% of the time, a skilled parathyroid surgeon can localize and remove a parathyroid adenoma without preoperative localization. For this reason, preoperative localization before standard bilateral neck exploration is not usually necessary. However, minimally invasive parathyroidectomy (MIP) using a small incision localized to one side of the neck is becoming the state-of-the-art surgical approach to treating primary HPT. Most surgeons require preoperative localization studies before MIP, reoperative parathyroid surgery, or surgery for suspected bilateral disease. The best preoperative parathyroid adenoma localization usually consists of combined parathyroid sestamibi scan and ultrasound. Minimally invasive radioguided parathyroidectomy (MIRP) uses radioactive sestamibi uptake with an intraoperative gamma probe and provides for the least invasive and most accurate tumor localization. With MIRP, the operative time is shorter, the procedure can be done on an outpatient basis with use of local anesthesia, accurate localization of multiple adenomas is possible, and the patient can be discharged within hours of the procedure. That being said, standard

neck exploration, MIP, and MIRP all require an experienced parathyroid surgeon. Often finding an experienced parathyroid surgeon is the most important and most difficult task in localizing and treating a parathyroid adenoma.

26. Do all asymptomatic patients with HPT require surgical treatment?

No. Many asymptomatic patients with mild primary HPT do not require surgery (see question 27). However, the only definitive therapy for HPT is parathyroidectomy, and it is usually appropriate to recommend parathyroidectomy for patients with asymptomatic primary HPT if they have access to an experienced parathyroid surgeon. Advantages of parathyroid surgery are cure of HPT and hypercalcemia in most cases with a single operation, no need for regular prolonged follow-up, decreased fracture rate, increased bone mass in most patients, and decreased rate of cardiovascular disease.

27. What are the indications for parathyroidectomy in patients with asymptomatic primary HPT?

1. Serum calcium more than 1.0 mg/dL above the upper normal limit
2. Decreased estimated glomerular filtration rate (GFR) (to < 60 mL/min)
3. Reduced bone density as shown by dual-energy x-ray absorptiometry (DEXA) (T-score < -2.5) at any site and/or previous fragility fracture
4. Age less than 50 years with mild hypercalcemia
5. Calcium nephrolithiasis
6. Patients for whom medical surveillance is neither desired nor possible

28. How should you monitor patients with asymptomatic HPT who have not had parathyroidectomy?

Initially, obtain serum calcium and PTH measurements, DEXA bone densitometry, and GFR estimation. Thereafter, serum calcium measurement and GFR estimation should be performed annually. Three-site DEXA bone densitometry (lumbar spine, hip, and forearm) should be performed every 1 to 2 years. Schedule office visits every 6 months and as needed. Evaluate for symptoms of HPT. Make sure patients maintain adequate hydration (at least 8 glasses of water daily), exercise, and a normal-calcium diet. Avoid thiazide diuretics, lithium, and excessive calcium input. Alert the primary physician to watch for any medical illness predisposing to dehydration.

29. How would you estimate GFR without performing a 24-hour urine collection?

There are multiple equations for estimating GFR; the easiest and most accurate way is to use a Web-based site or an automated GFR from your laboratory. A good Website with which to access most estimates for GFR is http://mdrd.com. This site give you access to Cockcroft-Gault, MDRD, and CKD EPI estimates of GFR. At this time the CKD EPI estimate of GFR is believed to be the most accurate.

30. What therapeutic options are available for patients unable to undergo surgery for HPT?

Calcimimetics bind to the extracellular CaSRs on parathyroid cells and increase chief cell sensitivity to extracellular calcium. This effect shifts the calcium-PTH curve to the left, increasing parathyroid sensitivity to the suppressive effects of calcium at all concentrations. Cinacalcet is the only calcimimetic available for treatment of secondary HPT in end-stage renal disease and for parathyroid carcinoma. It has also been approved for primary HPT with associated severe elevations in calcium. Cinacalcet also decreases calcium reabsorption from the renal tubule and thereby increases urinary calcium excretion. Bisphosphonates inhibit osteoclast-mediated bone resorption and can increase bone mass in osteopenic and osteoporotic patients with primary HPT. Raloxifene may also preserve bone mass in patients who cannot tolerate bisphosphonates. Estrogens preserve bone mass, but their use remains controversial because of the associated potential risk of breast cancer and cardiovascular disease. Denosumab is a monoclonal antibody to receptor activator of nuclear factor-kappa β ligand (RANK-L) that decreases osteoclastic bone resorption. It is approved for treatment of osteoporosis but is not yet approved for hypercalcemia treatment. Angiographic ablation or percutaneous alcohol injection of

parathyroid adenoma tissue can also be tried if a provider having adequate experience with this technique is available.

31. How would you evaluate and treat a patient with normocalcemic HPT?

Normocalcemic HPT (NCHPT) manifests as elevated PTH and normal corrected calcium level. Studies now suggest that NCHPT is more common than previously thought and may cause complications similar to those of hypercalcemic HPT. To diagnose NCHPT, one must evaluate and treat all secondary causes of HPT, such as vitamin D deficiency, CKD, and renal hypercalciuria. Ionized calcium should be measured to confirm the normocalcemia. Vitamin D deficiency should be corrected to a 25-OHD level higher than 30 ng/mL. After secondary HPT has been ruled out, the patient can be monitored and treated like a patient with hypercalcemic HPT. However, referral for parathyroid surgery should not be routine for the normocalcemic patient with HPT but instead should be based on symptoms and signs (see questions 27 and 28).

WEBSITES

1. Parathyroid.com (good review of all aspects of parathyroid disease): http://www.parathyroid.com.
2. Bilezikian JP: Primary hyperparathyroidism. Endotext.org: http://www.endotext.org/parathyroid/parathyroid5/parathyroidframe5.htm.

BIBLIOGRAPHY

Ambrogini E, Cetani F, Cianferotti L, et al: Surgery or surveillance for mild asymptomatic primary hyperparathyroidism: a prospective, randomized clinical trial, *J Clin Endocrinol Metab* 92:3114–3121, 2007.

Augustine MM, Bravo PE, Zeiger MA: Surgical treatment of primary hyperparathyroidism, *Endocr Pract* 17(Suppl 1):75–82, 2011.

Bilezikian JP, Khan AA, Potts JT: Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the third international workshop, *J Clin Endocrinol* 94:335–339, 2009.

Bilezikian JP, Silverberg SJ: Asymptomatic primary hyperparathyroidism, *N Engl J Med* 350: 1746–175, 2004.

Bringhurst FR, Demay MB, Kronenberg HM: Hormones and disorders of mineral metabolism. In Kronenberg HM, Melmed S, Polonsky KS, editors: *Williams Textbook of Endocrinology*, ed 12, Philadelphia, 2011, Elsevier Saunders, p 1237.

Farford R, Presutti J, Moraghan TJ: Nonsurgical management of primary hyperparathyroidism, *Mayo Clin Proc* 82:351–355, 2007.

Fraser WD: Seminar—hyperparathyroidism, *Lancet* 374:145–58, 2009.

Kukora JS, Zeiger MA, Clark OH, et al: AACE/AAES position statement on diagnosis and management of primary hyperparathyroidism, *Endocr Pract* 11:49–54, 2005.

Lew JI, Solorzano C: Surgical management of primary hyperparathyroidism: state of the art, *Surg Clin N Am* 89:1205–1225, 2009.

Lowe H, McMahon DJ, Rubin MR, et al: Normocalcemic primary hyperparathyroidism: further characterization of a new clinical phenotype, *J Clin Endocrinol Metab* 92:3001–3005, 2007.

Maruani G, Hertiga A, Paillard M, et al: Normocalcemic primary hyperparathyroidism: evidence for a generalized target-tissue resistance to parathyroid hormone, *J Clin Endocrinol Metab* 88:4641–4648, 2003.

Peacock M, Bilezikian JP, Klassen PS, et al: Cinacalcet hydrochloride maintains long-term normocalcemia in patients with primary hyperparathyroidism, *J Clin Endocrinol Metab* 90:135–141, 2005.

Quiros RM, Alioto J, Wilhelm SM, et al: An algorithm to maximize use of minimally invasive parathyroidectomy, *Arch Surg* 139:501–507, 2004.

Rejnmark L, Vestergtaard P, Mosekilde L: Clinical review—nephrolithiasis and renal calcifications in primary hyperparathyroidism, *J Clin Endocrinol Metab* 96(8):2377–2385, 2011.

Rodgers SE, Lew JI: Review article—the parathyroid hormone assay, *Endocr Pract* 17(Suppl 1):2–6, 2011.

Rubello D, Al-Nahhas A, Khan S: Is there an ideal algorithm in preoperative localization of primary hyperparathyroidism? *Nucl Med Rev* 9:105–107, 2006.

Shin JJ, Milas M, Mitchell J: Impact of localization studies and clinical scenario inpatients with hyperparathyroidism being evaluated for reoperative neck surgery, *Arch Surg* 146(12):1397–1430, 2011.

Siilin H, Rastad J, Ljunggren Ö, et al: Disturbances of calcium homeostasis consistent with mild primary hyperparathyroidism in premenopausal women and associated morbidity, *J Clin Endocrinol Metab* 93:47–53, 2008.

Vaid S, Pandelidis S: Minimally invasive parathyroidectomy, *Arch Surg* 146(7):876–878, 2011.

CHAPTER 15

HYPERCALCEMIA OF MALIGNANCY

Michael T. McDermott

1. What are the two major categories of hypercalcemia of malignancy?

- Humoral hypercalcemia of malignancy (HHM)
- Local osteolytic hypercalcemia (LOH)

2. What types of cancers are associated with HHM?

Carcinoma of the lung, particularly squamous cell carcinoma, is the most common. Other tumors associated with this disorder are squamous cell carcinomas of the head, neck, and esophagus and adenocarcinomas of the breast, kidney, bladder, pancreas, and ovary.

3. What is the cause of HHM?

HHM results when solid malignancies, both solitary and metastatic, secrete into the circulation one or more substances that cause hypercalcemia. The humoral mediator identified in more than 90% of cases is parathyroid hormone–related peptide (PTHrp). Other humoral substances that are occasionally secreted and contribute to the development of hypercalcemia include transforming growth factor-alpha (TGF-α), tumor necrosis factor (TNF), and various interleukins and cytokines.

4. What is PTHrp?

PTHrp is a protein that has sequence homology with the first 13 amino acids of parathyroid hormone (PTH). Both PTH and PTHrp bind to a common receptor (PTH/PTHrp receptor), resulting in stimulation of bone resorption and inhibition of renal calcium excretion. PTHrp is found in high concentrations in breast milk and amniotic fluid, but it can be detected in almost every tissue in the body; its level is increased in the circulation during pregnancy. The physiologic endocrine function of PTHrp may be to govern the transfer of calcium from the maternal skeleton and bloodstream into the developing fetus and into breast milk. As a generalized paracrine factor, it also regulates growth and development of many tissues, most prominently the skeleton and breast.

5. How does PTHrp cause hypercalcemia in patients with cancer?

Elevated circulating concentrations of PTHrp stimulate generalized bone resorption, flooding the bloodstream with excessive calcium; PTHrp also acts on the kidneys, preventing excretion of the greater calcium load. This combination produces an increase in the serum calcium concentration. Hypercalcemia induces polyuria, which leads to dehydration with impaired renal function, further reducing calcium excretion and leading to a cycle of progressive and eventually life-threatening hypercalcemia.

6. How do you make a diagnosis of HHM?

Hypercalcemia in any patient with a known malignancy should make one suspect this diagnosis. Occasionally, however, a raised serum calcium level is the first clue to an underlying cancer. The key to the diagnosis is a suppressed serum intact PTH level; this finding reliably excludes hyperparathyroidism, the other leading cause of hypercalcemia. Serum PTHrp levels are nearly always high, but the measurement of PTHrp, which is an expensive test, is not necessary for diagnosis in most instances. If a patient meeting these diagnostic criteria does not have a known tumor, a careful search for an occult malignancy should be undertaken.

7. What types of cancer are associated with LOH?

Breast cancer with skeletal metastases, multiple myeloma, and lymphoma are the major cancers associated with LOH.

KEY POINTS 1: HYPERCALCEMIA OF MALIGNANCY

1. Hypercalcemia of malignancy is most often due to tumor production of parathyroid hormone–related peptide (PTHrp), which binds to parathyroid hormone (PTH) and PTH/PTHrp receptors to stimulate bone resorption.
2. The key diagnostic test in hypercalcemic patients is measurement of serum PTH, which is elevated or high normal in primary hyperparathyroidism but low or undetectable in hypercalcemia of malignancy and most other hypercalcemic disorders.
3. The development of hypercalcemia of malignancy portends a poor prognosis in most patients with cancer, because it tends to occur with advanced tumor stages.
4. Serum calcium levels can be lowered effectively in patients with hypercalcemia of malignancy by the intravenous administration of saline, bisphosphonates and denosumab.

8. What is the cause of LOH?

LOH generally occurs when cancer cells are present in multiple sites throughout the skeleton. The pathogenesis involves the elaboration by malignant cells of osteoclast-stimulating factors directly onto the surface of bone. Such factors include PTHrp, the protein DKK1, lymphotoxin, interleukins, transforming growth factors, prostaglandins, and procathepsin D.

9. How do you make a diagnosis of LOH?

The diagnosis is fairly straightforward when hypercalcemia develops in a patient with one of the previously noted malignancies. Again, the key is demonstration of a suppressed serum intact PTH level, indicating that hyperparathyroidism is not the culprit. Patients without a known malignancy should undergo a complete blood count, serum and urine protein electrophoresis, and bone scan; if these studies are not informative, a bone marrow biopsy should be performed.

10. Can lymphomas cause hypercalcemia by other mechanisms?

Some lymphomas express 1α-hydroxylase activity. This enzyme converts 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D, which then stimulates increased intestinal calcium absorption and bone resorption. This process may eventually lead to hypercalcemia, particularly in patients who have reduced renal calcium excretion due to dehydration or intrinsic renal disease.

11. What is the prognosis for patients with hypercalcemia of malignancy?

Because hypercalcemia generally correlates with far-advanced disease, the overall prognosis is quite poor. In one study, the median survival of patients in whom hypercalcemia developed was only 30 days. Effective treatments are available to reduce the serum calcium levels, however.

12. How do you treat hypercalcemia of malignancy?

Treatment of the underlying malignancy is the most effective measure. For symptomatic patients, rapid reduction of serum calcium is also indicated. An intravenous saline infusion (200-500 mL/h, if tolerated) to enhance renal calcium excretion should be the initial measure in most patients. Furosemide 20 to 40 mg intravenous (IV) can be added after adequate hydration is achieved. Antiresorptive medications should be given concomitantly. The most effective of these are the intravenous bisphosphonates and denosumab. Suggested treatment regimens are shown in Table 15-1.

TABLE 15-1. TREATMENT REGIMENS FOR HYPERCALCEMIA OF MALIGNANCY

MEDICATION	DOSAGE
Zoledronic acid (Zometa)	4 mg in 50 mL normal saline IV over 15 min
Pamidronate (Aredia)	60–90 mg in 250–500 mL NS IV over 2–4 h
Denosumab (Xgeva)	120 mg SC every 4 weeks
Plicamycin	25 mg/kg IV over 4–6 h
Calcitonin	4–8 IU/kg SC or intramuscular twice daily
Gallium nitrate	100–200 mg/m^2/24 h for 5 days
Prednisone	60 mg daily for 10 days

IV, intravenous; SC, subcutaneous.

BIBLIOGRAPHY

Bilezikian JP: Management of acute hypercalcemia, *N Engl J Med* 326:1196–1203, 1992.

Grill V, Ho P, Body JJ, et al: Parathyroid hormone related protein: elevated levels in both humoral hypercalcemia of malignancy and hypercalcemia complicating metastatic breast cancer, *J Clin Endocrinol Metab* 73:1309–1315, 1991.

Hortobagyi GN, Theriault RL, Porter L, et al: Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases, *N Engl J Med* 335:1785–1791, 1996.

Major P, Lortholary A, Hon J, et al: Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized controlled clinical trials, *J Clin Oncol* 19:338–367, 2001.

Mundy GR, Guise TA: Hypercalcemia of malignancy, *Am J Med* 103:134–145, 1997.

Nussbaum SR, Younger J, Vandepol CJ, et al: Single dose intravenous therapy with pamidronate for the treatment of hypercalcemia of malignancy. Comparison of 30, 60 and 90 mg doses, *Am J Med* 95:297–304, 1993.

Ralston SH, Gallacher SJ, Patel U, et al: Cancer associated hypercalcemia: morbidity and mortality. Clinical experience in 126 treated patients, *Ann Intern Med* 112:499–504, 1990.

Roodman GD: Mechanisms of bone metastasis, *N Engl J Med* 350:1655–1664, 2004.

Stewart AF: Hypercalcemia associated with cancer, *N Engl J Med* 352:373–379, 2005.

Stewart AF, Broadus AE: Parathyroid hormone related proteins: coming of age in the 1990s, *J Clin Endocrinol Metab* 71:1410–1414, 1990.

HYPOCALCEMIA

Reed S. Christensen and Kimberly C. Zibert

1. Define hypocalcemia.

Hypocalcemia is the state in which the serum ionized calcium level drops below the normal range of 1.0 to 1.3 mmol/L. This corresponds, under normal conditions, to a total serum calcium level of 2.1 to 2.5 mmol/L (8.5-10.5 mg/dL).

2. How are serum calcium and serum albumin levels related?

Approximately 50% of serum calcium is bound to albumin, other plasma proteins, and related anions, such as citrate, lactate, and sulfate. Of this, 40% is bound to protein, predominantly albumin, and 10% to 13% is attached to anions. The remaining 50% is unbound or ionized calcium. The total serum calcium level reflects both the bound and the unbound portions with a normal range of 2.1 to 2.5 mmol/L (8.5-10.5 mg/dL).

3. How is the total serum calcium corrected for a low serum albumin level?

Total serum calcium levels are corrected for hypoalbuminemia by the addition of 0.8 mg/dL to the serum calcium level for every 1.0 g/dL that the albumin level is below 4.0 g/dL. The adjusted level of total serum calcium correlates with the level of ionized calcium, which is the physiologically active form of serum calcium.

$$\text{Corrected Ca (mg/dL)} = \text{serum Ca (mg/dL)} + 0.8(4.0 - \text{measured albumin (g/dL)}$$

4. What is the most common cause of low total serum calcium?

Hypoalbuminemia. The ionized calcium concentration is normal. Low serum albumin is common in chronic illness and malnutrition.

5. What factors other than albumin influence the levels of serum ionized calcium?

Serum pH influences the level of ionized calcium by causing decreased binding of calcium to albumin in acidosis and increased binding in alkalosis. As an example, respiratory alkalosis, seen in hyperventilation, causes a drop in the serum ionized calcium level. A shift of 0.1 pH unit is associated with an ionized calcium change of 0.04 to 0.05 mmol/L (0.16-0.20 mg/dL). Increased levels of chelators, such as citrate, which may occur during large-volume transfusions of citrate-containing blood products, also may lower the levels of ionized calcium. Heparin may act similarly.

6. How is serum calcium regulated?

Three hormones maintain calcium homeostasis: parathyroid hormone (PTH), vitamin D, and calcitonin. PTH acts in three ways to raise serum calcium levels: (1) stimulates osteoclastic bone resorption, (2) increases conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D, increasing intestinal calcium absorption, and (3) increases renal reabsorption of calcium. Calcitonin decreases the level of serum calcium by suppressing osteoclast activity in bone. The interplay of these hormones maintains calcium levels within a narrow range in a normal individual. Calcium levels are also influenced by the presence or absence of hyperphosphatemia.

7. What steps in vitamin D metabolism may influence serum calcium levels?

Vitamin D is obtained through the diet or is formed in the skin in the presence of ultraviolet light. Vitamin D is converted to 25-hydroxyvitamin D in the liver and finally to 1,25-dihydroxyvitamin D, the most active form of vitamin D, in the kidney. 1,25-dihydroxyvitamin D acts directly on intestinal cells to increase calcium absorption. Deficiency in any of these steps may cause hypocalcemia.

8. What are the major causes of hypocalcemia?

The multiple organ and hormonal regulatory systems involved in calcium homeostasis create the potential for multiple causes of hypocalcemia. The etiology of hypocalcemia must be considered in relation to the level of serum albumin, the secretion of PTH, and the presence or absence of hyperphosphatemia. Initially, hypocalcemia may be approached by a search for failure in one or more of these systems. The systems primarily involved are the parathyroid glands, bone, kidney, and liver; the following list shows the clinical entities followed by their mechanisms:

- Hypoparathyroidism: decreased PTH production
- Hypomagnesemia: decreased PTH release, responsiveness, and action
- Citrate toxicity from massive blood transfusion: complexing of calcium with citrate
- Pseudohypoparathyroidism: PTH ineffective at target organ
- Liver disease: decreased albumin production, decreased 25-hydroxyvitamin D production, drugs that stimulate 25-hydroxyvitamin D metabolism
- Renal disease: renal calcium leak, decreased 1,25-dihydroxyvitamin D production, elevated serum phosphate (Po_4) from decreased Po_4 clearance; drugs that increase renal clearance of calcium
- Bone disease: drugs suppressing bone resorption; “hungry bone syndrome”—recovery from hyperparathyroidism or hyperthyroidism
- Phosphate load: endogenous—tumor lysis syndrome, hemolysis, and rhabdomyolysis; exogenous—phosphate-containing enemas, laxatives, and phosphorus burns
- Pancreatitis: sequestration of calcium in the pancreas; other
- Toxic shock syndrome, other critical illness: decreased PTH production or PTH resistance

9. What physical signs suggest hypocalcemia?

The hallmark sign of acute hypocalcemia is tetany. This is characterized by neuromuscular irritability, which is usually seen when the serum ionized calcium concentration is less than 4.3 mg/dL (total serum calcium $<$ 7-7.5 mg/dL).

- Mild tetany: perioral numbness, acral paresthesias, and muscle cramps
- Severe tetany: carpopedal spasms, laryngospasm, and focal or generalized seizures
- Latent tetany: Trousseau’s and Chvostek’s signs

Testing for Chvostek’s and Trousseau’s signs is useful in detecting hypocalcemia. Chvostek’s sign is an ipsilateral facial twitch elicited by percussing the facial nerve below the zygomatic arch at the angle of the jaw. Trousseau’s sign is a forearm spasm induced by inflation of an upper arm blood pressure cuff to a pressure greater than systolic blood pressure for up to 3 minutes. The spasm causes flexion of the wrist and metacarpophalangeal joints, extension of the fingers, and adduction of the thumb. It is important to note that 4% to 25% of individuals with normal calcium levels have positive responses to these tests.

10. What laboratory tests are clinically useful in distinguishing among the causes of hypocalcemia?

Table 16-1 summarizes the laboratory findings in the conditions listed.

11. Describe the symptoms of hypocalcemia.

- Early symptoms: numbness and tingling involving fingers, toes, and circumoral region
- Neuromuscular symptoms: cramps, fasciculations, laryngospasm, and tetany

TABLE 16-1. DIFFERENTIAL DIAGNOSIS OF LABORATORY EVALUATION OF HYPOCALCEMIA

	CALCIUM	PHOSPHATE	PTH	25-OH VITAMIN D	$1,25(OH)_2$ VITAMIN D
Hypoparathyroidism	↓	↑	↓	Normal	↓
Pseudohypoparathyroidism	↓	↑	↑	Normal	↓ or Normal
Liver disease	↓	↓	↑	↓	↓ or Normal
Renal disease (secondary hyperparathyroidism)	↓	↑	↑	Normal	↓ or Normal

↑, increased; ↓, decreased; PTH, parathyroid hormone

- Cardiovascular symptoms: arrhythmias, bradycardia, and hypotension
- Central nervous system symptoms: irritability, paranoia, depression, psychosis, organic brain syndrome, and seizures; "cerebral tetany," which is not a true seizure (see question 13), may also be seen in hypocalcemia; subnormal intelligence has also been reported
- Chronic symptoms: papilledema, basal ganglia calcifications, cataracts, dry skin, coarse hair, and brittle nails

Symptoms reflect the absolute calcium concentration and the rate of fall in calcium concentration. Individuals may be unaware of symptoms because of gradual onset and may realize they have experienced an abnormality only when their sense of well-being improves with treatment.

12. What radiographic findings may be present with hypocalcemia?

Calcifications of basal ganglia may occur in the small blood vessels of that region. These occasionally may cause extrapyramidal signs but usually are asymptomatic. Of note, 0.7% of routine computed tomography (CT) scans of the brain show calcification of the basal ganglia.

13. What is cerebral tetany, and how does it differ from a true seizure?

Cerebral tetany manifests as generalized tetany without loss of consciousness, tongue biting, incontinence, or postictal confusion. Anticonvulsants may relieve the symptoms, but because they enhance 25-hydroxyvitamin D catabolism, they also may worsen the hypocalcemia.

KEY POINTS 1: HYPOCALCEMIA

1. Serum calcium levels must be corrected for serum albumin levels in hypocalcemia.
2. Multiple organ systems, minerals, anions, and drugs affect calcium levels and must be considered in the evaluation of hypocalcemia.
3. Hypocalcemia is a frequent problem in trauma and intensive care settings and is often a result of intravenous agents.
4. 1,25-dihydroxyvitamin D is the treatment for hypocalcemia in hypoparathyroidism and renal failure.
5. PTH is not currently an approved treatment for hypocalcemia.

14. How does hypocalcemia affect cardiac function?

Calcium is involved in cardiac automaticity and is required for muscle contraction. Hypocalcemia can therefore result in arrhythmias and reduced myocardial contractility. This decrease in the force of

contraction may be refractory to pressor agents, especially those that involve calcium in their mechanism of action. Through this process, beta-blockers and calcium channel blockers can exacerbate cardiac failure. With low serum calcium, the QT interval is prolonged, and ST changes may mimic those seen in ischemia. Although the relationship is variable, the calcium level inversely correlates moderately well with the interval from the Q-wave onset to the peak of the T wave.

15. What are the potential ophthalmologic findings in hypocalcemia?

Papilledema may occur with subacute and chronic hypocalcemia. Patients are most often asymptomatic, and the papilledema usually resolves with normalization of the serum calcium level. If symptoms develop or if papilledema does not resolve when the patient is normocalcemic, a cerebral tumor and benign intracranial hypertension must be excluded. Optic neuritis with unilateral loss of vision occasionally develops in hypocalcemic patients. Lenticular cataracts also may occur with long-standing hypocalcemia but usually do not change in size after hypocalcemia is corrected.

16. With which autoimmune disorders is hypocalcemia sometimes associated?

Hypoparathyroidism may result from autoimmune destruction of the parathyroid glands. This disorder has been associated with adrenal, gonadal, and thyroid failure as well as with alopecia areata, vitiligo, and chronic mucocutaneous candidiasis. This combination of conditions, each associated with organ-specific autoantibodies, has been termed the *autoimmune polyendocrinopathy syndrome, type 1* (see Chapter 52).

17. Hypocalcemia is frequently encountered in intensive care settings. What are the potential causes?

Low total serum calcium levels, which are found in 70% to 90% of patients receiving intensive care, result from multiple causes, including:

- Hypoalbuminemia
- Administration of anionic loads causing chelation (i.e., citrate, lactate, oxalate, bicarbonate, phosphate, ethylenediaminetetraacetic acid, and radiographic contrast media)
- Rapid blood transfusion with citrate ion as a preservative and anticoagulant therapy
- Parathyroid failure and decreased vitamin D synthesis in severe illness
- Sepsis inducing some degree of resistance to the biologic effects of PTH

Because of all the preceding factors, it is recommended that ionized serum calcium rather than total serum calcium be measured in patients with severe illness.

18. Hypercalcemia is not unusual in patients with cancer. What conditions may lead to hypocalcemia in this patient group?

- Tumor lysis syndrome, which causes hyperphosphatemia and associated formation of intravascular and tissue calcium-phosphate complexes.
- Multiple chemotherapeutic agents and antibiotics (amphotericin B and aminoglycosides) induce hypomagnesemia, which in turn impairs secretion of PTH and causes resistance to PTH in skeletal tissue.
- Thyroid surgery and neck irradiation with transient or permanent hypoparathyroidism.
- Medullary carcinoma of the thyroid and pheochromocytoma may secrete calcitonin and on rare occasions cause hypocalcemia.

19. What drugs may cause hypocalcemia?

Phenobarbital, phenytoin, primidone, rifampin, and glutethimide increase hepatic metabolism of 25-hydroxyvitamin D and may thereby cause hypocalcemia. Aminoglycosides, diuretics (furosemide), and chemotherapeutic agents that induce renal magnesium wasting, and laxatives or enemas that create a large phosphate load, also may be associated with hypocalcemia. Bisphosphonates, heparin, ketoconazole, isoniazid, fluoride, foscarnet, and glucagon may also induce hypocalcemia by a variety of mechanisms.

20. Which vitamin D metabolite is best for assessing total body vitamin D stores, 25-hydroxyvitamin D or 1,25-dihydroxyvitamin D?

The serum 25-hydroxyvitamin D level best reflects total body vitamin D stores. The conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D is tightly controlled, and the level of serum 1,25-dihydroxyvitamin D is usually maintained despite significant vitamin D depletion. Increases in PTH (secondary hyperparathyroidism) stimulate increased conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D in this situation.

21. How is hypocalcemia treated?

Asymptomatic hypocalcemia requires supplementation with oral calcium and vitamin D derivatives to maintain the serum calcium level at least in the 7.5 to 8.5 mg/dL range. When the serum calcium falls acutely to a level at which the patient is symptomatic, intravenous administration is recommended. The dosage of calcium depends on the amount of elemental calcium present in a given preparation (Table 16-2). For a hypocalcemic emergency, 90 mg of elemental calcium may be given as an intravenous bolus, or alternatively 100 to 300 mg of elemental calcium may be given intravenously over 10 minutes, followed by an infusion of 0.5 to 2.0 mg/kg/h.

22. When is treatment with 1,25 dihydroxyvitamin D (calcitriol) indicated?

Under normal conditions, 25-hydroxyvitamin D is converted to 1,25-dihydroxyvitamin D (calcitriol) in the kidney through the stimulatory influence of PTH. Two conditions can therefore make the body unable to produce adequate amounts of calcitriol: hypoparathyroidism and renal failure. Because calcitriol is essential for normal intestinal calcium absorption, oral calcitriol (Rocaltrol) supplementation is indicated in patients who have either hypoparathyroidism or chronic renal failure. Of note, because vitamin D has weak biologic activity, these patients may be given large dosages of vitamin D (50,000-100,000 U/day) if calcitriol is unavailable.

23. Can recombinant human PTH (rhPTH) be used in the treatment of hypocalcemia?

Subcutaneous injections of rhPTH (Forteo) are currently indicated only for osteoporosis but have been shown to be effective in normalizing serum calcium levels in hypoparathyroidism. Therapy for this indication, however, has not yet been approved by the U.S. Food and Drug Administration (FDA).

TABLE 16-2. ELEMENTAL CALCIUM CONTENT OF COMMONLY USED PREPARATIONS

Preparation	Oral Dose	Elemental Calcium (mg)
Calcium citrate:		
Citracal	950 mg	200
Calcium acetate:		
PhosLo	667 mg	169
Calcium carbonate:		
Tums	500 mg	200
Tums Ex	750 mg	300
Oscal	625 mg	250
Oscal 500	1250 mg	500
Calcium 600	1500 mg	600
Titralac (suspension)	1000 mg/5 mL	400
Intravenous Agent	**Volume**	**Elemental Calcium (mg)**
Calcium chloride	2.5 mL of 10% solution	90
Calcium gluconate	10 mL of 10% solution	90
Calcium gluceptate	5 mL of 22% solution	90

BIBLIOGRAPHY

Ariyan CE, Sosa JA: Assessment and management of patients with abnormal calcium, *Crit Care Medicine* 32:S146–S154, 2004.

Dickerson RN: Treatment of hypocalcemia in critical illness, *Nutrition* 23:358–361, 2007.

Kastrup EK, editor: *Drug Facts and Comparisons*, St. Louis, 2003, Wolters Kluwer Health.

Kronenberg HM, Melmed S, Polonsky KS, et al: Hypocalcemic disorders. In *Williams Textbook of Endocrinology*, ed 11, Philadelphia, 2008, Saunders, pp 1241–1249.

Lind L: Hypocalcemia and parathyroid hormone secretion in critically ill patients. *Crit Care Med* 28:93–98, 2000.

McEvoy GK, editor: Calcium salts. In *AHFS Drug Information*, Bethesda, MD, 2007, American Society of Health-System Pharmacists, pp 2655–2661.

Moe SM: Disorders involving calcium, phosphorus, and magnesium, *Primary Care* 35(2):215–237, 2008.

Potts JT: Hypocalcemia. In Kasper DL, editor: *Principles of Internal Medicine*, ed 16, New York, 2005, McGraw-Hill, pp 2263–2268.

Sarko J: Bone and mineral metabolism, *Emerg Med Clin North Am* 23:703–721, 2005.

Shane E: Hypocalcemia: pathogenesis, differential diagnosis and management. In Favus MJ, editor: *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*, ed 4, Philadelphia, 1999, Lippincott Williams & Wilkins, pp 223–226.

Winer KK, Ko CW, Reynolds JC, et al: Long-term treatment of hypoparathyroidism: a randomized controlled study comparing parathyroid hormone-(1–34) versus calcitriol and calcium, *J Clin Endocrinol Metab* 88:4214–4220, 2003.

NEPHROLITHIASIS

Leonard R. Sanders

CHAPTER 17

1. Define hypercalciuria, kidney (renal) stones, renal calculi, nephrolithiasis, urolithiasis, renal lithiasis, and nephrocalcinosis.

Hypercalciuria is urinary calcium excretion greater than 300 mg/day in men and greater than 250 mg/day in women. A more accurate definition is urinary calcium excretion greater than 4 mg per kg of ideal body weight per day in either sex. A good estimate of the 24-hour urine calcium excretion is 1.1 times the calcium-to-creatinine ratio (Ca/Cr) on a random urine specimen. For example, if urine calcium is 20 mg/dL and urine creatinine is 70 mg/dL, then the Ca/Cr would be 20:70 or 0.286 g (286 mg/day). The estimated 24-hour urinary calcium excretion would be $1.1 \times 286 = 315$ mg/day. Kidney stones, renal calculi, nephrolithiasis, urolithiasis, and renal lithiasis are synonymous terms that define the clinical syndrome of formation and movement of stones in the urinary collecting system. Renal calculi are abnormally hard, crystalline, insoluble substances that form in the renal collecting system. Nephrocalcinosis is deposition of calcium salts in the renal parenchyma.

2. Who is at risk for the development of kidney stones?

The average prevalence of kidney stones in the United States is approximately 5%, with the lifetime risk for a stone being 13% in men and 7% in women. The yearly cost of kidney stone disease in the United States is more than $5 billion. Fifty percent of patients with kidney stones have a recurrence within 5 to 10 years. Stones occur most often between ages 20 and 60 years and occur in Caucasians more than other ethnicities. Women have had more stones in recent years, possibly because of increased calcium and protein intake and greater exercise with the potential for dehydration. Review of nephrolithiasis in the Women's Health Initiative suggests that hormone replacement therapy is a risk for renal stones. Other risks for stones include a family history of stones, obesity, diabetes mellitus, hypertension, autosomal dominant polycystic kidney disease, medullary sponge kidney, renal tubular acidosis, urine volume less than 2 L/day, dietary sodium greater than 2 g/day, low water intake, and high protein intake (see question 4).

3. What are the compositions and approximate frequencies of kidney stones in the United States?

There are six major types of stones, as outlined in Figure 17-1, which also shows the approximate frequency of occurrence of each type of stone.

4. What are the main causes of nephrolithiasis?

The most common causes of nephrolithiasis are the various types of idiopathic hypercalciuria (IH): absorptive hypercalciuria (AH) types AH-I to AH-III (renal phosphate leak) and renal hypercalciuria (RH). Other causes are primary hyperparathyroidism, hyperoxaluria, hyperuricosuria, hyperphosphaturia, hypocitraturia, hypomagnesuria, infection stones, gouty diathesis, renal tubular acidosis, cystinuria, and, possibly, nanobacteria. Rarely, kidney stones may form from xanthine, triamterene, monosodium urate, ephedrine, guaifenesin, and indinavir (protease inhibitor). Patients with idiopathic nephrolithiasis make up 10% to 20% of "stone formers" in whom routine workup yields no identifiable cause.

5. Describe the conditions associated with both renal stone disease and hypercalciuria.

Calcium stones account for 80% of all kidney stones. Approximately 40% to 50% of calcium stone formers have hypercalciuria. Of those with hypercalciuria, 40% have IH, 5% have primary

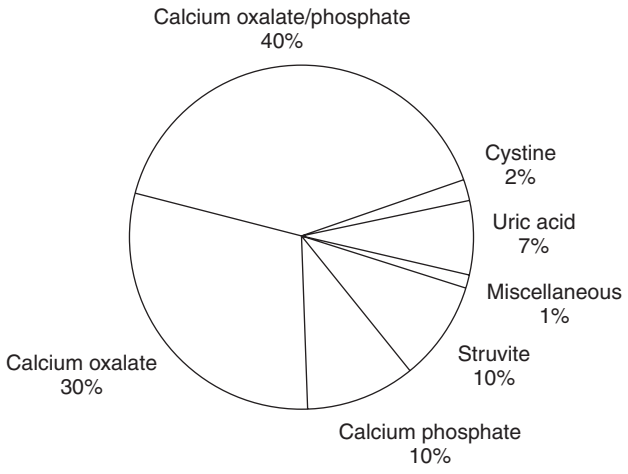


Figure 17-1. Frequency of the kinds of kidney stones.

hyperparathyroidism, and 3% have renal tubular acidosis. Other causes of hypercalciuria include excessive dietary vitamin D, excessive calcium and alkali intake, sarcoidosis, Cushing's syndrome, hyperthyroidism, Paget's disease of bone, and immobilization. Nephrolithiasis is also associated with infection, acute and chronic kidney injury, coronary artery disease, type 2 diabetes mellitus, hypertension, and the metabolic syndrome.

6. What are the most important causes of normocalciuric calcium nephrolithiasis?

The most important and most common causes of normocalciuric calcium nephrolithiasis are hypocitraturia (50%), hyperuricosuria (25%), hyperoxaluria (10%), and urinary stasis (5%).

7. Describe the process of renal stone formation.

Initially, urinary crystallization or precipitation of sparingly soluble salts and acids occurs. Nucleation follows as the initial crystals and urinary matrix ions form a stable framework for crystal enlargement through growth and aggregation. After they are sufficiently large, crystals become trapped in a narrow portion of the urinary collecting system (often at the end of collecting ducts), forming a nidus for further stone growth. Alternatively, crystals form in the medullary interstitium, are extruded, and adhere to the renal papilla and form a Randall's plaque nidus for further crystal accumulation and stone growth. Once stone growth occurs, the stone may detach from the renal papilla, move distally, and cause obstruction. Common sites for obstruction are the ureteropelvic junction, midureter, and ureterovesical junction.

8. Discuss the pathophysiologic factors that influence the formation of renal stones.

Renal stones result from hereditary or acquired disorders causing supersaturation of stone precursors, deficiency of stone inhibitors, and possibly excess promoters. Supersaturation causes crystallization with mineral precursors, such as calcium and oxalate. Calcium oxalate crystals bind to anionic, sialic acid–containing glycoproteins on the apical surfaces of renal tubular epithelial cells, allowing further growth. Other factors that increase stone formation include urinary stasis (medullary sponge kidney), decreased flow (obstruction), increased urine ammonium (infection), dehydration (concentrated urine), and increased urinary alkalinity (renal tubular acidosis [RTA]). Type I RTA promotes stone formation

through the increased release of calcium and phosphorus from bone to buffer the acidemia, with resulting hypercalciuria and hyperphosphaturia. The acidemia enhances proximal tubule reabsorption of citrate with resulting hypocitraturia. The alkaline urine of RTA promotes precipitation of calcium phosphate stones. Acidemia with a positive urine anion gap (UNa + UK − UCl) is a clue to the presence of RTA.

9. What are the main chemical precursors of renal stones?

Relatively high concentrations of salt and acid solutes are the main determinants of crystalluria and stone formation. Calcium oxalate is most common and is supersaturated to four to five times its solubility in normal urine. Other precursors are calcium phosphate (hydroxyapatite) and calcium phosphate monohydrate (brushite). Uric acid, cystine, struvite (magnesium ammonium phosphate), and mucoprotein are undersaturated stone precursors. Drugs such as ascorbic acid (conversion to oxalate) and triamterene (nidus for stone formation) also may promote renal stone formation.

10. What are the main inhibitors of renal stone formation? How do they work?

Inhibitors include urinary citrate, pyrophosphate, magnesium, nephrocalcin, uropontin, glycosaminoglycans, and Tamm-Horsfall protein. Most of them bind crystal precursors; for example, citrate binds calcium, making it less available to bind to oxalate. Inhibitors improve solubility and impair precipitation, nucleation, crystal growth, or aggregation. They also compete with stone precursor minerals, such as calcium oxalate, for binding to the apical surfaces of epithelial cells and inhibit epithelial cell adhesion and internalization of calcium oxalate crystals. Finally, inhibitors impair stone precursor transformation to a focus for crystallization and stone growth.

11. What is nephrocalcin? What role does it play in the formation of renal stones?

Nephrocalcin is an anionic protein produced by the proximal renal tubule and the loop of Henle. It normally inhibits the nucleation, crystal growth, and aggregation phases of stone formation. However, nephrocalcin isolated from some stone formers has defective structure and function and is found in the matrix of many calcium stones. Thus nephrocalcin may have a dual role in stone formation. When normal, it acts as an inhibitor of stone formation. When abnormal, it may act as a promoter by binding calcium and forming a nidus for crystallization.

12. What are the promoters of renal stone formation?

Promoters of renal stone formation are poorly characterized but are believed to be primarily urinary mucoproteins and glycosaminoglycans. Under certain conditions, promoters enhance the formation of renal stones.

13. How does the kidney handle calcium?

Approximately 60% of the serum calcium is ionized or complexed and freely filtered by the glomerulus. The kidney reabsorbs 98% of the filtered calcium passively throughout the nephron. Sixty percent of the reabsorption occurs in the proximal convoluted tubule, 30% in the loop of Henle, and 10% in the distal tubule. Furosemide impairs calcium reabsorption in the loop of Henle and increases urinary calcium excretion. Thiazide diuretics impair distal tubule reabsorption of sodium, thereby increasing intracellular negativity and calcium reabsorption. PTH increases distal tubular calcium reabsorption by enhancing calcium channel activity.

14. Calculate the normal filtered and excreted load of calcium per day.

The serum calcium concentration is normally 10 mg/dL. The kidney filters complexed and free calcium, which makes up 60% of the total, or 6 mg/dL. The normal glomerular filtration rate (GFR) is 120 mL/min. Thus the filtered load of calcium is 6 mg/100 mL × 120 mL/min × 1440 min/day = 10,368 mg/day. Because the kidney reabsorbs 98% of the filtered calcium, only 2% is excreted. Thus normally the kidney excretes about 200 mg of calcium/day (10,368 mg/day × 0.02 = 207 mg/day). If the excreted calcium level increases to 5%, the urinary calcium level increases to 500 mg/day.

KEY POINTS 1: INCIDENCE AND ETIOLOGY OF NEPHROLITHIASIS

1. Kidney stones are increasingly more common, possibly because of excessive dietary protein and calcium, exercise without adequate hydration, and rising rates of obesity.
2. Approximately 10% of the U.S. population has a lifetime risk for at least one kidney stone.
3. Stones form because of super saturation of urinary stone precursors (such as calcium and oxalate), insufficient stone inhibitors (such as citrate), abnormal urine pH, or insufficient urine volume.
4. Stones are most commonly calcium based and result from hypercalciuria caused by excess absorption of dietary calcium, resorption of bone calcium, and unusually decreased renal calcium reabsorption.
5. Restricting dietary calcium without restricting dietary oxalate increases oxalate absorption and the risk for calcium oxalate stones.

15. How do the serum calcium level and dietary sodium intake affect hypercalciuria?

To help prevent hypercalcemia, nonrenal elevation in serum calcium causes increase in both filtered calcium and urinary calcium. Increased sodium delivery to the loop of Henle and the distal tubule also raises urinary calcium. In non–stone formers, urinary calcium excretion increases about 40 mg for each 100 mEq of sodium excretion. In hypercalciuric stone formers, calcium excretion increases up to 80 mg per each 100 mEq of sodium. Because urinary sodium excretion equilibrates to dietary sodium intake, restricting dietary sodium reduces urinary calcium excretion. In patients with stones, recommended daily dietary sodium is no more than 100 mEq (2300 mg).

16. Describe the etiology and pathophysiology of IH.

IH affects 10% of the general population and 40% of stone formers. The four types of IH are AH-I to AH-III and RH. AH-I and AH-II result from increased intestinal sensitivity to calcitriol with intestinal calcium hyperabsorption and higher numbers of vitamin D receptors in osteoblasts, causing greater bone resorption and resorptive hypercalciuria. The latter accounts for decreased bone mass seen in many patients with AH-I and some of those with AH-II. AH-III, an unusual disorder, is due to a renal phosphate leak with urinary loss of phosphate, decreased serum phosphate, and increases in renal calcitriol production and intestinal calcium absorption. The level of the phosphaturic factor, fibroblast growth factor-23, is increased in some patients with calcium nephrolithiasis, hypophosphatemia, and renal phosphate leak. RH is characterized by impaired tubular reabsorption of calcium, which causes a decrease in serum calcium, elevations in parathyroid hormone (PTH) and calcitriol, and increases in bone resorption and intestinal calcium absorption.

17. Distinguish among the various forms of IH.

See Table 17-1.

TABLE 17-1. FORMS OF IDIOPATHIC HYPERCALCIURIA

LAB VALUE	AH-I	AH-II	AH-III	RH
Serum calcium	Normal	Normal	Normal	Normal
Serum phosphorus	Normal	Normal	↓	Normal
Serum intact PTH	Normal	Normal	Normal	↑
24-hour urinary calcium (1-g calcium diet)	↑	↑	↑	↑
Urine Ca/Cr ratio (1-g calcium load)	↑	↑	↑	↑
24-hour urinary calcium (400-mg calcium diet)	↑	Normal	↑	↑
Fasting urinary calcium (mg/dL GFR)	Normal	Normal	↑	↑

AH, absorptive hypercalciuria; Ca/Cr, calcium/creatinine; GFR, glomerular filtration rate; IH, idiopathic hypercalciuria; PTH, parathyroid hormone; RH, renal hypercalciuria (see questions 17-20); ↑, increased; ↓, decreased.

18. When is it necessary to distinguish among the various forms of IH?

Only complicated nephrolithiasis unresponsive to usual therapy requires differentiation (see Website reference on hypercalciuria review at the end of the chapter).

19. Explain the differences in serum levels of phosphorus and PTH in AH-III and RH.

Serum phosphorus is low in AH-III because of a primary renal phosphate leak. The level of intact PTH is high in RH because the primary defect is decreased renal tubular calcium reabsorption, causing relative hypocalcemia that stimulates PTH.

20. How do changes in calcium intake help distinguish the different types of absorptive hypercalciuria and renal leak hypercalciuria (see Table 17-1)?

In AH-II, the 24-hour urine calcium normalizes with a restricted calcium diet (400 mg/day) because the absorptive excess is not as severe. However, the 24-hour urine calcium during calcium restriction remains high in AH-I because of marked calcium hyperabsorption, in AH-III because hypophosphatemia decreases renal tubular calcium reabsorption, and in RH because decreased renal tubular calcium reabsorption is the primary defect.

High 24-hour urinary calcium is more than 4 mg per kg ideal body weight. Normal 24-hour urinary calcium with a 400-mg/day calcium restriction is less than 200 mg/day. For improved accuracy, urinary calcium measurements are at times expressed as mg/100 mL GFR to account for changes related to altered kidney function. Normal fasting urine calcium level is less than 0.11 mg per 100 mL glomerular filtration rate. Normal urine Ca/Cr is less than 0.20 after a 1-g oral load of calcium.

21. Define a low serum phosphorus level on an 800-mg/day phosphorus-restricted diet.

Low serum phosphorus is less than 2.5 mg/dL on an 800-mg/day phosphorus diet.

22. What causes hyperoxaluria?

Approximately 14% of urinary oxalate comes from dietary absorption and the remainder from metabolism of glyoxylate and ascorbic acid. Increased oxidation of glyoxylate to oxalate occurs in the rare autosomal recessive hereditary hyperoxaluria. The clinically more important enteric hyperoxaluria occurs with small bowel resection, bypass, or inflammation. Small bowel disease may cause bile salt and fat malabsorption, resulting in increased delivery of bile salts and fats to the colon. Bile salts damage colonic mucosa, increasing colonic permeability and oxalate absorption. Intestinal fatty acids are negatively charged and bind calcium and magnesium, decreasing the amounts of calcium and magnesium available for binding intestinal oxalate and leaving more oxalate free for intestinal absorption. Low-calcium diets do the same. Excess oxalate is primarily absorbed in the bile salt–damaged colon. Thus, patients with small bowel disease and an ileostomy do not hyperabsorb oxalate. Excessive dietary oxalate or ascorbic acid ($>$ 2 g/day) also leads to hyperoxaluria.

23. Why is hyperoxaluria important in nephrolithiasis?

Oxalate is a major component of the most commonly formed stones (calcium oxalate) and contributes to supersaturation. Previously it was believed to be a much stronger stimulus to calcium oxalate stone formation than calcium. Newer data suggest that calcium may be just as potent, however, and a high urinary concentration of either calcium or oxalate is a powerful stimulus for calcium oxalate stone formation.

24. How does hyperuricosuria contribute to renal stones?

Uric acid stones develop in approximately 25% of patients with symptomatic tophaceous gout. Excessive urinary uric acid ($>$ 600 mg/day) supersaturates the urine, crystallizes, and forms uric acid stones. However, most uric acid stone formers do not have gout, hyperuricemia, or hyperuricosuria. All do have a urinary pH lower than 5.5, which promotes uric acid stone formation. Approximately 25% of calcium stone formers have hyperuricosuria. Hyperuricosuria decreases the solubility of calcium oxalate. Monosodium urate may interfere with inhibitors, resulting in increased calcium

oxalate stone formation. This disorder, called *hyperuricosuric calcium nephrolithiasis,* is characterized by normal serum calcium, urinary uric acid greater than 600 mg/day, urine pH greater than 5.5, and recurrent calcium stones.

25. How does urinary pH relate to renal stones?

Because uric acid has a pKa of 5.5, acid urine shifts the equilibrium so that the concentration of uric acid is greater than the concentration of sodium urate. At urine pH 6.5, only 10% is in the form of uric acid, and approximately 90% in the form of sodium urate. Because uric acid is 100 times less soluble than urate, uric acid stones are more likely to form in acid urine. This equilibrium is so important that uric acid stones virtually never develop unless the urinary pH is less than 5.5. Because of low urinary pH, uric acid stones occur more frequently in obesity and diabetes. Obesity and type 2 diabetes are associated with insulin resistance, renal steatosis, and renal lipotoxicity. This association results in decreased insulin-dependent renal production of ammonia, decreased urinary ammonium excretion, a lower urinary pH, and a propensity for uric acid stones. Additionally, obesity and type 2 diabetes are associated with hyperinsulinemia, which decreases distal nephron calcium reabsorption and increases net calcium excretion and the risk for calcium stones. Cystine stones are also more likely in acid urine, whereas calcium phosphate (brushite) stones usually form primarily in alkaline urine (pH $>$ 7.0). Calcium oxalate stones may develop in either acid or alkaline urine.

26. What conditions cause low levels of urinary citrate?

Patients with hypocitraturia excrete less than 320 mg/day. Idiopathic hypocitraturia occurs in less than 5% of patients with calcium stones, and secondary hypocitraturia may occur in 30%. Citrate is freely filtered by the glomerulus, 75% is reabsorbed by the proximal renal tubule, and little citrate is secreted. Most secondary causes of hypocitraturia decrease urinary citrate by increasing proximal renal tubular reabsorption. Secondary causes of low citrate include dehydration, metabolic acidosis, hypokalemia, thiazide diuretics, carbonic anhydrase inhibitors, magnesium depletion, renal tubular acidosis, and diarrhea. Diarrhea also causes direct gastrointestinal loss of citrate and magnesium.

27. What is the role of diet in the formation of kidney stones?

The high animal protein (beef, poultry, pork, and fish) intake of many Americans ($>$ 1.5-2 g/kg/day) acidifies the urine with phosphoric, sulfuric, and uric acids; decreases urinary citrate; increases urinary calcium; and raises the risk for nephrolithiasis. Higher-protein diets, such as the Atkins diet, worsen these effects. Increased sulfates and uric acid may act as cofactors in the formation of calcium oxalate and uric acid stones. High sodium intake increases urinary calcium (see question 15). High calcium intake ($>$ 1200 mg) contributes to hypercalciuria. However, low calcium intake ($<$ 600 mg) without low oxalate intake decreases oxalate binding in the gut, increases oxalate absorption, and increases urinary oxalate. High dietary oxalate (Table 17-2) increases calcium oxalate crystalluria. Orange juice may help prevent kidney stones by increasing urinary potassium and citrate. Potassium citrate as Urocit-K is commonly prescribed to increase urinary citrate. From Micromedex, Urocit-K at 60 mEq/day raises urinary citrate by approximately 400 mg/day and increases urinary pH by approximately 0.7 units. An 8-oz glass of orange juice supplies 12 mEq potassium and 38 mEq citrate (more than a 10-mEq/1080-mg tablet of Urocit-K). Cranberry juice has mixed reviews, but data now suggest that it should not be used in excess in stone disease because it may increase urinary oxalate. Citric acid juices (lemon and lime) supply little potassium and only one third as much citrate as orange juice. Although potassium citrate juices are more powerful at stone inhibition, nearly all citrus drinks are useful. An exception is grapefruit juice, which may increase stone formation by 30% to 50%. The clinician should be flexible with the patient's choice of fluid, because the importance of the fluid intake may outweigh some of the theoretical negatives of the particular drink.

28. Summarize the presenting symptoms and signs of renal stones.

Approximately 30% of renal stones are asymptomatic and are found incidentally on radiographic studies. Seventy percent of renal stones are symptomatic. The patient may present with a dull ache in the posterior flank. However, the classic presenting symptom of renal stones is excruciating

TABLE 17-2. SELECTED HIGH-OXALATE FOODS

Fruits	Rhubarb
	Raspberries
	Blueberries
	Blackberries
	Gooseberries
	Strawberries
	Fruit cocktail
	Tangerines
	Purple grapes
	Citrus peel
Vegetables	Leafy dark greens
	Spinach
	Mustard greens
	Collard greens
	Cucumbers
	Green beans
	Beets
	Sweet potatoes
	Summer squash
	Celery
Others	Roasted coffee
	Ovaltine
	Tea
	Cocoa
	Chocolate
	Nuts
	Peanuts
	Wheat germ
	Baked beans
	Tofu

Adapted from Nelson JK, Moxness KE, Jensen MD, Gastineau CF, editors: Mayo Clinic Diet Manual, ed 7, St. Louis, 1994, Mosby, pp 315-362.

unilateral flank pain that waxes and wanes, and most patients have associated hematuria. The pain starts in the posterior lumbar area and then radiates anteroinferiorly into the abdomen, groin, genital region, and medial thigh. Intense pain may last several hours and may be followed by dull flank pain. Nausea, vomiting, sweating, fever, and chills may occur. Patients with renal colic appear acutely ill and restless and move from side to side in an attempt to relieve the pain. Physical examination shows tenderness and guarding of the respective lumbar area. Deep palpation worsens discomfort, but rebound tenderness is absent. Urinary tract infection may be present. Obstruction, if present, is usually unilateral. Clinical evidence of renal failure is usually absent.

29. What elements of the history and physical examination are important in patients with kidney stones?

Obtain present, past, and family histories and ask about previous stone disease. Because all of the following may be associated with stones, ask about use of guaifenesin, ephedrine, indinavir, triamterene, sulfonamides, acyclovir, and vitamins A, C, and D. Determine fluid intake and sources of excess calcium, salt, oxalate, uric acid, and protein. Physical examination is generally not helpful except during acute disease (see question 28).

30. What lab tests are appropriate in the diagnosis of kidney stones?

Perform a urinalysis with focus on pH, hematuria, pyuria, bacteriuria, and crystalluria. If pH is high or bacteriuria is seen, perform urine culture. Perform appropriate radiographic studies (see question 34). Have the patient strain all urine and save the stone, if passed, for stone analysis. If this is the patient's first stone, the pain subsides, and the stone is less than 5 mm, conservative management with follow-up for several months is acceptable. More than 50% of stones in the proximal ureter and 75% of stones in the distal ureter less than 5 mm pass spontaneously. Order a blood chemistry panel that includes serum sodium, potassium, chloride, carbon dioxide, creatinine, calcium, albumin, phosphorus, magnesium, and uric acid. Consider measurements of serum PTH and random urine for determination of the Ca/Cr ratio. If the patient has continued symptoms, if the stone is larger than 5 mm, or if obvious obstruction is present, consult a urologist and plan for a more extensive evaluation. Include a 24-hour urine test for creatinine, sodium, calcium, phosphorus, magnesium, oxalate, citrate, and uric acid. Consider repeating the 24-hour urine test to focus on abnormalities 6 weeks after medical intervention.

31. Summarize the therapeutic approach to patients with kidney stones.

Kidney stones do not require procedural intervention unless they are associated with pain, obstruction, infection, or significant bleeding. Ureteral stones may also be treated conservatively (monitored) if there is no renal failure, fever, infection, or pain. Pain can be controlled with nonsteroidal antiinflammatory drugs, but opioid analgesics may be necessary to treat acute pain exacerbations. Stones smaller than 5 mm usually pass but those larger than 10 mm do not. Passage of stones ranging from 5 mm to 10 mm in diameter is variable. Calcium channel blockers such as extended-release nifedipine and alpha-blockers such as tamsulosin, doxazosin, and terazosin may facilitate stone passage by reducing ureteral spasm and improving peristalsis during acute colic episodes. Patients with symptomatic stones, stones larger than 5 mm, or multiple stones should be referred for nephrologic or urologic evaluation. Unless contraindicated, preventing stone recurrence requires 2 to 3 L/day of fluid to increase urine output to more than 2 L/day; no more than 2 g/day of sodium; 0.8 to 1.0 g/kg ideal body weight of protein with more plant protein (2/3 of total) and less animal protein (1/3); 1000 mg/day of dietary calcium; and avoidance of grapefruit juice, calcium supplements, oxalate, and vitamin C.

KEY POINTS 2: TREATMENT OF NEPHROLITHIASIS

1. Stones smaller than 5 mm usually pass spontaneously and those larger than 10 mm usually do not. Stones 5-10 mm in diameter have variable outcomes. Distal ureteral stones are more likely to pass. If a ureteral stone is smaller than 10 mm, alpha$_1$-blockers or calcium channel blockers may help its passage.
2. Prevention of stone recurrence includes daily intake of 10 to 12 8-ounce glasses of fluid, increased ingestion of citrate-containing drinks, 1000 mg/day of dietary calcium, 0.8 to 1.0 g/kg/day of protein with less animal protein (1/3 of total) and more plant protein (2/3), and less than 2000 mg/day of sodium.
3. Addition of the Dietary Approaches to Stop Hypertension (DASH) as a basic diet with some modifications for sodium and oxalate as necessary has decreased stone recurrence.
4. Avoid grapefruit juice, reduce oxalate and ascorbic acid to less than 100 mg/day for calcium oxalate stones, and use calcium supplements only if dietary calcium is insufficient to allow intake of 800-1000 mg of calcium per day—calcium citrate preferred.
5. Although potassium citrate is preferred for urinary alkalization and citrate replacement, citrus drinks such as lemon, lime, and orange juice may be substituted. Avoid grapefruit juice completely and cranberry juice in excess.
6. Refer patients to a urologist for continued pain, obstruction, infection, severe bleeding, fever, or renal dysfunction.

32. Describe the clinical significance of a urinalysis in patients with renal stones.

Most stone formers have macroscopic or microscopic hematuria and may have some crystalluria. The remainder of the urinalysis findings are usually normal. Crystals are normally absent in warm, freshly voided urine but, if present, suggest a diagnosis. However, most urine specimens cool before examination, and crystals may form in normal urine with time and cooling. Thus, by the time urine is usually examined, the finding of crystalluria may have little clinical significance. An exception is the presence of cystine crystals, which are diagnostic of cystinuria. Persistently acidic urine (pH $<$ 5.5) suggests uric acid or cystine stones. More alkaline urine (pH $>$ 6.5-7.0) suggests calcium phosphate stones. Persistently alkaline urine (pH $>$ 7.0-7.5) and recurrent urinary tract infections strongly suggest struvite stones. Struvite stones never form unless the urine pH is alkaline.

33. What are the characteristics of urinary crystals in patients with renal stones?

Calcium oxalate monohydrate crystals may be dumbbell-shaped, needle-shaped, or oval, with the last resembling red blood cells. Calcium oxalate dihydrate crystals are pyramid-shaped and have an envelope appearance. Calcium phosphate and uric acid crystals are too small for standard light microscopic resolution and look like amorphous debris. Uric acid crystals are characteristically yellow-brown. Less commonly, uric acid dihydrate crystals may be rhomboid-shaped or resemble the four-sided diamonds on a deck of cards. Because all of these crystals may be found in normal urine, they are not necessarily diagnostic of disease. However, the presence of cystine crystals, which are flat, hexagonal plates resembling benzene rings, always means cystinuria. Struvite (magnesium ammonium phosphate) crystals are rectangular prisms that resemble coffin lids.

34. How do radiographic tests help to evaluate patients with renal stones?

A plain radiograph of the abdomen (kidney-ureters-bladder [KUB]) should be obtained in all stone formers and shows stones with the following features: calcium (small, dense, and circumscribed); cystine (faint, soft, and waxy); struvite (irregular and dense). Uric acid stones are radiolucent and not seen. Intravenous pyelography (IVP) localizes stones in the urinary tract and shows the degree of obstruction. Radiolucent obstruction on IVP suggests a uric acid stone. Ultrasonography reveals the size and location of larger stones, is sensitive for diagnosing obstruction, and may be best when radiation should be avoided, as in pregnancy. However, the initial radiographic procedure of choice for stone evaluation requires no patient preparation and is easy, sensitive, specific, and accurate. It should be ordered as follows: helical noncontrast computed tomography (CT) scan renal-stone protocol using 3- to 5-mm cuts. A new technique that is not widely available is dual-energy CT with advanced post-acquisition processing that can discriminate among several subtypes of urinary calculi without formal stone analysis. Indinavir stones are not seen on KUB or CT scan and may be missed on IVP. Indinavir stones, which are diagnosed after suspicion is raised by history, physical examination, and signs of obstruction, may require contrast-enhanced CT scanning.

35. Which medications are useful for treating the various stone-forming conditions?

See Table 17-3.

36. What are special considerations in the drug therapy of nephrolithiasis?

Potassium citrate, and not sodium citrate, for urine alkalinization to a pH $>$ 7.0 is recommended for uric acid and cystine stones. Sodium citrate increases urinary sodium and calcium, and in alkaline urine, sodium urate may increase calcium stone formation. Cystine stone formers require higher fluid intake to reduce urinary cystine below its solubility limit of 200 to 250 mg/L. Fluid and potassium citrate often are the only therapy necessary for uric acid stones if uricosuria is less than 800 mg/day. Use allopurinol with potassium citrate if uric acid stones continue or hyperuricemia is more severe. Use cellulose sodium phosphate (CSP) only for refractory stone disease in AH-I. CSP binds calcium and magnesium in the gut, decreases absorption of both, and may worsen osteopenia and increase urinary oxalate. Replace magnesium as required. Monitor bone mass, and treat osteopenia as necessary.

TABLE 17–3. ORAL DRUG THERAPY FOR RENAL STONES

DISORDER	DRUG	DOSAGE
Absorptive type I	Hydrochlorothiazide	12.5-25 mg b.i.d.
	Potassium citrate	10-30 mEq t.i.d.
	Cellulose sodium phosphate	5 g 1-3 times/day c.c.
	Magnesium gluconate	1-1.5 g b.i.d.
	Magnesium oxide	400 mg b.i.d.
Absorptive type II	Hydrochlorothiazide	12.5-25 mg b.i.d.
Renal phosphate leak	Neutral sodium phosphate	500 mg t.i.d.
RH	Hydrochlorothiazide	12.5-25 mg b.i.d.
Hypocitraturia	Potassium citrate	10-30 mEq b.i.d.-t.i.d.
Hyperuricosuria	Potassium citrate	10-30 mEq b.i.d.-t.i.d.
	Allopurinol	100-300 mg/day
Enteric hyperoxaluria	Potassium citrate	10-30 mEq t.i.d.
	Magnesium gluconate	1-1.5 g b.i.d.
	Calcium citrate	950 mg q.i.d.
	Calcium carbonate	250-500 mg q.i.d.
	Cholestyramine	4 g t.i.d.
	Pyridoxine	100 mg/day
Cystinuria	Potassium citrate	10-30 mEq t.i.d.
	α-Mercaptopropionylglycine	200-400 mg t.i.d.
	d-Penicillamine	250-500 mg q.i.d.
	Pyridoxine	50 mg/day
Struvite stones	Acetohydroxamic acid	250 mg 2-4 times/day
Antispasmodic therapy	Tamsulosin	0.4 mg once daily

b.i.d., twice daily; q.i.d., four times daily; t.i.d., three times daily; c.c., with meals.

Note: All medications are given orally. Dosages are estimated ranges and not absolute recommendations. Each drug must be adjusted according to the patient's tolerance. Use the lowest dosage necessary to attain the desired effect and avoid side effects. Always use drug therapy in addition to appropriate dietary changes and fluid input. Potassium citrate is better tolerated in lower dosages taken three times a day. However, twice-daily dosing may improve compliance. Potassium citrate is often required to correct thiazide-induced hypokalemia and hypocitraturia (see question 36). Chlorthalidone or indapamide may be substituted for hydrochlorothiazide for more convenient once-daily dosing (see question 37).

37. Why are thiazide diuretics the first-line drug therapy for hypercalciuria-induced nephrolithiasis?

Thiazides are first-line therapy because they increase proximal (indirectly) and distal (directly) tubular reabsorption of calcium. However, thiazides can cause depletion of potassium and citrate, which should be replaced with potassium citrate. Avoid triamterene, which can cause kidney stones. If potassium supplementation is added, use amiloride with caution to avoid hyperkalemia. The thiazide-like diuretics, chlorthalidone (12.5-50.0 mg daily) or indapamide (1.25-2.5 mg daily), may be preferred to hydrochlorothiazide for the convenience of once-daily dosing. Additionally, indapamide is less likely to cause lipid disturbances associated with the higher thiazide dosages needed to reduce urinary calcium.

38. How should you treat a symptomatic patient with a renal stone 1 to 2 cm in size?

Apply the therapeutic options in question 31. About 10% to 20% of all kidney stones require surgical removal because of size and symptoms. Many urologists treat symptomatic patients with calcium stones 1 to 2 cm in size in the renal pelvis or a significant proximally obstructing stone (0.5-2.0 cm) with extracorporeal shock wave lithotripsy (ESWL). If the stone is too large or too hard, as estimated

from CT scan, or is not in a good location for ESWL, percutaneous stone removal or a ureteroscopic approach may be indicated (see question 39). Additionally, because of the achievement of higher stone-free rates, many urologists choose percutaneous nephrolithotomy (PCNL) for 1- to 2-cm stones. Distal ureteral stones are best managed with ureteroscopic stone extraction or in situ ESWL.

39. How should you treat an asymptomatic patient with a renal stone of the same size?

Treatment of the asymptomatic patient with a 1- to 2-cm renal stone is a toss-up. Each expert has an opinion based on the experience of the local medical community. Many asymptomatic stones can be monitored without intervention other than that noted in question 31. Specifics of stone location, duration, and overall patient health are important in the decision. Recurrent, enlarging, or multiple asymptomatic stones probably should be treated. Nephrology and urology consultations are appropriate. Other forms of lithotripsy include percutaneous ultrasonic lithotripsy and endoscopic ultrasonic lithotripsy. Intracorporeal lithotripsy uses the holmium:yttrium-aluminum-garnet laser and electrohydraulic lithotripsy.

40. What treatment should be used if the stone is larger than 3 cm?

If the stone is larger than 3 cm, lithotripsy usually fails. The initial approach to patients with stones of this size is PCNL. However, many urologists choose this therapy for stones larger than 1.5 cm. Open lithotomy is now unusual. Therapy for stones larger than 2 cm depends on the patient's overall status, wishes, and experiences and the experiences of the patient's physician and urologist.

WEBSITES

1. EMedicine: Nephrolithiasis. http://www.emedicine.com/med/topic1600.htm.
2. EMedicine: Hypercalciuria review. http://www.emedicine.com/med/topic1069.htm.
3. EMedicine: Hyperuricemia and gout review. http://www.emedicine.com/med/topic3028.htm.
4. EMedicine: Hypocitraturia review. http://www.emedicine.com/med/topic3030.htm.
5. EMedicine: Intracorporeal lithotripsy. http://www.emedicine.com/med/topic3034.htm.
6. American Urological Association: Ureteral calculi guidelines). http://www.auanet.org/content/clinical-practice-guidelines/clinical-guidelines.cfm?sub=uc.
7. Favus MJ: Nephrolithiasis. http://www.endotext.org/parathyroid/parathyroid14/index.html
8. University of Miami Department of Urology: Kidney stones. http://urology.med.miami.edu/x58.xml.

BIBLIOGRAPHY

Alan G, Wasserstein AG: Nephrolithiasis, *Am J Kidney Dis* 45:422–428, 2005.

Cameron MA, Khashayar Sakhaee K: Uric acid nephrolithiasis, *Urol Clin North Am* 34:335–346, 2007.

Graham A, Luber S, Wolfson AB: Urolithiasis in the emergency department, *Emerg Med Clin N Am* 29:519–538, 2011.

Hollingsworth JM, Rogers MA, Kaufman SR, et al: Medical therapy to facilitate urinary stone passage: a meta-analysis, *Lancet* 368:1171–1179, 2006.

Lotan Y, Pearls MS: Economics of stone management, *Urol Clin North Am* 34:443–453, 2007.

Maalouf NM, Sato AH, Welch BJ, et al: Postmenopausal hormone use and the risk of nephrolithiasis, *Arch Intern Med* 170(18):1678–1685, 2010.

Meschi T, Nouvenne A, Borghi L: Lifestyle recommendations to reduce the risk of kidney stones, *Urol Clin N Am* 38: 313–320, 2011.

Monk RD, Bushinsky DA: Kidney stones. In Kronenberg HM, Melmed S, Polonsky KS, et al, editors: *Williams Textbook of Endocrinology,* ed 11, Philadelphia, 2011, Saunders Elsevier, p 1311.

Park S, Pearle MS: Pathophysiology and management of calcium stones, *Urol Clin North Am* 34:323–334, 2007.

Rendina D, Mossetti G, De Filippo G, et al: Fibroblast growth factor 23 is increased in calcium nephrolithiasis with hypophosphatemia and renal phosphate leak, *J Clin Endocrinol Metab* 91:959–963, 2006.
Sakhaee K, Maalouf NM, Sinnott B: Clinical review—kidney stones 2011. Pathogenesis, diagnosis and management, *J Clin Endocrinol Metab* 97:1847–1860, 2012.
Taylor EN, Fung TT, Curhan GC: DASH-style diet associated with reduced risk for kidney stones, *J Am Soc Nephrol* 20:2253–2259, 2009.
Wimpissinger F, Türk C, Kheyfets O, et al: The silence of the stones: asymptomatic ureteral calculi, *J Urol* 178:1341–1344, 2007.
Worcester EM, Coe FL: Calcium kidney stones, *N Engl J Med* 363:954–963, 2010.
Ziberman DE, Ferrandino MN, Preminger GM, et al: In vivo determination of urinary stone composition using dual energy computerized tomography with advanced post-acquisition processing, *J Urol* 184:2354–2359, 2010.

PITUITARY INSUFFICIENCY

John J. Orrego

1. What is pituitary insufficiency?

Pituitary insufficiency is a syndrome characterized by one or more anterior pituitary hormone deficiencies as a result of aplasia or hypoplasia, destruction, infiltration, compression, or displacement of the hypothalamus and/or pituitary gland (Fig. 18-1). Pituitary insufficiency can be congenital or acquired; familial or sporadic; partial or complete; and transient (reversible) or permanent. Posterior pituitary failure, characterized by decreased concentrations of antidiuretic hormone, is referred as central diabetes insipidus.

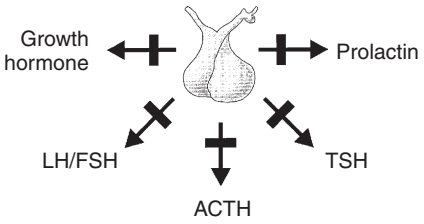


Figure 18-1. Pituitary insufficiency. ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone.

2. Is diabetes insipidus a manifestation of pituitary insufficiency?

Most patients with anterior pituitary insufficiency do not have concomitant posterior pituitary failure. In those in whom central diabetes insipidus is also present, hypophysitis, metastatic cancer, or sarcoidosis should be suspected.

3. How common is hypopituitarism in the general population?

According to a population study conducted in northwestern Spain, the annual incidence of hypopituitarism is 42 cases per million, and the prevalence ranges from 290 to 455 cases per million.

4. What causes pituitary insufficiency?

Almost any disease that disturbs the normal interaction between the hypothalamus and the pituitary gland can cause hypopituitarism. The most common etiology of pituitary insufficiency is pituitary damage associated with a pituitary adenoma and/or the effect of its treatment (surgery and/or radiation therapy). Among patients with pituitary macroadenomas, about one third have one or more pituitary hormone deficiencies. Other frequent causes are shown in Box 18-1.

5. How does a patient with pituitary insufficiency present?

The clinical manifestations of hypopituitarism depend on the extent and severity of the specific pituitary hormone deficiency. If the onset is acute, the patient may be critically ill and present with hypotension and shock, obtundation, and even coma. However, if the onset is chronic and the pituitary deficiency is mild, the patient may complain only of fatigue and malaise.

BOX 18–1. ETIOLOGY OF HYPOPITUITARISM

Functional
Neoplastic:
- Pituitary adenoma or carcinoma
- Metastatic disease
- Hematologic malignancies
- Craniopharyngioma
- Parasellar masses (meningioma, germinoma, glioma)

Traumatic:
- Surgery
- Radiation therapy
- Traumatic brain injury

Vascular:
- Sheehan's syndrome
- Apoplexy
- Aneurysm

Infiltrative/inflammatory:
- Hypophysitis
- Sarcoidosis
- Histiocytosis X
- Hemochromatosis

Infectious:
- Bacterial abscess
- Tuberculosis
- Fungal infections
- Parasitic infections

- *Adrenocorticotropic hormone (ACTH) deficiency (central adrenal insufficiency):* Fatigue, malaise, low-grade fever, weakness, anorexia, nausea, vomiting, abdominal pain, loose stools, and postural lightheadedness.
- *Thyroid-stimulating hormone (TSH) deficiency (central hypothyroidism):* Impaired mental activity, weight gain, fatigue, cold intolerance, weakness, alopecia, puffiness, and constipation.
- *Gonadotropin deficiency (central hypogonadism):* Men present with decreased libido, erectile dysfunction, hot flashes, gynecomastia, and infertility. Women complain of oligo/amenorrhea, infertility, decreased libido, hot flashes, vaginal dryness, and dyspareunia.
- *Growth hormone (GH) deficiency:* Fatigue, increased adiposity, exercise intolerance, and decreased social functioning.
- *Prolactin (PRL) deficiency:* Agalactia or hypolactia in postpartum women.

6. Are there any signs on physical examination that may suggest pituitary insufficiency?

Aside from delayed relaxation of tendon reflexes in hypothyroid patients, there are no specific or pathognomonic findings on physical exam. Physical findings for specific pituitary hormone deficiencies are as follows:

- *ACTH deficiency (central adrenal insufficiency):* Postural hypotension, pallor, and areolar hypopigmentation. Women with long-standing ACTH deficiency often have loss of pubic and axillary hair.
- *TSH deficiency (central hypothyroidism):* Bradycardia, facial/periorbital puffiness, madarosis (loss of the tail of the eyebrows), dysphonia, hypercarotinemia, and delayed relaxation of tendon reflexes.
- *Gonadotropin deficiency (central hypogonadism):* Men can have fine facial wrinkles, scarce body and facial hair, gynecomastia, increased adiposity and decreased muscle mass, and smaller and softer testicles. Women may have alopecia and hirsutism.
- *GH deficiency:* Fine facial wrinkles, increased adiposity, and decreased muscle mass.
- *PRL deficiency:* Postpartum agalactia.

7. How is hypopituitarism diagnosed?

In the setting of typical manifestations of hypopituitarism, measurement of basal serum hormone levels may be all that is needed. On the other hand, dynamic endocrine testing is usually indicated in patients with more subtle manifestations.

- *ACTH deficiency:* Nonspecific laboratory findings include hyponatremia, normochromic, normocytic anemia, and eosinophilia. A morning serum cortisol level lower than 3 μg/dL and/or a peak serum

cortisol level lower than 20 μg/dL 30 or 60 minutes after the administration of 250 μg of ACTH and an inappropriately low or normal plasma ACTH level are consistent with central adrenal insufficiency.

- *TSH deficiency:* Hyponatremia, macrocytosis, hyperlipidemia, and elevated creatine phosphokinase (CPK) can be seen. However, central hypothyroidism is confirmed when the serum free thyroxine (T_4) level is low in the setting of an inappropriately low or normal TSH concentration.
- *Gonadotropin deficiency:* Normochromic, normocytic anemia may be seen in men with hypogonadism. Decreased morning testosterone levels in men, and low estradiol concentrations in premenopausal women, in the setting of inappropriately low or normal LH and FSH levels are indicative of central hypogonadism. In postmenopausal women, a low or normal FSH level is consistent with gonadotropin deficiency.
- *GH deficiency:* If all other anterior pituitary hormones are deficient, an insulin-like growth factor-1 (IGF-1) level below the lower limit of normal for age and gender is indicative of GH deficiency. Otherwise, the IGF-1 measurement is not sensitive enough, and provocative GH secretion tests (insulin-induced hypoglycemia or growth hormone–releasing hormone (GHRH)/arginine stimulation) are required.
- *PRL deficiency:* Low or undetectable serum PRL concentration.

8. When should pituitary magnetic resonance imaging (MRI) be ordered in someone with hypopituitarism?

Any patient with two or more pituitary hormone deficiencies, unexplained or significant hyperprolactinemia, or symptoms of tumor mass effect should undergo dedicated pituitary MRI with and without contrast agent. Patients with isolated functional hypopituitarism do not usually need imaging studies. Men with isolated central hypogonadism with a serum testosterone level lower than 100 ng/mL should undergo imaging.

9. How common is pituitary insufficiency after traumatic brain injury?

The annual incidence of traumatic brain injury in industrialized countries is 180 to 250 cases per 100,000 people. Longitudinal studies that have included patients with different degrees of severity of traumatic brain injury have shown that pituitary insufficiency is common after head trauma. Although some of these deficiencies resolve within weeks or months after the cranial trauma, some new deficiencies may be detected during follow-up. Approximately 25% to 50% of patients have at least one anterior pituitary hormone deficiency a year after suffering traumatic brain injury. GH and gonadotropin deficiencies are the two most common disturbances. The causative mechanism seems to be hemorrhagic infarction of the pituitary and/or hypothalamus as a result of direct damage to these structures, increased intracranial pressure, hypoxia, or bleeding.

10. How soon after radiation therapy should pituitary insufficiency be expected?

Any radiation fields that impact the hypothalamic-pituitary area can cause neuroendocrine dysfunction. Irradiation for sellar and parasellar tumors, primary brain tumors, nasopharyngeal carcinoma, acute lymphoid leukemia, and tumors of the skull base have been shown to compromise pituitary function. Depending on the radiation dose and the presence of preexisting pituitary disease, it may take from several months to years for pituitary insufficiency to develop. The 5-year cumulative incidence of GH deficiency, gonadotropin deficiency, ACTH deficiency, and TSH deficiency in patients with pituitary tumors (radiation dose: 30-50 Gray [Gy]) and patients with nasopharyngeal carcinoma (radiation dose: $>$ 60 Gy) were 100%, 57%, 61%, and 27.5%; and 63.5%, 31%, 27%, and 15%, respectively. Regular testing is mandatory to ensure timely diagnosis and early treatment.

11. What is Sheehan's syndrome?

Sheehan's syndrome is a form of panhypopituitarism that occurs after delivery as a consequence of infarction in the adenohypophysis due to massive uterine hemorrhage and hypovolemia. Typically women have an inability to lactate for the newborn, persistent amenorrhea, and symptoms of hypocortisolemia and hypothyroidism. Pituitary imaging studies show an atrophic pituitary gland and sometimes an empty sella. Pathologic studies have shown replacement of organizing necrotic areas by a fibrous scar. The pituitary gland cannot regenerate; new cells do not form to replace the necrotized cells. With

modernization of medicine and improved obstetric care, the incidence of Sheehan's syndrome has plummeted in industrialized countries.

12. What is pituitary apoplexy?

Pituitary apoplexy is the abrupt destruction of most of the anterior pituitary cells as a result of an acute hemorrhage and/or infarction within an unrecognized pituitary adenoma. Precipitating factors for this complication include anticoagulation therapy, bleeding disorders, head trauma, diabetes mellitus, and radiation therapy. Patients usually present with severe headaches, obtundation, ophthalmoplegia, visual loss, hypotension, and shock. Biochemical panhypopituitarism and acute hemorrhage within a pituitary adenoma on pituitary MRI confirm the diagnosis. Rapid glucocorticoid and thyroid replacement therapies and surgical decompression, if needed, are life-saving. Of note, small hemorrhages within known pituitary adenomas may be incidentally detected during monitoring pituitary MRI.

13. What is hypophysitis?

Hypophysitis is chronic inflammation of the pituitary gland that has been classified according to the anatomic location of the pituitary involvement, cause, and histopathologic appearance. On the basis of clinical, radiologic, and pathologic findings, it is divided into adenohypophysitis, infundibuloneurohypophysitis, and panhypophysitis. Depending on the etiology, it can be classified as primary or secondary, the latter having a clear cause. According to pathology, it can be lymphocytic, granulomatous, or other less common forms. Lymphocytic hypophysitis is the most common and is characterized by a marked infiltration of lymphocytes that populate the pituitary gland both diffusely and occasionally in focal clusters. Lymphocytes are accompanied by scattered plasma cells, eosinophils, and fibroblasts, and in later disease stages by fibrosis. Lymphocytic hypophysitis is three times more common in women and uniquely manifests in association with pregnancy and the postpartum period in about 40% of affected women.

14. What is empty sella syndrome?

An empty sella turcica occurs as a result of intrasellar herniation of the suprasellar subarachnoid space with compression of the pituitary gland, producing in many cases a remodeling of the sella resulting from a combination of an incomplete diaphragma sella and increased cerebrospinal fluid (CSF) pressure. It is classified as primary or secondary. Primary empty sella syndrome is more common in obese multiparous women, who may complain of headaches and have hypertension; pituitary function is usually normal. Secondary empty sella syndrome is due to pituitary diseases, surgery, or irradiation. The predominant clinical finding in patients with this disorder is a visual abnormality, occurring from arachnoidal adhesions and traction on the optic apparatus. Some patients can also have mild hyperprolactinemia due to stretching of the pituitary stalk.

15. Describe functional causes of pituitary insufficiency.

It is important to exclude functional hypopituitarism in the patient presenting with an isolated pituitary deficiency. Patients who are receiving high doses of oral glucocorticoids for more than 6 weeks, are having frequent articular or epidural glucocorticoid injections, or are using high doses of potent inhaled glucocorticoids may demonstrate transient adrenal atrophy. As expected, these patients present with cushingoid features. Body builders using anabolic steroids can present with central hypogonadism. Hypothalamic amenorrhea can be caused by anorexia nervosa and strenuous exercise. Decreased testosterone or estrogen concentrations can normalize after correction of hyperprolactinemia with dopamine agonists. Critical illness and high-dose narcotics may suppress both the hypothalamic-pituitary-adrenal and hypothalamic-pituitary-gonadal axes.

16. Describe the treatment for pituitary insufficiency.

- *ACTH deficiency (central adrenal insufficiency):* Hydrocortisone 15-25 mg/day, in two or three divided doses, or prednisone 5 mg per day, are commonly used to replace cortisol. Because ACTH is not the main determinant of aldosterone secretion, patients with central adrenal insufficiency do not need

fludrocortisone. Some women with decreased libido and muscle weakness may benefit from taking 25 to 50 mg/day of dehydroepiandrosterone (DHEA). Patients should be educated about doubling the dose of hydrocortisone or prednisone in case of intercurrent or febrile illnesses.

- *TSH deficiency (central hypothyroidism):* Levothyroxine in doses sufficient to maintain the free T_4 level in the mid-normal range should be prescribed for treatment of central hypothyroidism. As opposed to primary hypothyroidism, measurement of TSH to monitor adequacy of thyroid replacement therapy is of no value in this condition.
- *Gonadotropin deficiency (central hypogonadism):* If no contraindications are present, men should be treated with testosterone (intramuscular, patches, gel, buccal) to relieve hypogonadal symptoms and improve bone mineral density. Premenopausal women should be treated with hormone replacement therapy until age 45 to 50 years. In men or women who want to conceive, gonadotropins can be administered.
- *GH deficiency:* In adults, GH replacement therapy may be indicated if symptoms of hypopituitarism persist after adequate replacement of other pituitary deficiencies. This treatment is very costly.

17. Can treatment of one pituitary deficiency unmask others?

The effect of GH on interconversion of T_4 to triiodothyronine (T_3) results in masking of TSH deficiency in the GH-deficient state with subsequent lowering of T_4 during GH replacement therapy.

Increased activity of 11β-hydroxysteroid dehydrogenase type 1 in GH deficiency results in an alteration of the set point of cortisol-to-cortisone interconversion in individual tissues in favor of cortisol. Thus, GH replacement, by increasing the conversion from cortisol to cortisone, may expose occult central adrenal insufficiency in patients with borderline ACTH reserve. Gonadal steroids influence GH-mediated hepatic IGF-1 generation. Oral estrogens decrease it, and DHEA sulfate increases it; therefore, women taking the former need higher doses of GH to achieve a normal IGF-1 level, whereas those taking DHEA need lower doses. Commencement of glucocorticoid replacement therapy can unmask central diabetes insipidus. Finally, because thyroid hormone increases the metabolic clearance rate of cortisol, initiating thyroid hormone replacement in a patient with coexistent but unrecognized adrenal insufficiency can precipitate an adrenal crisis.

18. Is life expectancy altered by hypopituitarism?

Rates of all-cause mortality and vascular death are higher in patients with hypopituitarism than in age- and sex-matched controls. A metaanalysis concluded that the standardized mortality ratio associated with hypopituitarism in men is 2.06 [95% confidence interval (CI), 1.94-2.20] and in women 2.80 (95% CI, 2.59-3.02). Pituitary irradiation seems to impose an increased risk of death from cerebrovascular disease.

KEY POINTS 1

1. The best test to confirm adequacy of thyroid replacement therapy in patients with central hypothyroidism is a free T_4 concentration in the mid-normal range.
2. A dedicated pituitary MRI (more slices through the sellar and parasellar regions), with and without contrast agent, rather than a brain MRI, should be ordered if indicated, in patients with hypopituitarism.
3. Traumatic brain injury and subarachnoid hemorrhage are increasingly recognized as causes of hypopituitarism.

WEBSITES

1. The Pituitary Foundation: http://www.pituitary.org.uk.
2. Pituitary Network Association: http://www.pituitary.org/intro.aspx.

BIBLIOGRAPHY

Aimaretti G, Ambrosio MR, Di Somma C, et al: Residual pituitary function after brain injury-induced hypopituitarism: a prospective 12-month study, *J Clin Endocrinol Metab* 90:6085–6092, 2005.

Appelman-Dijkstra NM, Kokshoorn NE, Dekkers OM, et al: Pituitary dysfunction in adult patients after cranial radiotherapy: systematic review and meta-analysis, *J Clin Endocrinol Metab* 96:2330–2340, 2011.

Darzy KH, Shalet SM: Hypopituitarism following radiotherapy, *Pituitary* 12:40–50, 2009.

Kovacs K: Sheehan syndrome, *Lancet* 361:520–522, 2003.

Nawar RN, Abdel-Mannan D, Selman WR, et al: Pituitary tumor apoplexy: a review, *J Intensive Care Med* 23:75–90, 2008.

Nielsen EH, Lindholm J, Laurberg P: Excess mortality in women with pituitary disease: a meta-analysis, *Clin Endocrinol (Oxf)* 67:693–697, 2007.

Orrego JJ, Barkan AL. Testing of hypothalamic-pituitary axis. In: Shepard MC, Stewart PM, eds. Pituitary disease, 1st ed. Netherlands: Kluwer Academic Publishers, 2002: 247-267.

Regal M, Paramo C, Sierra SM, et al: Prevalence and incidence of hypopituitarism in an adult Caucasian population in northwestern Spain, *Clin Endocrinol (Oxf)* 55:735–740, 2001.

Schneider HJ, Aimaretti G, Kreitschmann-Andermahr I, et al: Hypopituitarism, *Lancet* 369:1461–1470, 2007.

Sherlock M, Ayuk J, Tomlinson JW, et al: Mortality in patients with pituitary disease, *Endocrine Reviews* 31:301–342, 2010.

Toogood AA, Stewart PM: Hypopituitarism: clinical features, diagnosis, and management, *Endocrinol Metab Clin N Am* 37:235–261, 2008.

NONFUNCTIONING PITUITARY TUMORS

CHAPTER 19

Michael T. McDermott

1. Name the functioning pituitary tumors.

The normal pituitary gland secretes prolactin, growth hormone (GH), corticotropin (ACTH), thyrotropin (TSH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH). The major functioning pituitary tumors are prolactin-secreting tumors, GH-secreting tumors, ACTH-secreting tumors, TSH-secreting tumors, and gonadotropin (FSH- and/or LH-)- secreting tumors. Some tumors secrete a mixture of hormones. These are all covered in other chapters.

2. What is a nonfunctioning pituitary tumor?

A nonfunctioning pituitary tumor arises from pituitary cells but does not secrete clinically detectable amounts of a pituitary hormone. These tumors are usually benign adenomas.

3. What is the alpha subunit?

The alpha subunit is a component of three pituitary glycoprotein hormones: TSH, FSH, and LH. Each of these hormones consists of the common alpha subunit and a specific beta subunit (TSH beta, FSH beta, and LH beta). The alpha and beta subunits combine and become glycosylated before the intact hormone is secreted. Some nonfunctioning pituitary tumors secrete measurable amounts of the free alpha subunit, which may therefore serve as a tumor marker.

4. What other lesions can resemble nonfunctioning pituitary tumors?

Tumors that are not of pituitary origin may be found within the sella turcica; examples are metastatic carcinomas, craniopharyngiomas, meningiomas, and neural tumors. Nonneoplastic Rathke's pouch cysts, arterial aneurysms, and infiltrative pituitary diseases, such as sarcoidosis, histiocytosis, tuberculosis, lymphocytic hypophysitis, and hemochromatosis, may also be seen.

5. Differentiate between a microadenoma and a macroadenoma.

A pituitary microadenoma is less than 10 mm in its largest dimension, whereas a macroadenoma is 10 mm or larger. A macroadenoma may be contained entirely within the sella turcica or may have extrasellar extension.

6. Which structures may be damaged by growth of a pituitary tumor outside the sella turcica?

Pituitary tumors that grow superiorly may compress the optic chiasm and pituitary stalk. Those that grow laterally can invade the cavernous sinuses and compress cranial nerves III, IV, and VI or the internal carotid artery. Inferior growth may erode into the sphenoid sinus. Anterior and posterior growth often erodes the bones of the tuberculum sellae and dorsum sellae, respectively (Fig. 19-1).

7. What are the clinical features of nonfunctioning pituitary tumors?

Nonfunctioning pituitary tumors are often asymptomatic and are discovered incidentally during cranial imaging procedures performed for other reasons. This is true of both microadenomas and macroadenomas. Tumors that cause symptoms are usually large, space-occupying macroadenomas, which compress nearby neurologic or vascular structures (see Fig. 19-1). Clinical features include headaches, visual field defects, visual loss, and extraocular nerve palsies. Pituitary insufficiency also may result from destruction of normal pituitary tissue.

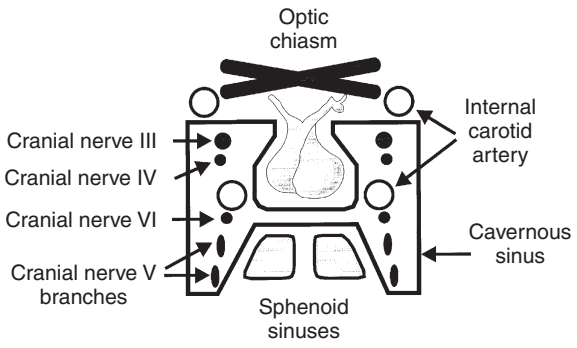


Figure 19-1. Pituitary fossa.

8. What anatomic evaluation is necessary for a pituitary tumor?

Magnetic resonance imaging (MRI) or computed tomography (CT) of the pituitary gland and parasellar regions often allows a precise diagnosis and determines the presence and extent of extrasellar invasion. Visual field testing helps assess function of the optic chiasm and tracts. Angiography may be necessary in some cases to rule out an aneurysm.

9. What evaluation is necessary to determine that a pituitary tumor is nonfunctioning?

A thorough history and physical examination can detect symptoms and/or signs of pituitary hormone excess. Hormone testing should include measurement of serum prolactin, GH, insulin-like growth factor-1 (IGF-1), TSH, free thyroxine (free T_4), LH, FSH, testosterone (men), estradiol (women), and 24-hour urinary cortisol excretion. Measurement of the serum alpha subunit is also helpful.

10. Does an elevated serum prolactin value indicate that a tumor is functioning?

No. Secretion of prolactin is negatively regulated by hypothalamic inhibitory factors, such as dopamine, which reach the anterior pituitary gland through the pituitary stalk. Stalk compression from a nonfunctioning tumor can impair dopamine delivery and thus increase the release of prolactin from the normal pituitary gland. The serum prolactin rarely exceeds 100 ng/mL in such cases, whereas it is usually much higher with prolactin-secreting tumors.

11. What is the natural history of nonfunctioning pituitary tumors?

Macroadenomas are three to four times more likely than microadenomas to exhibit progressive growth. Solid tumors grow much more often than cystic lesions. People with macroadenomas are more likely to demonstrate hypopituitarism, compressive symptoms, and pituitary apoplexy, although the latter occurrence is still quite rare.

12. What is the primary treatment for a nonfunctioning pituitary tumor?

A microadenoma can be managed with observation by serial imaging studies. Surgical removal should be considered for a macroadenoma; however, serial observation is an option if the tumor is not growing or causing compressive symptoms.

The treatment of choice for symptomatic tumors is transsphenoidal pituitary surgery. Primary radiation therapy may be used if surgery is contraindicated or not desired. Medications, such as dopamine agonists (bromocriptine, cabergoline) and somatostatin analogs (octreotide, lanreotide) are rarely helpful in the treatment of nonfunctioning pituitary tumors.

KEY POINTS 1: NONFUNCTIONING PITUITARY TUMORS

1. Nonfunctioning pituitary tumors cause symptoms primarily through mass effects, resulting in compression of the pituitary stalk and optic chiasm, invasion of the cavernous sinuses, and erosion into the bony sella turcica.
2. Pituitary tumors that do not produce detectable levels of pituitary hormones may raise serum prolactin levels modestly by pituitary stalk compression, which interferes with the flow of dopamine from the hypothalamus.
3. Lesions that can resemble pituitary tumors include metastatic carcinomas, craniopharyngiomas, meningiomas, neural tumors, Rathke's pouch cysts, aneurysms, and infiltrative pituitary diseases.
4. Treatment for nonfunctioning pituitary macroadenomas is transsphenoidal surgery with subsequent radiation therapy or close monitoring for incompletely resected tumors.
5. Diabetes insipidus or secretion of inappropriate antidiuretic hormone (SIADH) syndrome may occur in the immediate postoperative period and must be managed appropriately.
6. Anterior pituitary hormone deficiencies (hypopituitarism) can occur months to years after pituitary tumor removal, particularly if radiation therapy was used.

13. Is postoperative radiation therapy recommended for incompletely resected tumors?

Radiation therapy is not necessary in all cases of incomplete surgical resection. It is advised when the tumor remnants are large, compressive, or growing. Stereotactic radiotherapy is generally preferred over conventional radiation therapy because it delivers a greater focused radiation dose to neoplastic tissue with less radiation exposure to surrounding structures. Residual disease of lesser severity may be monitored with imaging studies and not treated unless growth occurs.

14. What endocrine complications occur in the immediate postoperative period?

Transient diabetes insipidus (vasopressin deficiency) manifested as high-volume urine output is common in the first few days. It may be followed by a short period (1-2 days) of water intoxication (vasopressin excess) causing hyponatremia. Both conditions result from removal, trauma, or edema of the neurohypophysis, where vasopressin is stored. Fluid balance and serum electrolytes must therefore be closely monitored. Secondary adrenal insufficiency is of little immediate concern because high-dose dexamethasone is often given postoperatively to prevent cerebral edema, but it may become apparent after dexamethasone is stopped. Deficiencies of other pituitary hormones are not usually early postoperative problems if their levels were normal preoperatively.

15. What is the management of postoperative diabetes insipidus and water intoxication?

Mild postoperative diabetes insipidus can be managed with isovolumetric, isotonic fluid replacement. More severe cases should be treated with desmopressin (DDAVP), 0.25 to 0.5 mL (1-2 μg) two times a day intravenously or subcutaneously or with aqueous vasopressin, 5 units subcutaneously every 4 to 6 hours, until urine volumes become normal. If hyponatremia develops, vasopressin must be reduced or stopped, and free water intake restricted. If diabetes insipidus persists beyond 1 week, patients may be switched to intranasal DDAVP, 0.1 to 0.2 mL once or twice daily, or oral DDAVP tablets, 0.1 to 0.4 mg daily.

16. What endocrine problems may occur during long-term follow-up?

Deficiencies of other pituitary hormones may develop weeks, months, or years later, especially if radiation therapy was given. The only major concern in the first month is adrenal insufficiency. During

TABLE 19-1. LONG-TERM MANAGEMENT OF PITUITARY INSUFFICIENCY

HORMONE DISORDER	MANAGEMENT
Adrenal insufficiency	Physiological glucocorticoid replacement
Hypothyroidism	Levothyroxine replacement
Hypogonadism (men)	Androgen gels, patches, or injections
Hypogonadism (women)	Oral or transdermal contraceptives or postmenopausal hormone replacement
Growth hormone (GH)	Growth hormone replacement
Diabetes insipidus	Desmopressin nasal spray or oral tablets

this time, one should question patients about suggestive symptoms and, if present, measure a morning cortisol level. If the morning cortisol level is low (<10 μg/dL), hydrocortisone replacement should be initiated, and the patient retested in 3 to 6 months with a cosyntropin stimulation test. At that time, levels of serum free thyroxine (T_4), TSH, IGF-1, LH, FSH, testosterone (men), and estradiol (women) should also be checked, and replacement therapy considered for any identified deficiencies. It is recommended that these levels then be monitored at 6 months, 1 year, and annually thereafter.

17. Summarize the long-term management of pituitary insufficiency.

See Table 19-1.

18. Describe the clinical features of pituitary carcinomas.

Pituitary carcinomas, which are extremely rare, expand rapidly and have mass effects. Some secrete hormones causing endocrine syndromes similar to those seen with adenomas. Metastatic disease to the central nervous system, cervical lymph nodes, liver, and bone is commonly associated.

19. What is the treatment for pituitary carcinoma?

Transsphenoidal surgery followed by radiation therapy is the treatment of choice. No successful use of chemotherapy has been reported for pituitary carcinoma.

20. What is the prognosis for pituitary carcinoma?

The mean survival is approximately 4 years.

21. Which cancers metastasize to the pituitary gland?

Metastatic disease to the pituitary gland occurs in approximately 3% to 5% of patients with widely disseminated carcinoma. The most commonly reported primary tumors are those of breast, lung, kidney, prostate, liver, pancreas, and nasopharynx, plasmacytoma, sarcoma, and adenocarcinoma of unknown primary site.

BIBLIOGRAPHY

Arafah BM, Kailani SH, Nekl KE, et al: Immediate recovery of pituitary function after transsphenoidal resection of pituitary macroadenomas, *J Clin Endocrinol Metab* 79:348–354, 1994.

Arafah BM, Prunty D, Ybarra J, et al: The dominant role of increased intrasellar pressure in the pathogenesis of hypopituitarism, hyperprolactinemia, and headaches in patients with pituitary adenomas, *J Clin Endocrinol Metab* 85:1789–1793, 2000.

Barker FG, Klibanski A, Swearingen B: Transsphenoidal surgery for pituitary tumors in the United States, 1996–2000: mortality, morbidity, and effects of hospital and surgeon volume, *J Clin Endocrinol Metab* 88:4709–4719, 2003.

Branch Jr CL, Laws Jr ER: Metastatic tumors of the sella turcica masquerading as primary pituitary tumors, *J Clin Endocrinol Metab* 65:469–474, 1987.

Dekkers GM, Pereira AM, Romijn JA: Treatment and follow-up of clinically non-functioning pituitary macroadenomas, *J Clin Endocrinol Metab* 93:3717–3726, 2008.
Dudziak K, Honegger J, Bornemann A, et al: Pituitary carcinoma with malignant growth from first presentation and fulminant clinical course – case report and review of the literature, *J Clin Endocrinol Metab* 96:2665–2669, 2011.
Famini P, Maya MM, Melmed S: Pituitary magnetic resonance imaging for sellar and parasellar masses: ten-year experience in 2598 patients, *J Clin Endocrinol Metab* 96:1633–1641, 2011.
Fernandez-Balsells MM, Murad MH, Barwise A, et al: Natural history of nonfunctioning pituitary adenomas and incidentalomas: a systematic review and metaanalysis, *J Clin Endocrinol Metab* 96:905–912, 2011.
Freda PU, Beckers AM, Katznelson L, et al: Pituitary incidentalomas: an Endocrine Society clinical practice guideline, *J Clin Endocrinol Metab* 96:894–904, 2011.
Hannon JM, Finucane FM, Sherlock M, et al: Disorders of water homeostasis in neurosurgical patients, *J Clin Endocrinol Metab* 97:1423–1433, 2012.
Kaltsas GA, Mukherjee JJ, Plowman PN, et al: The role of cytotoxic chemotherapy in the management of aggressive and malignant pituitary tumors, *J Clin Endocrinol Metab* 83:4233–4238, 1998.
Loeffler JS, Shih HA: Radiation therapy in the management of pituitary adenomas, *J Clin Endocrinol Metab* 96:1992–2003, 2011.
Mukherjee JJ, Islam N, Kaltsas G, et al: Clinical, radiological and pathological features of patients with Rathke's cleft cysts: tumors that may recur, *J Clin Endocrinol Metab* 82:2357–2362, 1997.
Pernicone PJ, Scheithauer BW, Sebo TJ, et al: Pituitary carcinoma: a clinicopathological study of 15 cases, *Cancer* 79:804–812, 1997.
Ramirez C, Cheng S, Vargas G, et al: Expression of Ki-67, FGFFR4, and SSTR 2, 3, and 5 in nonfunctioning pituitary adenomas: a high throughput TMA, immunohistochemical study, *J Clin Endocrinol Metab* 97:1745–1751, 2012.
Shin JL, Asa SL, Woodhouse LJ, et al: Cystic lesions of the pituitary: clinicopathological features distinguishing craniopharyngioma, Rathke's cleft cyst, and arachnoid cyst, *J Clin Endocrinol Metab* 84:3972–3982, 1999.
Swords FM, Allan CA, Plowman PN: Stereotactic radiosurgery XVI: a treatment for previously irradiated pituitary adenomas, *J Clin Endocrinol Metab* 88:5334–5340, 2003.
Wilson CB: Extensive personal experience: surgical management of pituitary tumors, *J Clin Endocrinol Metab* 82:2381–2385, 1997.

CHAPTER 20

PROLACTIN-SECRETING PITUITARY TUMORS

Virginia Sarapura

1. Describe the normal control of prolactin secretion. How is it altered in prolactin-secreting tumors?

Multiple factors affect prolactin secretion (Fig. 20-1). However, the principal influence on prolactin secretion is tonic inhibition by dopamine input from the hypothalamus. Dopamine interaction with receptors of the D2 subtype on pituitary lactotroph membranes activates the inhibitory G-protein, leading to decreased adenylate cyclase activity and decreased levels of cyclic adenosine monophosphate (cAMP). In prolactin-secreting pituitary adenomas, a monoclonal population of prolactin-producing cells escapes the normal physiologic input of dopamine from the hypothalamus, apparently by acquiring a peripheral blood supply. In almost all cases, responsiveness to a pharmacologic dose of dopamine is maintained.

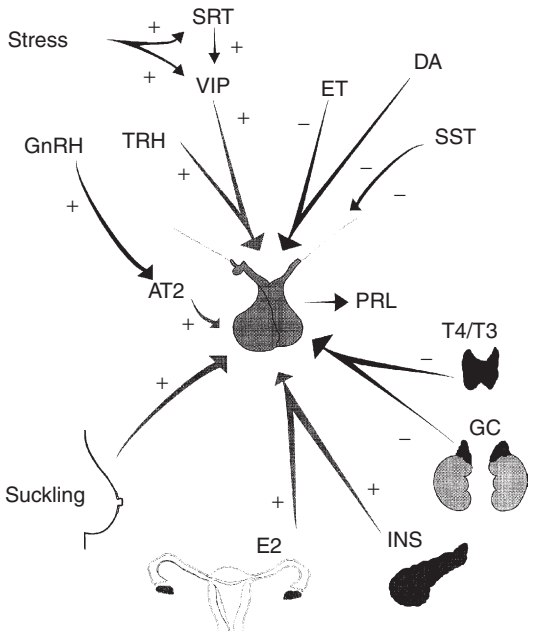


Figure 20-1. The multiple pathways controlling prolactin secretion. Plus (+), stimulatory effect; minus (−), inhibitory effect. Input from above the pituitary gland (*depicted*) arises in the hypothalamus; input from below arises in the breast nipple, ovary, pancreas, adrenal gland, and thyroid gland, as depicted. AT2, angiotensin 2; DA, dopamine; E2, estradiol; ET, endothelin; GC, glucocorticoids; GnRH, gonadotropin-releasing hormone; INS, insulin; PRL, prolactin; SRT, serotonin; SST, somatostatin; T4/T3, thyroxine/triiodothyronine; TRH, thyrotropin-releasing hormone; VIP, vasoactive intestinal peptide.

2. What are the normal levels of serum prolactin? Are they different in men and women? What levels are seen in patients with prolactin-secreting tumors?

The normal serum prolactin level is less than 15 or 30 ng/mL, depending on the laboratory. Women tend to have slightly higher levels than men, probably because of estrogen stimulation of prolactin secretion. In patients with prolactin-secreting tumors, the levels are usually higher than 100 ng/mL but may be as low as 30 to 50 ng/mL if the tumor is small. A level greater than 200 ng/mL is almost always indicative of a prolactin-secreting tumor. Very high prolactin levels may be found to be falsely normal because of the high-dose hook effect of the assay; if clinically indicated, the sample should be assayed again after dilution.

3. What are the physiologic causes of an elevated prolactin level that must be considered in the differential diagnosis of prolactin-secreting tumors? What levels can be reached under these circumstances?

The most important physiologic states in which prolactin is found to be elevated are pregnancy and lactation. During the third trimester of pregnancy, the prolactin level may reach 200 to 300 ng/mL. It then gradually decreases during the first week postpartum, despite continued lactation, but may continue to rise acutely at the time of breastfeeding. Prolactin values are also elevated during sleep, strenuous exercise, stress, and nipple stimulation. In these cases, the elevation is mild, below 50 ng/mL.

4. List the abnormal causes of an elevated serum prolactin value other than a prolactin-secreting tumor, and state the mechanisms underlying the abnormal prolactin production.

See Table 20-1.

TABLE 20-1. ABNORMAL CAUSES OF ELEVATED SERUM PROLACTIN LEVEL OTHER THAN PROLACTIN-SECRETING TUMORS AND UNDERLYING MECHANISM OF ABNORMAL PROLACTIN PRODUCTION

CAUSES	MECHANISM
Pituitary stalk interruption Trauma Surgery Pituitary, hypothalamic, or parasellar tumor Infiltrative disorders of the hypothalamus	Interference with the hypothalamic-pituitary pathways: Prolactin production increases because the tonic inhibition of prolactin secretion is interrupted; often accompanied by hypopituitarism
Pharmacologic agents: Phenothiazines Tricyclic antidepressants Alpha-methyldopa Metoclopramide Cimetidine Estrogens	Specific interference with dopaminergic input to the pituitary gland
Hypothyroidism	Increased thyrotropin-releasing hormone that stimulates prolactin release
Renal failure and liver cirrhosis	Decreased metabolic clearance of prolactin; also, increased production in chronic renal failure
Intercostal nerve stimulation Chest wall lesions Herpes zoster	Mimicking of the stimulation caused by suckling

5. What are the typical levels of serum prolactin associated with these causes?
In all these cases, the prolactin value is usually mildly elevated, 30 to 50 ng/mL, and rarely above 100 ng/mL.

6. How does prolactin elevation result in gonadal dysfunction? What are the symptoms associated with gonadal dysfunction?
Elevated prolactin values suppress the hypothalamic-pituitary-gonadal axis by interfering with the secretion of gonadotropin-releasing hormone (GnRH) in the hypothalamus, resulting in a decrease in circulating levels of estrogen or testosterone. Symptoms include infertility, loss of libido, menstrual irregularity, and amenorrhea in women, and loss of libido and impotence in men.

7. What is galactorrhea? Do most patients with prolactin-secreting tumors present with this symptom?
Galactorrhea is the discharge of milk from the breast not associated with pregnancy or lactation. Although a typical symptom of prolactin-secreting tumors, it may be absent in up to 50% of women, particularly when estrogen levels are very low. Galactorrhea is uncommon in men but may be seen in conjunction with gynecomastia when decreased gonadal function results in a low ratio of testosterone to estrogen.

8. Why do men with prolactin-secreting tumors often present with more advanced disease than women?
The major symptoms of elevated prolactin values in men are decreased libido and impotence. These symptoms may be ignored or attributed to psychological causes. Many years may go by before an evaluation is sought, often when the patient experiences headaches and visual field defects related to the mass effect of the tumor. Women are more likely to seek evaluation early in the disease process, when infertility or menstrual irregularities prompt an evaluation of their hormonal status. Interestingly, studies have suggested that large ($\geq$ 10 mm) and small ($<$ 10 mm) tumors may be biologically different at their onset. It has been found that there is no difference in the prevalence of large tumors between men and women; however, there is a much higher prevalence of small tumors in women. This difference suggests that factors in women, possibly estrogen, may promote the appearance of prolactin-secreting tumors, but when these appear, they may be smaller and less aggressive.

9. What is the imaging technique of choice when a prolactin-secreting tumor is suspected? Why?
Magnetic resonance imaging (MRI) of the pituitary with a contrast agent, such as gadolinium, is the imaging technique of choice for the evaluation of pituitary tumors. In particular, discrimination of small tumors is improved. Computed tomographic (CT) allows better visualization of bone structures, such as the floor of the sella, in cases of large tumors. However, the relationship of the tumor to other soft tissue structures, such as the cavernous sinuses and carotid arteries, is better visualized with MRI. Skull radiographs and tomograms are not helpful.

10. Bone metabolism is altered when prolactin values are elevated. What is the mechanism for this effect? Is it reversible?
The resulting decrease in circulating estrogen or testosterone levels causes a corresponding decrease in osteoblastic bone formation and an increase in osteoclastic bone resorption. Consequently there is a decrease in bone mineral density and progression to osteoporosis. Studies suggest that normalization of prolactin levels restores bone density in most but not all patients, particularly those affected at an early age, before reaching peak bone mass in the third decade of life.

KEY POINTS 1: PROLACTIN-SECRETING PITUITARY TUMORS

1. When a mild prolactin elevation is found (30-50 ng/mL), physiologic, pathologic, and iatrogenic causes must be excluded before the diagnosis of a small prolactin-secreting tumor can be made.
2. A prolactin level higher than 200 ng/mL is almost always indicative of a prolactin-secreting tumor, except during late pregnancy.
3. Elevated prolactin values cause galactorrhea and suppress the hypothalamic-pituitary-gonadal axis, resulting in hypogonadism and a progressive decrease in bone mineral density.
4. Untreated prolactin-secreting tumors grow very slowly: Less than 5% of small tumors are noticeably larger after 2 to 5 years.
5. Treatment with dopamine agonists is well tolerated and quickly effective in normalizing the prolactin level and shrinking the tumor mass of even very large prolactin-secreting tumors.

11. If a prolactinoma is left untreated, what is the risk of tumor enlargement?

Many longitudinal studies agree that progression of the disease is rare and occurs at a slow pace. This is particularly true of small prolactin-secreting tumors ($<$ 10 mm), fewer than 5% of which enlarge significantly over 25 years of observation. There is no reliable way to predict which tumors will show progression. Spontaneous resolution, attributed to necrosis, has also been described in some patients, particularly after pregnancy.

12. Is medical treatment available for prolactin-secreting tumors? What is the mode of action?

Medical treatment with dopamine agonists has been available since the early 1980s. The most commonly used drugs are bromocriptine and cabergoline; pergolide and hydergine are also commercially available dopamine agonists, but they are not approved specifically for treatment of prolactin-secreting tumors. Both bromocriptine and cabergoline are highly effective in reducing both prolactin level and tumor size.

13. Describe the mode of action of commonly used drugs.

Dopamine agonists bind to the pituitary-specific D2 dopamine receptors on the cell membrane of prolactin-secreting cells, decreasing intracellular levels of cAMP and Ca^{2+}. This process inhibits the release and synthesis of prolactin. An increase in cellular lysosomal activity causes involution of the rough endoplasmic reticulum and Golgi apparatus. The action of dopamine agonists on D1 dopamine receptors in the brain has the side effects nausea and dizziness; dopamine agonists with more D2 specificity, such as cabergoline, are less likely to have these side effects.

14. If a woman with a prolactin-secreting tumor becomes pregnant while undergoing medical treatment, should the treatment be continued? Should she breast-feed her infant?

Even though many studies have found that maternal treatment with dopamine agonists is safe for the fetus, it is recommended that the drug be stopped as soon as pregnancy is diagnosed. The risk of tumor reexpansion is low: less than 5% for small prolactin-secreting tumors and 15% to 35% for large tumors. Assessment of symptoms, particularly headaches, and visual field tests should be performed monthly; any evidence of tumor reexpansion should prompt the reinstitution of treatment. Breast-feeding does not appear to add any significant risk for these patients, but close follow-up should be continued.

15. How long does it take for medical treatment to reduce the serum prolactin level? To reduce the size of the tumor?

The onset of action of dopamine agonists is rapid; because prolactin has a serum half-life of 50 minutes, a decrease in the prolactin level may be noted within 2 hours. However, normalization of prolactin levels may take weeks or months, with the maximal decrease usually seen by 3 months. Tumor size reduction can occur within 48 hours and may be demonstrated by improvement in visual fields when these are affected by the tumor. Tumor shrinkage is usually evident by 3 months; for larger tumors it is recommended that the MRI be performed again at this time. Maximal tumor shrinkage, however, is not usually observed until after at least 12 months of treatment. Another MRI after 1 year of treatment is therefore recommended.

16. How long is medical treatment of prolactin-secreting tumors required? Why?

Lifelong treatment is usually required because prolactin levels rise and tumors reexpand when treatment is interrupted, suggesting that the effect is mostly cytostatic. Later reports, however, suggest that about 20% of cases may be cured after 2 to 5 years of treatment (longer time required for larger tumors), and some evidence suggests that dopamine agonists may have a cytolytic effect.

17. When is surgical removal of a prolactin-secreting tumor indicated?

With the availability of dopamine agonists, surgery has become a secondary choice in the treatment of prolactin-secreting tumors, particularly because the long-term surgical cure rate for large tumors is only 25% to 50%. The principal indications for surgical treatment of a prolactin-secreting tumor are intolerance or resistance to dopamine agonists and acute hemorrhage into the tumor. A cerebrospinal fluid leak due to erosion of the floor of the sella turcica is another indication for surgical debulking and repair.

18. When is radiotherapy indicated to treat a prolactin-secreting tumor?

Radiotherapy has rarely been used because hypopituitarism is a common side effect. This complication is of critical concern, particularly in patients under treatment for infertility. However, radiotherapy may be a useful adjunct in patients who require additional treatment after surgery and who do not tolerate dopamine agonists. Some experts advocate the use of radiotherapy 3 months before attempting pregnancy in women with large tumors to avoid tumor reexpansion during pregnancy. The development of new stereotactic radiosurgical techniques, such as the gamma knife, may improve outcomes and minimize radiation side effects.

WEBSITES

1. National Institute for Diabetes, Digestive and Kidney Disorders: http://www.endocrine.niddk.nih.gov/pubs/prolact/prolact.htm.
2. UpToDate: Patient information): http://patients.uptodate.com/topic.asp?file=endocrin/8753.
3. Pituitary Society: Information for patients: Prolactinoma http://www.pituitarysociety.org/public/specific/prolactinoma.

BIBLIOGRAPHY

Bronstein MD: Prolactinomas and pregnancy, *Pituitary* 8:31–38, 2005.
Casanueva FF, Molitch ME, Schlechte JA, et al: Guidelines of the Pituitary Society for the diagnosis and management of prolactinomas, *Clin Endocrinol (Oxf)* 65:265–273, 2006.
Colao A, Abs R, Bárcena DG, et al: Pregnancy outcomes following cabergoline treatment: extended results from a 12-year observational study, *Clin Endocrinol (Oxf)* 68:66–71, 2008.
Gillam MP, Molitch ME, Lombardi G, et al: Advances in the treatment of prolactinomas, *Endocr Rev* 27:485–534, 2006.
Molitch ME: Pharmacologic resistance in prolactinoma patients, *Pituitary* 8:43–52, 2005.
Schlechte JA: Long-term management of prolactinomas, *J Clin Endocrinol Metab* 92:2861–2865, 2007.

GROWTH HORMONE–SECRETING PITUITARY TUMORS

CHAPTER 21

Mary H. Samuels

1. What is the normal function of growth hormone in children and adults?

In children, growth hormone (GH) is responsible for linear growth. In children and adults, GH has many effects on intermediary metabolism, including protein synthesis and nitrogen balance, carbohydrate metabolism, lipolysis, and calcium homeostasis.

2. How are levels of GH normally regulated?

Pituitary secretion of GH is regulated primarily by two hypothalamic hormones: stimulatory GH-releasing hormone (GH-RH) and inhibitory somatostatin. Secretion of GH is also affected by adrenergic and dopaminergic hormones as well as by other central nervous system and peripheral factors.

3. Does GH directly affect peripheral tissues?

No. Most (although not all) effects of GH are mediated by another hormone called insulin-like growth factor 1 (IGF-1). IGF-1 is made by the liver and other organs in response to stimulation by GH. IGF-1 feeds back to the pituitary gland and suppresses GH secretion. Unlike GH, IGF-1 has a long half-life in plasma; thus plasma IGF-1 levels are helpful in the diagnosis of GH abnormalities.

4. What are the clinical features of excessive production of GH in children?

In children who have not yet undergone puberty and whose long bones still respond to GH, excessive GH causes accelerated linear growth. The result is gigantism.

5. Describe the clinical features of excessive production of GH in adults.

In adults, excessive GH causes acromegaly. Acromegaly is rare, with an incidence of approximately 5 cases per million people per year, and often progresses gradually and insidiously. The pathologic and metabolic effects of acromegaly are summarized in Table 21-1.

TABLE 21-1. CLINICAL EFFECTS OF ACROMEGALY

CLINICAL EFFECT	CAUSE
Coarse features	Periosteal formation of new bone
Enlarged hands and feet	Soft tissue hypertrophy
Excess sweating	Hypertrophy of sweat glands
Deepened voice	Hypertrophy of larynx
Skin tags	Hypertrophy of skin
Upper airway obstruction and sleep apnea	Hypertrophy of tongue and upper airway
Osteoarthritis	Hypertrophy of joint cartilage and osseous overgrowth
Carpal tunnel syndrome	Hypertrophy of joint cartilage and osseous overgrowth
Hypertension, congestive heart failure	Cardiac hypertrophy
Hypogonadism	Multifactorial
Diabetes mellitus, glucose intolerance	Insulin antagonism, other factors
Colonic polyps	Colonic hypertrophy

6. What is the single best clue in examining a patient suspected of having acromegaly?

An old driver's license picture or other old photographs provide the best clues. Patients with acromegaly are often unaware of the gradual disfigurement due to the disease or attribute it to aging. Comparing serial photographs can help establish the diagnosis as well as date its onset.

7. From what do patients with acromegaly die?

Acromegaly increases cardiovascular and metabolic risk factors, including hypertension, glucose intolerance, cardiomyopathy, and sleep apnea. The mortality from inadequately treated acromegaly is about double the expected rate in healthy age-matched subjects. Major causes of death are hypertension, cardiovascular disease, heart failure, and diabetes. Improved treatment has decreased this risk, but there is still a 30% higher risk of mortality in patients with acromegaly.

8. The husband of a patient with acromegaly complains that he cannot sleep because his wife snores. Is this relevant?

Sleep apnea occurs in 50% to 70% of patients with acromegaly. It can be due to soft tissue overgrowth of the upper airway or to altered central respiratory control. Sleep apnea may contribute to morbidity and mortality in acromegaly by producing hypoxia and pulmonary hypertension.

9. If I suspect that a patient may have acromegaly, what test should I order?

The single best screening test for acromegaly is measurement of the plasma level of IGF-1. Unlike those for GH levels, which are pulsatile and higher at night, blood specimens for IGF-1 measurement can be drawn any time of day. In adults, acromegaly is essentially the only condition that causes elevated IGF-1 values. In children, IGF-1 levels are more difficult to interpret because IGF-1 is normally high in growing children. IGF-1 levels may be less accurate in mild acromegaly, malnutrition, or hepatic or renal disease.

10. The patient's IGF-1 value is not elevated, but I still think that she may have acromegaly. What other test should I order?

The gold standard test to rule out acromegaly is the measurement of serum GH levels in the fasting state and after glucose suppression. Healthy subjects suppress GH levels to less than 1 ng/mL 2 hours after an oral glucose load (75 g), whereas patients with acromegaly show insufficient suppression of GH levels. This test may be unreliable in patients with diabetes mellitus, hepatic or renal disease, obesity, or pregnancy, or in patients undergoing estrogen therapy.

11. After the biochemical diagnosis of acromegaly or gigantism is made, what is the next step?

Excessive secretion of GH is almost always due to a benign pituitary tumor. Therefore the next step is to obtain a radiologic study of the pituitary gland. The optimal study is magnetic resonance imaging (MRI) with special cuts through the pituitary gland.

12. What causes GH-secreting pituitary tumors?

GH-secreting pituitary tumors are monoclonal, indicating that a spontaneous somatic mutation is a key event in neoplastic transformation of somatotrophs. Further studies have clarified the nature of the mutation in some GH tumors that appear to have an altered stimulatory subunit (G_S) of the G-proteins that regulate adenylate cyclase activity. In a mutated cell, alterations in the G_S subunit cause autonomous adenylate cyclase activity, somatotroph proliferation, and elevated GH secretion. However, the mutant G_S is found in only about 40% of patients with acromegaly. The mechanisms of GH regulation and tumor growth differ in other patients with acromegaly.

13. Are other endocrine syndromes possible in patients with acromegaly or gigantism?

Yes. Otherwise acromegaly and gigantism would not be endocrine disorders. Three endocrine syndromes include acromegaly (Table 21-2).

TABLE 21–2. ENDOCRINE SYNDROMES ASSOCIATED WITH ACROMEGALY

SYNDROME	MAJOR INVOLVED ORGANS	CLINICAL FINDINGS	OTHER CLUES
Multiple endocrine neoplasia type 1 (MEN 1)	Pituitary tumors Parathyroid hyperplasia Islet-cell tumors	Hypercalcemia (most) Peptic ulcer disease (if gastrinoma) Hypoglycemia (if insulinoma)	Autosomal dominant Check calcium levels in patients with acromegaly
McCune-Albright syndrome	Bones Skin Gonads Others	Polyostotic fibrous dysplasia Café-au-lait spots Sexual precocity	Mostly in girls
Carney's complex	Heart Skin Adrenals Other	Cardiac myomas Pigmented skin lesions Pigmented nodular adrenal hyperplasia Many other tumors	Autosomal dominant

14. Do other tumors besides pituitary tumors make GH and cause acromegaly or gigantism?

Yes. Rare tumors of the pancreas, lung, ovary, and breast may produce GH.

15. Do tumors ever cause acromegaly or gigantism by making excessive GH-RH?

Yes. Rare cases of GH-RH production by various tumors have been described in the lung, gastrointestinal tract, and adrenal glands. They cause acromegaly by stimulating pituitary secretion of GH. The clinical and biochemical features of acromegaly are indistinguishable from those of acromegaly due to a pituitary adenoma. Pituitary enlargement also occurs as a result of hyperplasia of somatotrophs. Some patients have undergone transsphenoidal surgery before the correct diagnosis was made. Therefore the plasma level of GH-RH should be measured in any acromegalic patient with an extrapituitary abnormality or in whom hyperplasia is shown by pituitary pathology.

16. If MRI of the pituitary confirms a tumor in the acromegalic patient, what issues other than the metabolic effects of excessive GH should be considered?

1. Is the tumor making any other pituitary hormones besides GH? For example, many GH-secreting tumors also produce prolactin; rare tumors also make thyroid-stimulating hormone or other pituitary hormones. In patients with acromegaly, prolactin levels should be measured, as well as other hormones when clinically indicated.
2. Is the tumor interfering with the normal function of the pituitary gland? Specifically, how are the patient's thyroid, adrenals, and gonads functioning? Does the patient have diabetes insipidus? It is important to diagnose and treat pituitary insufficiency before therapy for the excessive secretion of GH, especially if the patient is scheduled for surgery.
3. Is the tumor causing effects owing to its size and location? Possible effects include headache, visual field disturbances, and extraocular movement abnormalities. Formal visual field examination should be carried out in patients with large pituitary tumors.

17. How big are GH-secreting pituitary tumors?

GH-secreting tumors vary considerably in size, but most are more than 1 cm in diameter when diagnosed (i.e., macroadenomas), and some can be very large. Tumor size is an important issue because it determines the likelihood that treatment will be successful.

KEY POINTS 1: ACROMEGALY

1. Acromegaly leads to gradual soft tissue enlargement and disfigurement over many years, and the patient may be unaware of the changes.
2. Acromegaly causes damage to bones, joints, the heart, and other organs and is associated with considerable morbidity and excess mortality.
3. The best screening test for acromegaly is measurement of the plasma level of insulin-like growth factor type 1.
4. The best initial treatment for acromegaly is usually surgery, performed by an experienced pituitary surgeon.
5. There are new medical treatments for acromegaly that are effective in controlling the metabolic effects of excess growth hormone secretion.

18. How should acromegaly or gigantism be treated?

Goals of therapy for GH-secreting tumors include mortality reduction, tumor shrinkage, and control of GH hypersecretion. The treatment of choice for GH-secreting tumors is transsphenoidal surgery by an experienced pituitary surgeon. Most patients with microadenomas are cured by such a procedure, and larger tumors are debulked. When it is performed by experienced hands, surgical complications are unusual. Significant reduction in GH levels and improvement in symptoms typically follow surgery, even when further treatment is required. Certain patients may benefit from medical therapy before surgery to reduce surgical risks, including those with congestive heart failure, severe sleep apnea, intubation problems, or other comorbidites of acromegaly. There are no conclusive data that presurgical treatment improves cure rates, however.

19. What are the options for medical therapy of acromegaly?

Approximately 40% to 60% of GH macroadenomas are not controlled by surgery alone, and adjuvant therapy is indicated. Three drug classes are available for the treatment of acromegaly: somatostatin analogs (octreotide and lanreotide), the GH receptor antagonist pegvisomant, and dopamine agonists. Dopamine agonists are not discussed further here, because their efficacy is limited.

20. Discuss the mechanism of action of somatostatin analogs.

Most GH-secreting tumors have somatostatin receptors and respond to exogenous somatostatin with decreases in GH levels. The development of long-acting forms of octreotide, an analog of somatostatin, was a major advance in the treatment of acromegaly.

21. How effective are somatostatin analogs?

Somatostatin analogs markedly decrease GH levels in most acromegalic patients, with amelioration of many of the symptoms and side effects of acromegaly. Up to 70% of patients receiving somatostatin analogs achieve biochemical remission. Significant tumor shrinkage occurs in approximately 70% of patients. However, these agents do not cure acromegaly; stopping the drugs usually leads to increases in GH levels and tumor regrowth. Somatostatin analogs are commonly used indefinitely after surgery has failed to achieve biochemical control of GH hypersecretion. They can also be used before surgery to improve comorbidities, temporarily after surgery during the wait for radiation therapy to take effect (see later), or instead of surgery in carefully selected patients. Common side effects include gastrointestinal symptoms and gallstone formation.

22. Describe the mechanism of action of pegvisomant.

Pegvisomant blocks GH action at peripheral GH receptors, thereby improving IGF-1 levels, reducing clinical GH effects, and correcting metabolic defects. It does not appear to affect tumor size in the great majority of patients, but tumor size should be monitored, given the drug's mechanism of action. It is usually used for patients whose disease is resistant to or who do not tolerate somatostatin analogs, or in combination with somatostatin analogs to improve biochemical control. The main side effect of pegvisomant is liver function abnormalities, which are usually transient. Note that GH levels cannot be monitored in patients taking pegvisomant.

23. What about radiation therapy for acromegaly?

Conventional radiation therapy of GH-secreting tumors causes a gradual decline in GH levels over many years, with maximal effect occurring at 10 to 15 years. Therefore, it is generally reserved as a third-line therapy for acromegaly. It may also increase long-term mortality. Stereotactic radiotherapy, which consists of applying a highly concentrated high-energy radiation therapy beam to the tumor, may be more effective and work more quickly than conventional radiation therapy for pituitary tumors. However, stereotactic radiotherapy still takes months to years to work. If radiation therapy is deemed necessary in acromegaly, the choice of a conventional or stereotactic approach depends on the residual tumor size and location. Hypopituitarism eventually develops in many patients from radiation therapy, and there may also be small risks of vision deficits, secondary tumors, cerebrovascular events, and cognitive effects.

24. How can one tell whether a patient has been cured of acromegaly?

Older studies defined cure as a randomly measured GH level below 5 ng/mL. Later studies have shown that this criterion is inadequate, and more rigorous criteria have been developed as GH assays have become more sensitive. For complete control of GH secretion, patients should have normal age-adjusted IGF-1 and basal GH levels, and GH levels less than 0.4 ng/mL following an oral glucose load.

25. The patient has undergone transsphenoidal surgery for acromegaly and now has normal IGF-1 and GH levels and suppressed levels of GH following an oral glucose load. How should this patient be monitored?

It appears that the patient is cured, but GH tumors can slowly regrow over years. At the least, measurements of GH and IGF-1 should be repeated every 6 to 12 months. Some physicians measure GH levels following glucose administration as well. Tumor mass should be monitored at intervals with pituitary MRI. The patient also needs an evaluation for colonic neoplasia, because some studies suggest that the incidence of premalignant colonic lesions may be increased in acromegaly. In addition, one must assess whether the surgery damaged normal pituitary function by determining the patient's thyroid, adrenal, gonadal, and posterior pituitary function. The effects of surgery on visual fields should be assessed, especially if the patient had preoperative defects.

26. The patient asks which symptoms and physical abnormalities will improve after cure is confirmed. What is the appropriate answer?

Most soft tissue changes improve, including coarsening of facial features, increased size of hands and feet, upper airway hypertrophy, carpal tunnel syndrome, osteoarthritis, and excessive sweating. Unfortunately, bony overgrowth of the facial bones does not regress after treatment. Hypertension, cardiovascular disease, and diabetes also improve. However, not all comorbidities resolve with successful treatment of GH hypersecretion, and hypertension, cardiac dysfunction, diabetes, hyperlipidemia, osteoarthritis, and sleep apnea may require additional management.

27. For bonus points, name an actor with acromegaly and the movie in which he starred.

Andre the Giant starred in *The Princess Bride.*

BIBLIOGRAPHY

Giustina A, Chanson P, Bronstein MD, et al: A consensus on criteria for cure of acromegaly, *J Clin Endocrinol Metab* 95:3141–3148, 2010.

Katznelson L: Approach to the patient with persistent acromegaly after pituitary surgery, *J Clin Endocrinol Metab* 95:4114–4123, 2010.

Melmed S: Acromegaly pathogenesis and treatment, *J Clin Investigation* 119:3189–3202, 2009.

Melmed S, Colao A, Barkan A, et al: Guidelines for acromegaly management: an update, *J Clin Endocrinol Metab* 94: 1509–1517, 2009.

Sherlock M, Woods C, Sheppard MC: Medical therapy in acromegaly, *Nat Rew Endocrinol* 7:291–300, 2011.

GLYCOPROTEIN-SECRETING PITUITARY TUMORS

CHAPTER 22

Shon Meek and Robert C. Smallridge

1. What are glycoprotein hormones?

The glycoprotein hormones, luteinizing hormone (LH), thyrotropin (TSH), follicle-stimulating hormone (FSH), and chorionic gonadotropin (CG), are composed of two noncovalently bound subunits. The alpha subunits (α-SUs) are similar in all four hormones. In contrast, the beta subunits (LHβ, FSHβ, and so on) are unique both immunologically and biologically for each hormone.

2. Name two types of glycoprotein-secreting pituitary tumors and their secretory products.

- Gonadotropinomas: LH, FSH, LHβ, FSHβ, alpha subunit
- Thyrotropinoma: TSH, alpha subunit

3. Do pituitary tumors secrete only a single hormone?

No. Many tumors make two or more hormones or subunits. At times, sufficient quantities of multiple hormones are secreted to produce clinical symptoms characteristic of several syndromes within the same patient.

4. Under what circumstances should a TSH-secreting tumor be considered?

- Suspected hyperthyroidism
- Increased serum free thyroxine (T_4) or FT_4 index with detectable TSH
- Pituitary tumors

5. Describe the differential diagnosis for patients with a transient increase in serum T_4 and detectable or elevated TSH.

Exogenous causes:

- L-Thyroxine (L-T_4) therapy (patient noncompliant with therapy who took L-T_4 just before blood was drawn)
- Other drugs (amiodarone, ipodate, amphetamines)

Endogenous causes (subgroup of nonthyroidal illness):

- Acute psychiatric illness
- Acute liver disease

6. Describe the differential diagnosis for patients with a permanent increase in serum total T_4 and detectable or elevated level of serum TSH.

Binding protein disorders:

- Excessive thyroxine-binding globulin (TBG)
- Abnormal thyroxine-binding prealbumin (TBPA) (transthyretin)
- Familial dysalbuminemic hyperthyroxinemia (FDH)
- T_4 autoantibody
- TSH heterophile antibody (requires separate cause for T_4 elevation)

Inappropriate TSH secretion:

- Resistance to thyroid hormone (generalized, central)
- Pituitary tumor

7. What tests aid in the differential diagnosis of the patient with elevated serum total T_4 and detectable or elevated TSH?

The history and physical examination usually rule out medications and nonthyroidal illnesses. The most important laboratory test is the free T_4 measurement. A normal free T_4 value with an elevated total T_4 value strongly suggests one of the binding protein disorders. An elevated free T_4 value, in contrast, generally narrows the differential to two disorders: a thyroid hormone resistance syndrome or a TSH-secreting pituitary tumor. Clinical thyrotoxicosis is commonly present in patients with either condition. One should confirm the abnormal test results in a second laboratory before initiating a workup for these uncommon disorders.

8. How can one distinguish between the hyperthyroid patient with thyroid hormone resistance and one with a pituitary tumor?

TSH tumors may secrete α-SU in excess of the whole TSH molecule. Therefore, the molar ratio of serum α-SU to TSH is increased in many patients with TSH tumors but is normal in those with thyroid hormone resistance. A thyrotropin-releasing hormone (TRH; protirelin) test is also helpful. Fewer than 20% of patients with a TSH tumor have a twofold increase in serum TSH after TRH administration, whereas those with resistance show a brisk response. T_3 (triiodothyronine) suppression does not lower TSH in TSH-producing pituitary tumors but does do so in thyroid hormone resistance disorders. T_3 suppression reduces Doppler color-flow and peak systolic velocity on thyroid ultrasound in most patients with thyroid hormone resistance, but not usually in patients with TSH-producing tumors. If a tumor is suspected, magnetic resonance imaging (MRI) of the pituitary should be obtained. Most TSH tumors (approximately 90%) are macroadenomas (i.e., $\geq$10 mm). Most microadenomas ($<$10 mm) are also visualized on MRI, but rarely, sampling of inferior petrosal sinus blood may be helpful in localizing a tumor. Dynamic MRI or somatostatin receptor scintigraphy (OctreoScan) is also useful. Long-term (2-month) administration of a long-acting somatostatin analog decreases serum free T_4/T_3 and TSH in patients with TSH tumors. Rarely, patients with TSH-secreting pituitary adenomas may have coexisting Graves' hyperthyroidism or thyroid carcinoma.

9. Describe how to calculate an alpha subunit/TSH molar ratio.

TSH values are expressed as μU/mL (or mU/L). One must know the bioactivity and convert these units to ng/mL, the units of α-SU. Furthermore, the molecular weight of the subunit is only half the molecular weight of the whole TSH molecule; this fact must also be considered in calculating the molar ratio. From a practical standpoint, the following formula can be used:

$$\text{Molar ratio} = \left[\frac{\alpha\text{-SU (ng/mL)}}{\text{TSH (mU/L)}}\right] \times 10$$

The following are normal alpha subunit/TSH molar ratios:
If TSH is normal:
- Molar ratio is less than 5.7 in normogonadotrophic individuals.
- Molar ratio is less than 29.1 in hypergonadotrophic individuals.

If TSH is elevated:
- Molar ratio is less than 0.7 in normogonadotrophic individuals.
- Molar ratio is less than 1.0 in hypergonadotrophic individuals.

10. Name the treatment of choice for TSH-secreting tumors.

Pituitary surgery is the treatment of choice and produces remission in up to 50% of patients. Results are somewhat better if surgery is followed by radiation therapy. Because more microadenomas are being identified, results of cure or control of disease are improving.

11. How effective is radiation as the sole therapy?

Because so few cases have been reported, effectiveness of irradiation alone is uncertain.

12. List the medical therapies used for TSH-secreting tumors.

Octreotide or lanreotide (somatostatin analog) decreases TSH in more than 90% of cases and normalizes free T_4 in 75% of cases. Tumor size decreases, and vision improves. Bromocriptine has limited success. Dexamethasone reduces TSH, but its side effects exclude long-term use. Iopanoic acid is effective preoperatively.

13. Summarize the role of thyroid gland ablation in the treatment of TSH-secreting tumors.

Thyroidectomy and radioactive iodine (I 131) should be avoided. They do not control TSH secretion and may enhance pituitary activity and growth, although two reported patients monitored for 8 and 12 years had no tumor growth.

14. Do all patients with an enlarged pituitary gland and an elevated serum TSH value have thyrotropinomas?

No. In patients with long-standing hypothyroidism, pituitary hyperplasia and a pseudotumor may develop (Fig. 22-1). The mass can extend into the suprasellar region, causing visual field defects. The serum T_4 value is always low. Shrinkage of the enlarged gland usually occurs with L-T_4 therapy. Hyperplasia of lactotrophs may also occur, causing elevated prolactin levels. No patient should undergo pituitary gland surgery without preoperative measurement of serum T_4 and TSH.

15. What clinical features raise suspicion of a TSH-secreting pseudotumor?

Almost all patients have symptoms of hypothyroidism and the serum T_4 level is always low. The underlying abnormality is usually autoimmune thyroiditis. About 80% of cases of pituitary enlargement with hypothyroidism have occurred in women, whereas only 55% of true TSH tumors are in

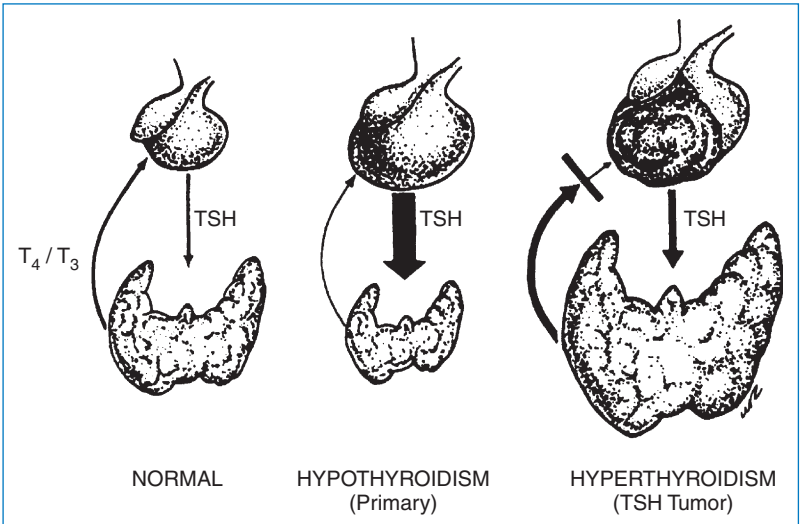


Figure 22-1. Pituitary-thyroid axis in normal persons and patients with thyrotropin (TSH)-secreting pituitary tumors. L*eft,* The appropriate feedback loop in euthyroid persons, with the width of the *arrows* representing the normal serum concentration of TSH and thyroxine (T_4). *Middle,* A small thyroid gland due to primary hypothyroidism. The low T_4 levels result in markedly increased secretion of TSH and, in some patients, a generalized hyperplasia of the anterior pituitary gland. *Right,* An autonomous pituitary tumor secreting TSH. Serum TSH levels may vary greatly but in all cases are sufficiently biologically active to raise levels of T_4 above normal. The elevated T_4 level has little, if any, ability to suppress tumor function.

women. In children, precocious puberty may occur. Thyroid antibodies are present in more than 75% of patients with pseudotumor, compared with about 10% of patients with TSH tumors that produce hyperthyroidism.

16. Does the presence of abnormal visual fields help distinguish between pituitary hyperplasia due to primary hypothyroidism and TSH-secreting tumors?

No. Abnormal visual fields have been reported in 28% of patients with hyperplasia versus 42% of those with tumors. In contrast, patients with thyroid hormone resistance have normal vision.

17. Does family history provide any clues for distinguishing these disorders?

In pseudotumor from thyrotroph hyperplasia, the family history may be positive for autoimmune diseases (e.g., thyroiditis, Graves' disease, type 1 diabetes mellitus, rheumatoid arthritis, systemic lupus erythematosus, Sjögren syndrome, vitiligo, Addison disease, pernicious anemia). In TSH tumors, family history is usually absent. Most cases of generalized thyroid hormone resistance are familial with autosomal dominant inheritance (i.e., 50% of the family members have the abnormality).

18. Which hormones are elevated in the serum of patients with gonadotroph adenomas?

Serum FSH is increased much more often than LH. An increase in alpha subunit level is not specific for gonadotrophs because it may also derive from thyrotrophs. Furthermore, determination of alpha subunit/LH (or alpha subunit/FSH) molar ratio has not been clinically useful.

KEY POINTS 1: GLYCOPROTEIN-SECRETING PITUITARY TUMORS

1. Glycoprotein-secreting pituitary tumors include gonadotropinomas (luteinizing hormone– or follicle-stimulating hormone–secreting) and thyrotropinomas (TSH-omas).
2. Hyperthyroid patients with detectable serum TSH should always be evaluated for inappropriate TSH secretion (either a TSH tumor or thyroid hormone resistance).
3. TSH tumors are managed by transsphenoidal surgery and possibly a somatostatin analog.
4. Gonadotropinomas may manifest as neurologic symptoms due to mass effect and may require pituitary surgery.
5. Hypothyroidism can produce thyrotroph hyperplasia and pituitary pseudotumors.

19. List the presenting symptoms of patients with gonadotropinomas.

Mass effect (common)	Large tumors with extrasellar growth
	Visual impairment/diplopia
	Headaches
	Apoplexy
	Hypopituitarism
Endocrine excesses (uncommon)	Ovarian hyperstimulation
	Testicular enlargement
	Precocious puberty

20. In a patient in whom gonadotropin values are elevated, how can one distinguish a gonadotroph adenoma from primary hypogonadism?

This distinction can be difficult, especially in women, because their levels of LH and FSH increase after menopause. This fact may be why most gonadotroph adenomas are recognized in men. Historically, men with such tumors experienced normal puberty and may have fathered children.

On examination, testicular size may be normal. In contrast, men with hypogonadism may have had abnormal pubertal development or a history of testicular injury; the testes are small.

21. What laboratory tests are helpful?

In primary hypogonadism, both FSH and LH are increased, whereas FSH is elevated, but LH is usually normal in patients with gonadotropinomas. When LH is high in men with gonadotropinomas, testosterone also is high rather than low, as in hypogonadism. For unclear reasons, about one third of patients with such a tumor have an anomalous rise in serum FSH or LHβ when given a TRH injection. MRI of the pituitary reveals a large tumor. Occasionally, a patient with long-standing hypogonadism may have some pituitary enlargement.

22. How are gonadotropinomas treated?

Pituitary surgery is the treatment of choice. Although cure is often impossible, substantial reductions in tumor size and hormone secretion are common. Reduced hormone secretion provides a convenient marker for monitoring tumor recurrence; an abrupt increase in FSH or alpha subunit should prompt repeat imaging. Radiation therapy is often given after surgery to prevent tumor recurrence.

23. Is medical therapy effective?

Agonist analogs of gonadotropin-releasing hormone (GnRH) reduce secretion from normal gonadotrophs. Unfortunately, they often have the opposite effect on gonadotropinomas. An antagonist analog (Nal-Glu-GnRH) reduced serum FSH in a small group of men with gonadotropinomas but did not reduce tumor size. Bromocriptine has reduced hormone levels in an occasional patient, whereas octreotide has lowered alpha subunit and improved visual fields in certain patients. Cabergoline can reduce estradiol levels and ovarian size in women with ovarian hyperstimulation.

24. Are pituitary tumors malignant?

Carcinomas are rare but occasionally have been reported for adrenocorticotropic hormone (ACTH), prolactin (PRL), GH, and TSH.

25. What causes pituitary tumors?

- Oncogene overexpression (e.g., pituitary tumor-transforming gene)
- Silencing of tumor suppressor genes (e.g., hypermethylation)
- Corticotropin-releasing factor (CRF_2) expression

WEBSITE

Thyroid Disease Manager: http://www.thyroidmanager.org.

BIBLIOGRAPHY

Al-Gahtany M, Horvath E, Kovacs K: Pituitary hyperplasia, *Hormones* 2:149–158, 2003.

Beck-Peccoz P, Brucker-Davis F, Persani L, et al: Thyrotropin-secreting pituitary tumors, *Endocr Rev* 17:610–638, 1996.

Beck-Peccoz P, Persani L, Mannavola D, et al: TSH-secreting adenomas, *Best Practice and Research Clinical Endocrinology and Metabolism* 23:597–606, 2009.

Bogazzi F, Manetti L, Tomisti L, et al: Thyroid color flow Doppler sonography: an adjunctive tool for differentiating patients with inappropriate thyrotropin (TSH) secretion due to TSH-secreting pituitary adenoma or resistance to thyroid hormone, *Thyroid* 16(10):989–995, 2006.

Brown RL, Muzzafar T, Wollman R, et al: A pituitary carcinoma secreting TSH and prolactin: a non-secreting adenoma gone awry, *Eur J Endocrinol* 154:639–643, 2006.

Buchfelder M: Thyrotroph pituitary adenomas, *Endocrinologist* 12:117–125, 2002.

Caron P, Arlot S, Bauters C, et al: Efficacy of the long-acting octreotide formulation (octreotide-LAR) in patients with thyrotropin-secreting pituitary adenomas, *J Clin Endocrinol Metab* 86:2849–2853, 2001.

Chaidarun SS, Klibanski A: Gonadotropinomas, *Semin Reprod Med* 20:339–348, 2002.

Clarke M, Erickson D, Castro R, et al: Thyroid-stimulating hormone pituitary adenoma, *J Neurosurg* 109:17–22, 2008.
Cooper O, Geller J, Melmed S: Ovarian hyperstimulation syndrome caused by an FSH-secreting pituitary adenoma, *Nat Clin Pract Endocrinol Metab* 4(4):234–238, 2008.
Daousi C, Foy PM, MacFarlane IA: Ablative thyroid treatment for thyrotoxicosis due to thyrotropin-producing pituitary tumours, *J Neurol Neurosurg Psychiatry* 78:93–95, 2007.
Dhillon KS, Cohan P, Kelly DF, et al: Treatment of hyperthyroidism associated with thyrotropin-secreting pituitary adenomas with iopanoic acid, *J Clin Endocrinol Metab* 89:708–711, 2004.
Elhadd T, Ghosh S, Leng Teoh W, et al: A patient with thyrotropinoma cosecreting growth hormone and follicle-stimulating hormone with low alpha-glycoprotein: a new subentity, *Thyroid* 19(8):899–903, 2009.
Knoepfelmacher M, Danilovic DLS, Rosa Nasser RHR, et al: Effectiveness of treating ovarian hyperstimulation syndrome with cabergoline in two patients with gonadotropin-producing pituitary adenomas, *Fertil Steril* 86(719):715–718, 2006.
Lee M, Wang C: Concomitant Graves hyperthyroidism with thyrotrophin-secreting pituitary adenoma, *South Med J* 103: 347–349, 2010.
Mannavola D, Persani L, Vannucchi G, et al: Different responses to chronic somatostatin analogues in patients with central hyperthyroidism, *Clin Endocrinol* 62:176–181, 2005.
McGrath GA, Goncalves RJ, Udupa JK, et al: New technique for quantitation of pituitary adenoma size: use in evaluating treatment of gonadotroph adenomas with a gonadotropin-releasing hormone antagonist, *J Clin Endocrinol Metab* 76:1363–1368, 1993.
Nguyen H, Galitz M, Mai V, et al: Management of coexisting thyrotropin/growth-hormone-secreting pituitary adenoma and papillary thyroid carcinoma: a therapeutic challenge, *Thyroid* 20(1):99–103, 2009.
Page K, Roehmholdt B, Jablonski M, et al: Development of thyroid storm after surgical resection of a thyrotropin-secreting pituitary adenoma, *Endocr Pract* 14:732–737, 2008.
Refetoff S, Weiss RE, Usala SJ: The syndromes of resistance to thyroid hormone, *Endocr Rev* 14:348–399, 1993.
Reubi JC, Waser B, Vale W, et al: Expression of CRF1 and CRF2 receptors in human cancers, *J Clin Endocrinol Metab* 88:3312–3320, 2003.
Scheithauer BW, Kovacs K, Nose V, et al: Multiple endocrine neoplasia type 1-associated thyrotropin-producing pituitary carcinoma: report of a probable de novo example, *Human Pathology* 40:270–278, 2009.
Shorts-Cary L, Xu M, Ertel J, et al: Bone morphogenetic protein and retinoic acid-inducible neural specific protein-3 is expressed in gonadotrope cell pituitary adenomas and induces proliferation, migration, and invasion, *Endocrinology* 148:967–975, 2007.
Simard MF: Pituitary tumor endocrinopathies and their endocrine evaluation, *Neurosurg Clin N Am* 14:41–54, 2003.
Smallridge RC: Thyrotropin- and gonadotropin-producing tumors. In: Korenman SG, Molitch ME, editors: *Atlas of clinical endocrinology: neuroendocrinology and pituitary disease*, Philadelphia, 2000, Blackwell Science, pp 95–113.
Smallridge RC: Thyrotropin-secreting pituitary tumors: clinical presentation, investigation, and management, *Curr Opin Endocrinol Diabetes* 8:253–258, 2001.
Smallridge RC, Czervionke LF, Fellows DW, et al: Corticotropin- and thyrotropin-secreting pituitary microadenomas: detection by dynamic magnetic resonance imaging, *Mayo Clin Proc* 75:521–528, 2000.
Snyder PJ: Extensive personal experience: gonadotroph adenomas, *J Clin Endocrinol Metab* 80:1059–1061, 1995.
Socin HV, Chanson P, Delemer B, et al: The changing spectrum of TSH-secreting pituitary adenomas: diagnosis and management in 43 patients, *Eur J Endocrinol* 148:433–442, 2003.
Young Jr WF, Scheithauer BW, Kovacs KT, et al: Gonadotroph adenoma of the pituitary gland: a clinicopathologic analysis of 100 cases, *Mayo Clin Proc* 71:649–656, 1996.

CUSHING SYNDROME

Mary H. Samuels

1. Describe the normal function of cortisol in healthy people.

Cortisol and other glucocorticoids have many effects as physiologic regulators. They increase glucose production and protein breakdown, inhibit protein synthesis, stimulate lipolysis, and affect immunologic and inflammatory responses. Glucocorticoids are important for the maintenance of blood pressure and form an essential part of the body's response to stress.

2. How are cortisol levels normally regulated?

Adrenal production of cortisol is stimulated by the pituitary hormone adrenocorticotropin (adrenocorticotropic hormone [ACTH]). ACTH production is stimulated by the hypothalamic hormones corticotropin-releasing hormone (CRH) and vasopressin (antidiuretic hormone [ADH]). Cortisol feeds back to the pituitary and hypothalamus to suppress levels of ACTH and CRH. Under nonstress conditions, cortisol is secreted in a pronounced circadian rhythm, with higher levels early in the morning and lower levels late in the evening. Under stressful conditions, secretion of CRH, ACTH, and cortisol increases, and the circadian variation is blunted. Because of the wide variation in cortisol levels over 24 hours and appropriate elevations during stressful conditions, it may be difficult to distinguish normal secretion from abnormal secretion. For this reason, the evaluation of a patient with suspected Cushing's disease is often complex and confusing.

3. What are the clinical symptoms of excessive levels of cortisol?

Prolonged and inappropriately high cortisol levels lead to Cushing syndrome, characterized by:

- Obesity, especially central (truncal) obesity, with wasting of the extremities, moon facies, supraclavicular fat pads, and buffalo hump
- Thinning of the skin, with facial plethora, easy bruising, and violaceous striae
- Muscular weakness, especially proximal muscle weakness, and atrophy
- Hypertension, atherosclerosis, congestive heart failure, and edema
- Gonadal dysfunction and menstrual irregularities
- Psychologic disturbances (e.g., depression, emotional lability, irritability, sleep disturbances)
- Osteoporosis and fractures
- Increased rate of infections and poor wound healing

4. All of my clinic patients look like they have Cushing syndrome. Are some clinical findings more specific for Cushing syndrome than others?

Some manifestations of Cushing syndrome are common but nonspecific, whereas others are less common but quite specific. These two groups of clinical findings are listed in Table 23-1.

5. A patient presents with a history of obesity, hypertension, irregular menses, and depression. Does she have excessive production of cortisol?

Excessive cortisol is highly unlikely. Although the listed findings are consistent with glucocorticoid excess, they are nonspecific; most patients with such findings do not have Cushing syndrome (see Table 23-1). True Cushing syndrome is uncommon, with an incidence of 2 to 3 cases per million people per year, although it may be higher in patients with hypertension, diabetes, osteoporosis, or incidental adrenal masses.

TABLE 23-1. SYMPTOMS AND SIGNS OF CUSHING SYNDROME

More specific, less common	Easy bruising, thin skin (in young patient)
	Facial plethora
	Violaceous striae
	Proximal muscle weakness
	Hypokalemia
	Osteoporosis (in young patient)
More common, less specific	Hypertension
	Obesity/weight gain
	Abnormal glucose tolerance or diabetes mellitus
	Depression, irritability
	Peripheral edema
	Acne, hirsutism
	Decreased libido, menstrual irregularities

6. The patient also complains of excessive hair growth and has increased terminal hair on the chin, along the upper lip, and on the upper back. Is this finding relevant?

Hirsutism is a common, nonspecific finding in many female patients. However, it is also consistent with Cushing syndrome. If it is due to Cushing syndrome, hirsutism is caused by excessive production of adrenal androgens under ACTH stimulation. Thus hirsutism in a patient with Cushing syndrome is a clue that the disorder is due to excessive production of ACTH. (The only other condition associated with excessive production of glucocorticoids and androgens is adrenal cancer, which is usually obvious on presentation.)

7. The patient also has increased pigmentation of the areolae, palmar creases, and an old surgical scar. Are these findings relevant?

Hyperpigmentation is a sign of elevated production of ACTH and related peptides by the pituitary gland. It is uncommon (but possible) in Cushing syndrome due to benign pituitary tumors, because ACTH levels do not usually rise high enough to cause hyperpigmentation. It is more common in the ectopic ACTH syndrome, because ectopic tumors produce more ACTH and other peptides. The combination of Cushing syndrome and hyperpigmentation may be bad news.

8. What is the cause of death in patients with Cushing syndrome?

Patients with inadequately treated Cushing syndrome have a markedly increased mortality rate (four-to fivefold above the normal rate), usually from cardiovascular disease or infections. Hypertension, impaired glucose tolerance, dyslipidemia, and visceral obesity all contribute to the excess risk for cardiovascular mortality. This excess mortality normalizes with adequate therapy.

9. What causes Cushing syndrome?

Cushing syndrome is a nonspecific name for any source of excessive glucocorticoids. There are four main causes, which are further detailed in Table 23-2:

- Exogenous glucocorticoids (ACTH-independent)
- Pituitary Cushing syndrome (ACTH-dependent)
- Ectopic ACTH production (ACTH-dependent)
- Adrenal tumors (ACTH-independent)

10. Of the various types of Cushing syndrome, which is the most common?

Overall, exogenous Cushing syndrome is most common. It rarely presents a diagnostic dilemma, because the physician usually knows that the patient is receiving glucocorticoids. Of the endogenous causes of

TABLE 23-2. CAUSES OF CUSHING SYNDROME AND THEIR RELATIVE FREQUENCY

ACTH-dependent (80%)	Pituitary (85%):
	Corticotroph adenoma
	Corticotroph hyperplasia (rare)
	Ectopic ACTH syndrome (15%):
	Oat-cell carcinoma (50%)
	Foregut tumors (35%)
	Bronchial carcinoid
	Thymic carcinoid
	Medullary thyroid carcinoma
	Islet-cell tumors
	Pheochromocytoma
	Other tumors (10%)
	Ectopic CRH (>1%)
ACTH-independent (20%)	Adrenal tumors:
	Adrenal adenoma (>50%)
	Adrenal adenoma (>50%)
	Micronodular hyperplasia (rare)
	Macronodular hyperplasia (rare)
	Exogenous glucocorticoids (common):
	Therapeutic (common)
	Factitious (rare)

ACTH, adrenocorticotropin; CRH, corticotropin-releasing hormone.

Cushing syndrome, pituitary Cushing's disease accounts for about 70% of cases. Ectopic ACTH secretion and adrenal tumors cause approximately 15% of cases each (see Table 23-2 for frequencies).

11. Do age and gender matter in the differential diagnosis of Cushing syndrome?

Of patients with Cushing's disease (pituitary tumors), 80% are women, whereas the ectopic ACTH syndrome is more common in men. Therefore, in a male patient with Cushing syndrome, the risk of an extrapituitary tumor is higher. The age range in Cushing's disease is most frequently 20 to 40 years, whereas ectopic ACTH syndrome has a peak incidence at 40 to 60 years. Therefore, the risk of an extrapituitary tumor in an older patient with Cushing syndrome is increased. Children with Cushing syndrome have a higher risk of malignant adrenal tumors.

12. The patient with obesity, hypertension, irregular menses, depression, and hirsutism looks like she may have Cushing syndrome. What should I do?

There are three widely used screening tests for Cushing syndrome that have comparable sensitivities and specificities, and each can be used in the initial evaluation of a patient with suspected Cushing syndrome (Fig. 23-1); they are as follows:

1. The overnight low-dose dexamethasone suppression test. The patient takes 1 mg of dexamethasone at 11 PM, and the serum cortisol level is measured at 8:00 the next morning. In healthy unstressed subjects, dexamethasone (a potent glucocorticoid that does not cross-react with the cortisol assay) suppresses production of CRH, ACTH, and cortisol. In contrast, patients with endogenous Cushing syndrome should not suppress cortisol production (serum cortisol remains > 1.8 μg/dL) when given 1 mg of dexamethasone.
2. Measurement of cortisol in saliva samples collected on two separate evenings between 11 PM and midnight. Salivary cortisol levels are low in nonstressed subjects late at night but are high in patients with Cushing syndrome because of loss of the normal diurnal rhythm in cortisol production.

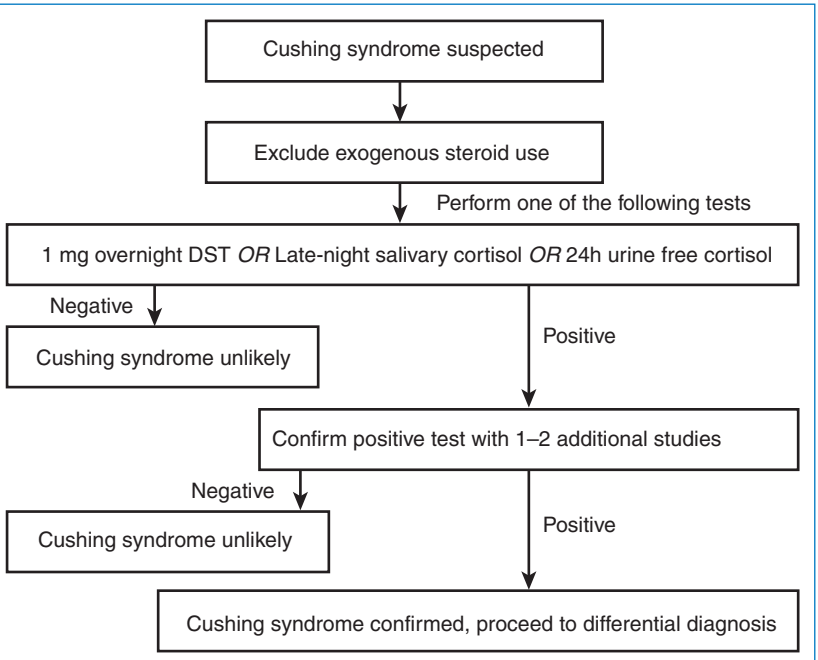


Figure 23-1. Diagnosis of Cushing syndrome.

3. Urine free cortisol (UFC) levels, measured in a 24-hour collection of urine. UFC is elevated in most patients with Cushing syndrome, but only a value fourfold above the normal range is diagnostic of Cushing syndrome, as more mild elevations can be seen in stress or illness.

13. The patient underwent a low-dose dexamethasone suppression test. The morning cortisol level is 7 μg/dL. Does she have Cushing syndrome?

Probably not. Acute or chronic illnesses, depression, and alcohol abuse activate the hypothalamic-pituitary-adrenal axis because of stress and make the patient resistant to dexamethasone suppression. In fact, because Cushing syndrome is so rare, a nonsuppressed cortisol level after dexamethasone is more likely to be a false-positive result, rather than truly indicating the presence of Cushing syndrome. Similar limitations exist for the other two screening tests. Further evaluation is best conducted by an endocrinologist and may include performing the alternate screening tests to see if their results are concordant, as well as additional biochemical tests (see Fig. 23-1).

14. Further biochemical testing confirms that the patient has Cushing syndrome. What should I do next?

After you have made the biochemical diagnosis of Cushing syndrome, the next step is to determine whether she has ACTH-dependent or ACTH-independent disease. This distinction is made by measuring plasma levels of ACTH. Measurements should be repeated a number of times because secretion of ACTH is variable.

15. The patient's ACTH level is "normal." Was the original suspicion of Cushing syndrome incorrect?

No. A normal or slightly elevated ACTH value is the usual finding in ACTH-secreting pituitary adenomas. More marked elevations of ACTH suggest ectopic secretion of ACTH, although small carcinoid tumors

also have normal or mildly elevated ACTH values. Suppressed ACTH levels (< 10 pg/mL), in contrast, suggest an adrenal tumor. If ACTH levels are indeterminate, measurements of ACTH during stimulation with CRH can be helpful.

16. After the diagnosis of ACTH-dependent Cushing syndrome, what is the next step?

Because the most common site of excessive secretion of ACTH is a pituitary tumor, radiologic imaging of the pituitary gland is the next step. The best study is high-resolution magnetic resonance imaging (MRI) of the pituitary gland.

17. The pituitary MRI findings in the patient with ACTH-dependent Cushing syndrome are normal. Is the next step a search for a carcinoid tumor, under the assumption that the pituitary is not the source of excessive ACTH?

Not so fast. At least half of pituitary MRI results are negative in proven pituitary-dependent Cushing syndrome because most corticotroph adenomas are tiny and may not be visible on MRI.

18. The pituitary MRI shows a 3-mm hypodense area in the lateral aspect of the pituitary gland. Is it time to call the neurosurgeon?

Again, not so fast. This finding is nonspecific and occurs in up to 10% of healthy people. It may or may not be related to Cushing syndrome. The odds are good that the patient has a pituitary tumor, but the MRI findings do not prove this. The MRI is diagnostic only if it shows a large tumor.

19. So what is the next step?

One option is to proceed directly to pituitary surgery because a patient with abnormal MRI findings has a 90% chance of having an ACTH-secreting pituitary tumor. To achieve more diagnostic certainty, one has to perform bilateral simultaneous inferior petrosal sinus sampling (IPSS) for ACTH levels. Catheters are advanced through the femoral veins into the inferior petrosal sinuses, which drain the pituitary gland, and blood samples are obtained for ACTH levels. If ACTH levels in the petrosal sinuses are significantly higher than those in peripheral samples, the pituitary gland is the source of excessive ACTH. If there is no gradient between petrosal sinus and peripheral levels of ACTH, the patient probably has a carcinoid tumor somewhere. The accuracy of the test is further increased if ACTH responses to injection of exogenous CRH are measured. Bilateral IPSS should be performed by experienced radiologists at referral centers.

20. IPSS shows no gradient in ACTH levels. Now what?

Start the search for a carcinoid tumor. Because the most likely location is the lung, computed tomography (CT) of the lungs should be ordered. If the results are negative, CT of the abdomen should be ordered because carcinoids also occur in the pancreas, intestinal tract, and adrenal glands.

21. IPSS shows a marked central-to-peripheral gradient in ACTH levels. Now what?

Transsphenoidal surgery (TSS) should be scheduled with an experienced neurosurgeon who is comfortable examining the pituitary for small adenomas. ACTH levels from the right and left petrosal sinuses obtained during the sampling study may tell the neurosurgeon in which side of the pituitary gland the tumor is likely to be found, but this information is not 100% accurate.

22. What if surgery is unsuccessful?

If TSS does not cure a patient with Cushing's disease, alternative therapies must be tried because patients with inadequately treated hypercortisolism have increased morbidity and mortality rates. Of the various options after failed surgery, none is ideal. Patients may require repeat pituitary surgery, radiation therapy, medical therapy to block cortisol secretion, bilateral adrenalectomy, or a combination of these. Medical therapy may include ketoconazole, metyrapone, mitotane, or etomidate, all of which directly suppress adrenal cortisol production. Also available are centrally acting agents that suppress ACTH secretion, and mifepristone, which blocks glucocorticoid action at its receptor. These decisions should be made by an experienced endocrinologist.

23. Why not just take out the patient's adrenal glands?

Bilateral adrenalectomy can be safely performed via a laparoscopic approach, with low morbidity in experienced hands. However, this procedure leads to lifelong adrenal insufficiency and dependence on exogenous glucocorticoids and mineralocorticoids. The other main drawback is the development of Nelson syndrome in up to 30% of patients after adrenalectomy. Nelson syndrome is the appearance, sometimes years after adrenalectomy, of an aggressive corticotroph pituitary tumor.

24. What are the correct diagnostic and treatment options for patients with ACTH-independent (adrenal) Cushing syndrome?

Such patients usually have either an adrenal adenoma or carcinoma, so an adrenal CT scan should be ordered. A mass is usually present, and surgery should be planned. If the mass is obviously cancer, surgery may still help in debulking the tumor and improving the metabolic consequences of hypercortisolemia. If there are multiple adrenal nodules, the patient may have a rare form of Cushing syndrome and should be evaluated by an endocrinologist. As a caveat, there is also a high prevalence of incidental, nonfunctioning adrenal adenomas in the general population (up to 5%), and the CT findings may not be conclusive.

25. What happens to the hypothalamic-pituitary-adrenal axis after a patient undergoes successful removal of an ACTH-secreting pituitary adenoma or a cortisol-secreting adrenal adenoma?

The axis is suppressed, and clinical adrenal insufficiency develops, unless the patient is given gradually decreasing doses of exogenous glucocorticoids for a time after surgery.

26. What would be the most likely diagnosis if the original patient had all the signs of Cushing syndrome but *low* urinary and serum levels of cortisol?

The most likely scenario would be that the patient is surreptitiously or accidentally ingesting a glucocorticoid that gives all the findings of glucocorticoid excess but is not measured in the cortisol assay. The patient and family members should be questioned about possible access to medications, and special assays can measure the various synthetic glucocorticoids.

27. Do tumors ever cause Cushing syndrome by making excessive CRH?

Yes. Occasionally patients who undergo TSS for a presumed corticotroph adenoma have corticotroph hyperplasia instead. At least some of these cases are secondary to ectopic production of CRH from a carcinoid tumor in the lung, abdomen, or other location. Therefore serum levels of CRH should be measured in patients with Cushing syndrome and corticotroph hyperplasia. If the levels are elevated, a careful search should be performed for possible ectopic sources of CRH.

KEY POINTS 1: CUSHING SYNDROME

1. The clinical manifestations of Cushing syndrome can be subtle or nonspecific.
2. Most patients who look like they might have Cushing syndrome do not.
3. Screening biochemical tests for Cushing syndrome can be misleading, and repeated testing or more extensive confirmatory testing is often necessary.
4. Most patients with Cushing syndrome have a small pituitary tumor producing adrenocorticotropin.
5. Patients with pituitary tumors causing Cushing syndrome should undergo pituitary surgery by an experienced neurosurgeon because none of the other treatment options is ideal.

BIBLIOGRAPHY

Boscaro M, Arnaldi G: Approach to the patient with possible Cushing syndrome, *J Clin Endocrinol Metab* 94:3121–3131, 2009.
Carroll TB, Findling JW: The diagnosis of Cushing syndrome, *Rev Endocr Metab Disord* 11:147–153, 2010.
Nieman LK, Biller BMK, Findling JW, et al: The diagnosis of Cushing syndrome: an Endocrine Society clinical practice guideline, *J Clin Endocrinol Metab* 93:1526–1540, 2008.
Sharma ST, Neiman LK: Cushing syndrome: all variants, detection, and treatment, *Endocrinol Metab Clin North Am* 40:379–391, 2011.
Tritos NA: Advances in medical therapies for Cushing syndrome, *Discover Med* 13:171–179, 2012.

CHAPTER 24

WATER METABOLISM

Leonard R. Sanders

1. What is the water composition of the human body?

Water composition of the body depends on age, sex, muscle mass, body habitus, and fat content. Various body tissues have the following water percentages: lungs, heart, and kidneys (80%); skeletal muscle and brain (75%); skin and liver (70%); bone (20%); and adipose tissue (10%). Clearly, people with more muscle than fat have more water. Generally, thin people have less fat and more water. Men are 60% water and women 50% water by weight. Older people have more fat and less muscle. The average man and woman older than 60 years are made up of 50% and 45% water, respectively (see Table 24-1). Most discussions of total body water (TBW) consider a man who is 60% water, weighs 70 kg, and is 69 inches (175 cm) tall.

2. Where is water located within the body?

TBW comprises water located inside the cells (intracellular fluid [ICF]) and outside the cells (extracellular fluid [ECF]). TBW is 60% of body weight—40% ICF (⅔) and 20% ECF (⅓). Of the ECF, approximately ¾ is interstitial fluid (ISF) and ¼ is intravascular fluid (IVF). IVF is a major component of the total blood volume necessary to maintain effective vascular pressure. ISF is 15% of body weight, and IVF is 5% of body weight. In a 70-kg man, TBW = 42 L, ICF water = 28 L, and ECF water = 14 L. ISF is 10.5 L and IVF (plasma) is 3.5 L. Tight regulation of the relatively small volume of IVF maintains blood pressure and avoids symptomatic hypovolemia and congestive heart failure. Normal plasma is 93% water and 7% proteins and lipids. The arterial volume is only 15% of IVF. Although arterial volume is small, its integrity is most important for maintaining the effective circulation and preventing abnormalities of water balance (Fig. 24-1).

3. What is transcellular water (TCW)?

TCW is water formed by cellular transport activities and is located in various ducts and spaces throughout the body. This water includes cerebrospinal fluid (CSF) and aqueous humor; secretions in the sweat, salivary, and lacrimal glands; secretions in pancreas, liver, biliary, gastrointestinal, and respiratory tracts; and peritoneal, pleural, and synovial fluids.

4. Explain the significance of TCW.

TCW carries secretions to specific sites for enzymatic and lubricant activity and is normally quite small—1.5% of body weight. In disease states, excess or deficiency of TCW can cause dysfunction. Marked excess TCW formation—third spacing—may decrease effective circulating volume (ECV), stimulate antidiuretic hormone (ADH) and aldosterone release, increase retention of salt and water, and cause edema and hyponatremia.

TABLE 24-1. WATER AS A PERCENT OF BODY WEIGHT

BODY HABITUS	PERCENTAGE BODY WEIGHT		
	Infant	*Man*	*Woman*
Thin	80	65	55
Medium	70	60	50
Obese	65	55	45

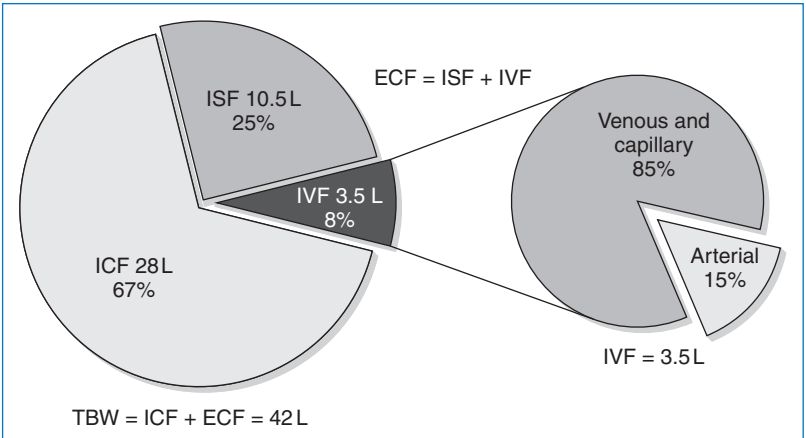


Figure 24-1. *Left,* distribution of body water; *right,* total blood volume. ECF, extracellular fluid; ICF, intracellular fluid; ISF, interstitial fluid; IVF, intravascular fluid; TBW, total body water.

5. What controls distribution of body water?

With few exceptions (e.g., ascending loop of Henle [LOH] and distal nephron), water moves freely across cell membranes, depending on tonicity. Because tonicity depends on impermeable solutes, such as sodium (Na), disorders of water metabolism are reflected by changes in solute concentrations. In addition to changes in water distribution, changes in TBW, blood volume, and ECV affect overall water balance. A thorough understanding of disorders of water metabolism requires a clear understanding of changes in plasma Na concentration (P_{Na}), plasma osmolality (P_{osm}), and ECV.

KEY POINTS 1: WATER METABOLISM

1. Changes in body water or distribution are usually reflected by changes in plasma sodium concentration (P_{Na}) and may occur in states of low, normal, or high total body sodium. Low P_{Na} reflects high TBW, and high P_{Na} reflects low total body water (TBW).
2. Water always moves across cell membranes from lower to higher osmolality. This movement is determined by the concentration of effective osmotic solute in the intracellular or extracellular fluid and is responsible for the neurologic symptoms and signs associated with changes in P_{Na}.
3. Hyponatremia may occur with low, normal, or high osmolality, whereas hypernatremia is always associated with hyperosmolality and hypertonicity.
4. Water content of the body is a balance of input and output.
5. Water balance is controlled by thirst, access to water, solute intake, antidiuretic hormone (ADH), cortisol, aldosterone, natriuretic peptides, baroreceptor sensors, ADH receptors, renal water channels called aquaporins, level of kidney function, and drugs.

6. What is effective circulating volume (ECV)?

ECV is the arterial volume required to maintain normal baroreceptor pressure that is appropriate for a given level of vascular resistance. ECV is also called effective arterial blood volume (EABV). By inducing changes in baroreceptor tone, alterations in ECV have a major impact on water balance. Low ECV causes renal salt and water retention, whereas high ECV causes renal salt and water loss. Depending

on the patient's water intake, these changes may produce significant hyponatremia. Maintaining normal ECV preserves circulatory homeostasis.

7. How do baroreceptors affect ECV?

Baroreceptors are the major sensors of changes in ECV (Fig. 24-2). However, their main role is to maintain normal pressure (not volume) at the level of the baroreceptor sensors located primarily in the carotid sinus, aortic arch, atria, pulmonary veins, and afferent renal arterioles. These anatomic locations are important because perfusion to these areas affects the three main effectors of circulatory homeostasis and ECV: brain, heart, and kidneys.

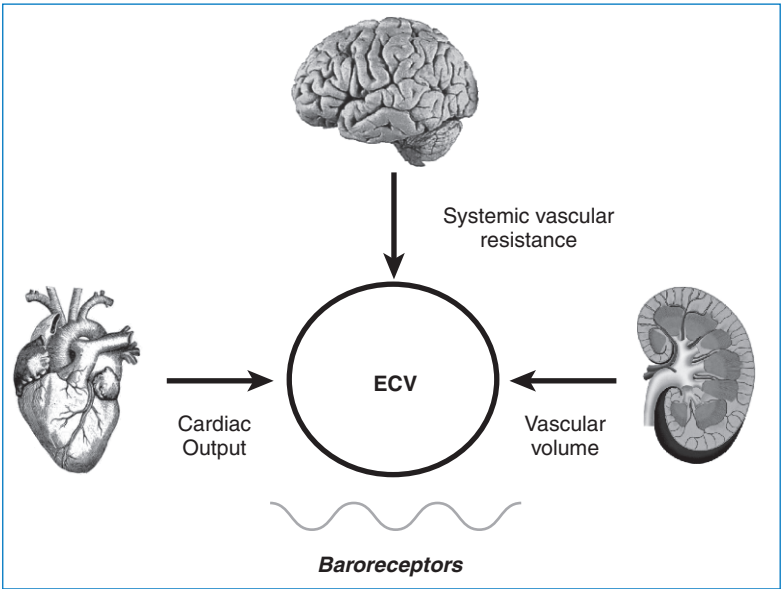


Figure 24-2. Primary components of the effective circulation (ECV = effective circulating volume). By stimulating changes in the brain, the heart, and the kidney, baroreceptors have a major impact on vascular pressure and volume and overall water balance.

8. How does vascular pressure, as sensed by the baroreceptors, relate to ECV and hyponatremia?

Baroreceptors normally maintain tonic inhibition of vasoconstrictor nerves and natriuretic hormone release but tonic stimulation of vagal cardiac nerves. A drop in ECV decreases effective vascular pressure (EVP), baroreceptor tone, tonic inhibition, and tonic stimulation. This causes vasoconstriction; increases heart rate; and increases renin, aldosterone, angiotensin II, and ADH secretion. It decreases atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) from brain and ventricles, and urodilatin (kidney). These alterations enhance renal Na and water retention. If the patient receives unlimited water, these changes may lead to hyponatremia. Hyponatremia cannot develop unless the patient retains more water than is excreted. Decreased ECV/EVP predisposes to water retention, but the patient must receive free water for hyponatremia to develop. The venous system, through atrial stretch receptors, has similar effects but responds to changes in ECV earlier than the arterial system.

9. Define osmolality and tonicity, and outline their effects on water movement.

Osmolality is the concentration of a substance in 1 L of water divided by its molecular weight. Tonicity is effective osmolality—the osmotic pressure caused by dissolved particles restricted to one side of the cell

membrane. Because Na and glucose are partially restricted to the ECF, they are effective osmols and account for normal tonicity. Mannitol, sorbitol, glycerol, and glycine are also effective osmols. Urea freely crosses cell membranes and distributes evenly in TBW, and therefore it changes osmolality but not tonicity. Thus, except during early and rapid solute and water changes, urea is an ineffective osmol. Ethanol and methanol are other ineffective osmols. Water always moves across cell membranes from lower osmolality to higher osmolality until osmolality on the two sides is equal. At equilibrium, the following is always true:

$$\text{ICF osmolality} = \text{ECF osmolality} = P_{osm}$$

10. What formulas are useful in evaluating osmolality and tonicity?

$$\text{ECF osmolality} = 2\,P_{Na} + \frac{\text{glucose}}{18} + \frac{\text{blood urea nitrogen (BUN)}}{2.8}$$

$$\text{Normal osmolality} = 2(140) + \frac{90}{18} + \frac{14}{2.8} = 280 + 5 + 5 = 290\ \text{mOsm/kg}$$

$$\text{ECF tonicity (effective osmolality)} = 2\,P_{Na} + \frac{\text{glucose}}{18}$$

$$\text{Normal tonicity} = 2(140) + \frac{90}{18} = 280 + 5 = 285\ \text{mOsm/kg}$$

The normal range for P_{osm}, 275 to 295 mOsm/kg, varies with the normal ranges for plasma Na, urea, and glucose. Correction factors for other effective solutes (osmols) are mannitol/18, sorbitol/18, and glycerol/9. Correction factors for other ineffective solutes (osmols) are ethanol/4.6 and methanol/3.2.

11. How does P_{Na} relate to TBW, osmolality, and tonicity?

The following formulas are useful in understanding the relationship of P_{Na}, plasma potassium (P_K), total body sodium and potassium [$Na^+ + K^+$], and TBW. [$Na^+ + K^+$] estimates total body solute:

1. $P_{Na} \cong \dfrac{\text{total body } [Na^+ + K^+]}{TBW}$

2. $TBW \cong \dfrac{[Na^+ + K^+]}{P_{Na}}$

3. $P_{Na} \cong P_{osm} \cong [\text{total body osmolality}] \cong [\text{total body solutes}] \cong \dfrac{1}{TBW}$

Thus P_{Na} is proportional to [$Na^+ + K^+$] and inversely proportional to TBW. An increase or decrease in total plasma Na particles can proportionately change the P_{Na}. However, in clinical medicine, changes in P_{Na} usually reflect changes in plasma water. When P_{Na} is high, plasma water is low. When P_{Na} is low, plasma water is high. Low P_{Na} may occur with low, normal, or high osmolality, whereas high P_{Na} is always associated with hyperosmolality and hypertonicity.

12. How does P_K relate to P_{Na} and TBW?

Although 98% of K^+ is intracellular, a K^+ infusion increases P_{Na}. This occurs as follows. In hypokalemia, infused K^+ enters cells. To preserve electroneutrality, Na^+ leaves or chloride (Cl^-) enters cells. ECF water follows K^+ and Cl^- into cells because of increased ICF osmolality. Both mechanisms increase P_{Na}. Hypokalemic patients infused with equal amounts of KCl or NaCl have equal increases in P_{Na}. Thus addition of KCl to isotonic saline makes hypertonic saline, and infusion of saline with KCl may correct hyponatremia too rapidly (see questions 36 and 44).

13. Describe the input and output of water.

TBW is a balance of input (including endogenous production) and output. In an average adult, input approximates 1600 mL (liquids), 700 mL (foods), and 200 mL (metabolic oxidation of carbohydrate

and fat) for a total of 2500 mL/day. Average water losses are 1500 mL (kidneys), 500 mL (skin [400 mL evaporation and 100 mL perspiration]), 300 mL (lung—respiration), and 200 mL from the gastrointestinal tract (stool) for a total of 2500 mL/day. Large losses of water (increased output) occur with excessive sweating, respiration (exercise), burns, diarrhea, vomiting, and diuresis. Decreased water input occurs when defects in thirst and altered mental or physical function (especially in the elderly) prevent access to water.

14. What are the normal limits of urine output?

Water intake and osmotic products of metabolism determine the usual daily output of urine. On a normal diet, a normal adult must excrete 800 to 1000 mOsm of solute per day. The range of normal renal concentrating function is 50 to 1200 mOsm/kg. On this basis, the obligate water excretion varies from 0.8 to 20 L/day. The calculations are as follows:

$$1000 \text{ mOsm/day} \div 1200 \text{ mOsm/L} = 0.8 \text{ L/day at maximal concentration}$$

$$1000 \text{ mOsm/day} \div 50 \text{ mOsm/L} = 20 \text{ L/day at maximal dilution}$$

Note that higher solute loads (e.g., dietary) require more water excretion. For example, body builders consuming high-protein and high-carbohydrate diets with 1400 mOsm solute/day require a urine output of (1400/1200) to (1400/50) or 1.2 to 28 L/day. Alternatively, a low solute intake (starvation) with high water intake predisposes to water retention and water intoxication. This combination exists in binge beer drinkers, in whom the solute load may be only 300 mOsm/day. Low solute intake may also occur in starvation and in an elderly person on a "tea and toast diet." The range of urine output would drop to (300/1200) – (300/50) or 0.25 to 6 L/day in such patients.

15. What are the main factors controlling water metabolism?

Thirst, hormonal, and renal mechanisms are tightly integrated for control of water metabolism. This integration is strongly influenced by nervous system and baroreceptor control (see Fig. 24-2).

16. What are the stimuli of thirst?

Osmoreceptors in the organum vasculosum of the anterior hypothalamus control thirst. Increasing plasma tonicity stimulates thirst at a threshold about 5 mOsm/kg higher than the value that stimulates ADH release. However, oropharyngeal receptors are also important in thirst regulation. A dry mouth increases thirst. Drinking and swallowing water decrease thirst even without changing P_{osm}. Volume depletion changes afferent baroreceptor input and increases angiotensin II—both changes increase thirst. An unusual idiosyncratic effect of angiotensin-converting enzyme (ACE) inhibitors causes central polydipsia, increased ADH release, and propensity to hyponatremia.

17. What hormonal mechanisms are involved in control of body water?

Although natriuretic peptides, aldosterone, angiotensin II, prostaglandins, and neurohumoral changes affect renal water retention and excretion, ADH is most important. ADH is also called arginine vasopressin (AVP). Supraoptic and paraventricular nuclei in the hypothalamus secrete ADH in response to increased osmolality and decreased volume. ADH attaches to vasopressin 2 receptors (V2-Rs) on the basolateral membrane of renal collecting tubular cells. This activates cyclic adenosine monophosphate (cAMP) and protein kinase A, causing intracellular water channels called aquaporins (AQPs) to insert into the luminal membrane. Water moves down osmotic gradients from tubular lumen through AQP channels into the cell and interstitium. At least seven AQP isoforms (AQP1-4, AQP6-8) are present in the kidney. AQP1 is constitutively expressed in the proximal tubule and descending loop of Henle and is important for isotonic fluid reabsorption and water conservation. The collecting duct has high concentrations of AQP2 that serve as the major target for ADH-mediated water reabsorption. Abnormalities of the V2-R cause most cases of nephrogenic diabetes insipidus (DI), but some are caused by abnormalities of AQP2. Increased AQP2 may cause water retention in conditions such as pregnancy and congestive heart failure.

Twenty percent of ADH receptors in the collecting tubular cells are vasopressin 1 receptors (V1-Rs). ADH activates V1-Rs only at very high levels. This increases prostaglandin E_2 and prostacyclin, which opposes the antidiuretic effects of excessive ADH.

18. What are the major conditions that influence ADH secretion?

ADH functions to maintain osmotic and volume homeostasis. Secretion starts at an osmotic threshold of 280 mOsm/kg and increases proportionately to further rises in tonicity. Maximum diuresis (urine dilution) occurs at ADH levels of 0.5 pmol/L, and maximum reabsorption (urine concentration) occurs at ADH levels of 3 to 4 pmol/L. A 1% to 2% increase in osmolality stimulates ADH secretion, whereas an 8% to 10% drop in vascular volume is required for the same effect. Through action on baroreceptors, increased ECV raises the osmotic threshold for ADH secretion, and decreased ECV lowers this threshold. Severe volume depletion and hypotension may completely override the hypo-osmotic inhibition of ADH secretion. This finding has been called the "law of circulating volume." In severe volume depletion and hypotension, ADH secretion continues despite low osmolality, thereby worsening the hyponatremia. Nausea, pain, and stress (as seen postoperatively) are potent stimuli of ADH release and may cause lifethreatening hyponatremia if hypotonic fluid is given. This is particularly true if patients with these symptoms also receive hypotonic fluid and drugs that potentiate the release or action of ADH.

19. What are the major causes of ADH secretion?

Major causes of ADH secretion include hyperosmolality, hypovolemia, nausea, pain, stress, human chorionic gonadotropin as in pregnancy (reset osmostat), hypoglycemia, corticotropin-releasing hormone (CRH), central nervous system (CNS) infections, CNS tumors, vascular catastrophes (thrombosis, hemorrhage), and ectopic ADH of malignancy (carcinomas of lung [primarily small cell], duodenum, pancreas, ureter, bladder, and prostate, and lymphoma). ADH secretion may be increased by any major pulmonary disorder, including pneumonia, tuberculosis, asthma, atelectasis, cystic fibrosis, positive pressure ventilation, and adult respiratory distress syndrome. Human immunodeficiency virus (HIV) infection may have the multifactorial role of causing CNS dysfunction, pulmonary disease, and malignancy. Excessive exogenous ADH or desmopressin acetate (DDAVP) in patients with DI directly increases ADH effect. Oxytocin also has significant ADH activity in the large dosages used to induce labor. Other drugs that affect ADH secretion and action are listed in Table 24-2.

KEY POINTS 2: SYNDROMES AND TREATMENT OF WATER DYSFUNCTION

1. Clinical syndromes of water dysfunction include syndrome of inappropriate secretion of antidiuretic hormone, diabetes insipidus, and changes in effective circulating volume that can cause marked retention of salt and water, pulmonary and peripheral edema, and severe neurologic dysfunction.
2. Effective correction of water problems requires correcting abnormalities of P_{Na} and a clear understanding of changes in plasma and urine osmolality, urine sodium and potassium, and effective circulating volume (ECV). Additionally, a thorough assessment of patient volume and neurologic symptoms is essential.
3. If neurologic symptoms occur rapidly or are severe, correction of P_{Na} toward normal should be rapid; if symptoms are absent, there is no urgency, and P_{Na} correction should occur more slowly.
4. Depending on the water disturbance, treatment includes water restriction or administration; hypertonic, isotonic, or hypotonic saline; sodium; diuretics; antidiuretic hormone; and aquaretics or other medications.

TABLE 24–2. DRUGS THAT AFFECT ANTIDIURETIC HORMONE (ADH) SECRETION AND ACTION*

Increase ADH secretion	**Antidepressants**
	Amitriptyline
	Protriptyline
	Desipramine
	Fluoxetine
	Selective serotonin reuptake inhibitors
	Duloxetine
	Antipsychotics*
	Fluphenazine
	Haloperidol
	Phenothiazines
	Butyrophenones
	Monoamine oxidase inhibitors
	Ecstasy
	Nicotine
	Bromocriptine
	Carbamazepine
	Chlorpropamide
	Clofibrate
	Cyclophosphamide
	Ifosfamide
	Morphine
	Nicotine
	Thioridazine
	Vincristine
	Angiotensin-converting enzyme inhibitors
	Amiodarone
	Methyldopa
Increase ADH effect	Acetaminophen
	Carbamazepine
	Chlorpropamide
	Cyclophosphamide
	Nonsteroidal anti-inflammatory drugs
	Tolbutamide
Decrease ADH secretion	Ethanol
	Phenytoin
Decrease ADH effect	Demeclocycline
	Lithium
	Acetohexamide
	Tolazamide
	Glyburide
	Methoxyflurane
	Propoxyphene
	Colchicine
	Amphotericin
	Vinblastine
	Prostaglandin E_2
	Prostacyclin

*Because psychosis itself may cause the syndrome of inappropriate secretion of ADH (SIADH), one must question the true ADH-stimulatory effect of the antipsychotic drugs. Changes in ADH secretion may be direct or indirect.

20. How does the kidney handle salt and water?

To control excess or deficient water intake, there must be an adequate glomerular filtration rate (GFR) and delivery of filtrate to the LOH and distal nephron. Solute is separated from water in the ascending limb of the LOH, distal convoluted tubule (DCT), and cortical connecting segment; normal action of ADH allows controlled reabsorption of water in the cortical and medullary collecting tubules. The proximal convoluted tubule reabsorbs 65% and the descending limb of the LOH 25% of filtered solute and water isotonically. The ascending limb is impermeable to water but removes solute, resulting in dilution of the luminal filtrate, concentration of the interstitium (important for ADH action), and delivery of 10% of the filtrate to the cortical collecting tubules with an osmolality of 100 mOsm/kg. In the absence of ADH, this fluid ($\approx$18 L/day) would be lost in the urine and cause marked dehydration. In the presence of ADH, the collecting duct becomes permeable to water and reabsorbs all but 1% of the filtrate. Thus the final urine volume is only 1.5 to 2.0 L/day. Because normal GFR is 125 mL/min, the normal kidneys filter 180 L of plasma each day and reabsorb 99%. In normal adults, 99% of all Na and H_2O filtered is reabsorbed.

21. What are the causes and consequences of decreased renal water excretion?

Any reduction in water excretion predisposes to hyponatremia and hypo-osmolality. Conditions that impair GFR, delivery of tubular fluid to the distal nephron, or the ability of the distal nephron to separate solute from water, or that increase the permeability of the collecting tubule to water impair water excretion. Such conditions include renal failure, decreased ECV, diuretics (thiazides and loop), and excessive ADH or ADH action.

22. How do hypothyroidism and adrenal insufficiency cause hyponatremia?

Hypothyroidism and adrenal insufficiency reduce cardiac output and thereby decrease ECV and increase ADH release. A hypothyroidism-associated decrease in ECV reduces renal blood flow, glomerular filtration, and maximal solute-free water excretion. Failure to dilute the urine maximally results from nonosmotic ADH release and increased ADH-mediated AQP2 receptors and action. The main effect of glucocorticoid deficiency is altered systemic hemodynamics, and not salt and water loss. Low cortisol impairs cardiac output and the systemic vascular responses to catecholamines, reducing both blood pressure and ECV. The resulting drop in absolute and effective vascular filling pressure reduces stretch on the arterial baroreceptors and thereby decreases tonic vagal and glossopharyngeal inhibition of ADH release. These baroreceptor changes override the hypo-osmotic inhibition of ADH release, and consequently, ADH secretion increases. The decreased ECV also lowers GFR, thereby reducing delivery of filtrate to the distal nephron and enhancing proximal tubular water reabsorption. Normally, CRH and ADH are co-secreted from the same neurons in the paraventricular nuclei of the hypothalamus, and both hormones work synergistically to release adrenocorticotropic hormone (ACTH) from the anterior pituitary—ADH via the vasopressin V1b receptor. Cortisol feeds back negatively at the hypothalamus and pituitary to inhibit the release of both CRH and ADH. Cortisol deficiency decreases this negative feedback and increases ADH release to further enhance water reabsorption.

Unlike secondary adrenal insufficiency, mineralocorticoid deficiency associated with primary adrenal insufficiency causes a hyperkalemic non–anion gap metabolic acidosis. This is due to retention of K^+ and H^+ that are normally excreted under aldosterone influence. The aldosterone deficiency also causes renal NaCl loss and associated volume (ECF) depletion. The resulting low ECV stimulates ADH release. There is also upregulation of collecting duct AQP2 and AQP3, which enhances ADH action. The combination of increased ADH secretion and augmented ADH responsiveness promotes the development of hyponatremia. A high-sodium diet compensates for the mineralocorticoid deficiency and improves the hyponatremia. Although hyponatremia may occur with both primary and secondary adrenal insufficiency, it occurs more commonly in primary adrenal insufficiency. This fact emphasizes the importance of aldosterone deficiency in renal salt wasting, volume depletion, and ADH secretion. All of these events combined with continued water intake synergistically contribute to hyponatremia.

23. What P_{Na} concentrations are causes for concern?

The seriousness of hyponatremia or hypernatremia depends on the rapidity of development. Acute changes in P_{Na} (within 48 hours) are always of more concern. Normal P_{Na} ranges from 136 to

145 mEq/L. Patients with a P_{Na} value of 115 or 165 mEq/L may not show any clinical features if the problem develops over several days to weeks. However, both conditions may produce major neurologic dysfunction if they develop over hours to days. As a rule, however, Na concentrations of 120 to 155 mEq/L are not usually associated with symptoms. P_{Na} values outside these limits and occasionally rapidly developing disturbances within these limits may be of major concern. With appropriate care, patients have been reported to survive with P_{Na} as low as 85 mEq/L and as high as 274 mEq/L without permanent sequelae. Although elderly individuals with chronic P_{Na} levels of 120 to 125 mEq/L may appear asymptomatic, they may have associated gait disturbances and may be at increased risk for falls and fractures. Thus treatment of this mild hyponatremia may benefit this group.

24. What causes the symptoms and signs of increased or decreased TBW?

The main symptoms and signs of TBS excess (decreased P_{Na}) or TBW deficiency (increased P_{Na}) result, respectively, from brain swelling or contraction. If TBW changes occur more rapidly than the brain can adapt, symptoms and signs occur. The severity of the symptoms and signs depends on the degree and rapidity of the TBW change. After adaptation occurs, correcting the disturbance in body water too rapidly may be more deleterious than the initial disturbance.

25. What are the symptoms and signs of hyponatremia and hypernatremia?

- Hyponatremia: headache, confusion, muscle cramps, weakness, lethargy, apathy, agitation, nausea, vomiting, anorexia, altered levels of consciousness, seizures, depressed deep tendon reflexes, hypothermia, Cheyne-Stokes respiration, respiratory depression, coma, and death.
- Hypernatremia: weakness, irritability, lethargy, confusion, somnolence, muscle twitching, seizures, respiratory depression, paralysis, and death.

26. How does the brain adapt to hyponatremia?

Because ICF and ECF osmolalities must always be equal, developing hyponatremia and decreased P_{osm} immediately shift water into the brain, raising intracranial pressure (ICP). The increased ICP causes loss of NaCl into the CSF. Over the next several hours, there is also loss of intracellular K and, over the next few days, loss of organic solute. These changes lower ICF osmolality and return the brain volume to normal. However, if severe hyponatremia occurs too rapidly, there is not enough time for cerebral adaptation. Brain edema occurs, further increasing ICP; the brain herniates, and the patient dies.

27. How does the brain adapt to hypernatremia?

With acute hypernatremia and increased P_{osm}, water immediately shifts out of the brain and decreases ICP. The decreased ICP promotes movement of CSF with NaCl into the brain ICF, partially correcting volume. Within hours, further brain adaptation occurs, increasing brain ICF K^+, Na^+, and Cl^-. The resulting increase in osmolality pulls water from the ECF and restores about 60% of the brain volume. Over the next several days, the brain accumulates organic solutes (osmolytes), previously called idiogenic osmoles, that return the brain volume to a near-normal level. These solutes include glutamine, taurine, glutamate, myoinositol, and phosphocreatine. If the brain has no time to adapt to rapidly developing hypernatremia, it shrinks, retracts from the dura, and tears vessels, causing intracranial hemorrhage, increased ICP, compressive injury, herniation, and death.

28. How should you approach the patient with hyponatremia?

Hyponatremia occurs in 1% of outpatients, more than 4% to 15% of hospitalized patients, 18% of elderly nursing home residents, and nearly 30% of intensive care unit (ICU) patients. Hyponatremia always means too much ECF water relative to Na. Serum osmolality (reflective of P_{osm}) should be measured, and volume status carefully assessed. With hyponatremia, the osmolality should be low. If P_{osm} is elevated (hypertonic hyponatremia), the ECF is high in other osmotically active substances, such as glucose (uncontrolled diabetes) and mannitol (treatment of increased ICP). Large-volume bladder irrigation with mannitol and glycine is sometimes responsible as well. When P_{osm} is normal (isotonic hyponatremia), there may be displacement of H_2O in the assay volume by excess lipid (hypertriglyceridemia) or

protein (multiple myeloma), causing pseudohyponatremia. With pseudohyponatremia, the osmolar gap is increased to more than 10 mOsm/kg, and measurement of P_{Na} without dilution with a Na-selective electrode gives the true P_{Na} concentration. Lastly, when P_{osm} is appropriately low (hypotonic hyponatremia), the common causes of hyponatremia to consider are listed in Table 24-3. Measuring U_{osm} is helpful in this differential diagnosis; if U_{osm} is less than 100 mOsm/kg, primary polydipsia, beer potomania, or malnutrition may be present (see questions 45 and 48). If U_{osm} is greater than 100 mOsm/kg, there is usually a diluting defect and an ADH effect (appropriate or not). Because total body volume is proportional to total body Na, a thorough assessment of the patient's volume status helps determine ECV and therapy. Patients whose neck veins are flat while they are supine and who have postural changes in blood pressure and pulse (standing blood pressure decreases more than 20 systolic/10 diastolic mm Hg and pulse increases greater than 20 beats/min) are hypovolemic and invariably saline (NaCl and H_2O) depleted. Patients with distended neck veins and edema are hypervolemic and have salt and water (saline) excess. Hyponatremic patients with no postural changes and no edema are clinically euvolemic, but volume may be subclinically increased. If possible, always direct treatment to correct the underlying disorder (Tables 24-3 and 24-4). If patients have lost saline, give them saline. If they have retained too much water, restrict their water. If they have retained too much salt and water but more water than salt, restrict their salt and water but water more than salt. It sounds simple and it is in concept. However, sometimes it is difficult to determine the subtle changes in volume status that are key to this assessment (see question 29). Carefully use loop diuretics in hypervolemic patients and 3% saline in acutely symptomatic patients (see question 47).

TABLE 24-3. CAUSES OF HYPONATREMIA*

PATHOPHYSIOLOGY	ASSOCIATED CONDITIONS
Renal saline loss and decreased ECV $U_{Na} > 20$ mEq/L	Diuretics Osmotic diuresis (glucose, urea, mannitol) Primary adrenal insufficiency Renal tubular acidosis ($NaHCO_3$ loss) Salt-losing nephritis Ketonuria Cerebral salt wasting
Nonrenal saline loss and decreased ECV $U_{Na} < 20$ mEq/L	Vomiting Diarrhea Pancreatitis, rhabdomyolysis, burns Peritonitis, bowel obstruction
Water excess $U_{Na} > 20$ mEq/L	SIADH Drugs (see Table 24-2) Secondary adrenal insufficiency Hypothyroidism
Na and H_2O excess with decreased ECV $U_{Na} < 20$ mEq/L	Congestive heart failure Cirrhosis Nephrotic syndrome
Na and H_2O excess with increased ECV $U_{Na} > 20$ mEq/L	Acute renal failure Chronic renal failure Pregnancy

*Hyponatremia always means too much plasma water relative to Na. Thorough volume assessment is crucial. Volume loss (renal or nonrenal) usually means saline (salt > H_2O) loss, and is associated with decreased ECV. Volume excess (hypervolemic) usually means saline (H_2O > salt) excess with associated edema and may be associated with decreased or increased ECV. Water excess usually causes mild excess of volume that affects baroreceptor activity. U_{Na} reflects renal perfusion, tubular integrity, and hormonal status. When $U_{Na} > 20$ mEq/L, the kidney contributes to Na loss and; when $U_{Na} < 20$ mEq/L, the kidney is conserving Na. ECV, effective circulating volume; SIADH, syndrome of inappropriate antidiuretic hormone.

TABLE 24-4. APPROACH TO HYPONATREMIA*

CONDITION	POSTURAL SIGNS	EDEMA	U_{NA} (MEQ/L)	TREATMENT
Renal saline loss	Yes	No	> 20	Give isotonic saline
Nonrenal saline loss	Yes	No	< 20	Give isotonic saline
Water excess	No	No	> 20	Restrict water
Na and water excess	No	Yes	< 20	Restrict water > salt
Na and water excess	No	Yes	> 20	Restrict water > salt

*Marked hyperlipidemia or hyperproteinemia causes pseudohyponatremia and artifactually lowers the standard measurement for P_{Na}. Measuring P_{Na} undiluted with Na-selective electrodes corrects for the excess lipid and protein and provides a true P_{Na} reading. However, routine measurement or prior dilution gives falsely low results for the P_{Na}. Measuring P_{osm} helps differentiate pseudohyponatremia. Osmometer-measured P_{osm} measures only the osmotic activity of plasma water that excludes lipids and proteins. Measured P_{osm} is normal in pseudohyponatremia, and the osmolar gap is increased to >10 mOsm/kg. Use loop diuretics carefully to treat edema and 3% saline for symptomatic acute hyponatremia.

29. What is the importance of an initial thorough volume assessment in patients with hyponatremia?

A thorough volume assessment is essential to help determine the underlying cause of hyponatremia (see Table 24-3) and to guide treatment (see Table 24-4). The volume status is best assessed by looking at neck veins, postural vital signs, and edema. At times the best clinician cannot get a good evaluation of ECV, but central venous catheterization is rarely necessary. Urinary Na and edema are other valuable ECV clues. Body weight should be measured daily, and postural vital signs should be assessed serially as necessary. Initial lab tests should include P_{osm}, general blood chemistry panel (Na, K, Cl, CO_2, Cr, BUN, glucose, albumin, Ca, Mg); urinary Na, Cl, Cr; U_{osm}; and fractional excretion of Na. The presence or absence of edema and the U_{Na} value are most helpful.

30. How should you characterize and diagnose the patient with syndrome of inappropriate secretion of antidiuretic hormone?

Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) has recently been called SIAD or syndrome of inappropriate antidiuresis because many of patients with the disorder do not have measurable ADH levels. Clinical euvolemia, hypotonic plasma, and less than maximally dilute urine are the clues to SIADH. The patient should be approached as discussed in question 28. It is important to establish normovolemia by physical examination. Then P_{osm}, U_{osm}, P_{Na}, U_{Na}, and urinary potassium (U_K) should be ordered. Finally, pituitary, adrenal, and thyroid dysfunction must be excluded before a diagnosis of SIADH can be made. Confirmatory criteria of SIADH include low P_{Na} (<135 mEq/L), low P_{osm} (<280 mOsm/kg), U_{osm} higher than 100 mOsm/kg, U_{Na} higher than 40 mEq/L, and [U_{Na} + U_K] higher than P_{Na}. Patients with SIADH are usually said to have normal volume status. However, they actually have excess TBW. Unlike excess saline, which is limited to ECF, excess water distributes ⅔ to the ICF and ⅓ to the ECF (see Fig. 24-1). Thus, the ECF excess is minor and not usually perceptible by clinical examination. Nonetheless, patients with SIADH have mildly increased ECV, which is sensed by the kidneys. The GFR is increased, causing low serum levels of uric acid, BUN, and creatinine. The increased ECV also increases atrial natriuretic peptide (ANP) and, along with increased GFR, promotes natriuresis. These are the classic findings in SIADH. Obviously, SIADH does not protect against dehydration and other conditions that can obscure the classic presentation. For example, a patient with ectopic ADH from lung cancer may present with dehydration from diarrhea, lack of food intake (solute), and lack of water intake from debilitation. In this instance, the U_{Na} and U_{Cl} may be less than 20 mEq/L, and measuring ADH may help.

31. How do you treat the patient with SIADH?

SIADH should be treated initially with water restriction (500-1500 mL/day). The fluid restriction needed to correct the hyponatremia is often not tolerated, especially when [U_{Na} + $_{UK}$] is much greater

P_{Na}. The combination of a high-sodium diet (4-8 g), a loop diuretic, and water restriction may be more practical. The treatment of markedly symptomatic hyponatremia is discussed in question 40. It is also important to correct the underlying abnormality (see questions 18 and 19). If the patient has unresectable cancer and water restriction is not tolerated, demeclocycline, 600 to 1200 mg/day, or lithium carbonate, 600 to 1200 mg/day, in 2 to 4 divided doses, may be given. Because lithium carbonate can cause neurologic, cardiovascular, and other toxicities, it should be avoided unless there are no other therapeutic options. Demeclocycline may cause severe renal failure in patients with cirrhosis. Thus it is contraindicated in patients with cirrhosis and severe liver disease. Oral and intravenous (IV) V2-R antagonists have also proved useful for SIADH treatment (see question 42). Although careful monitoring of P_{Na} is important and the expense of these aquaretics may be prohibitive, the V2-R antagonists are probably the agents of choice.

32. What are the four patterns of SIADH?

The four patterns of SIADH are distinguished according to responses of ADH to P_{osm}:

- *Type A:* Erratic ADH secretion with no predictable response to P_{osm} (≈30% of cases).
- *Type B:* ADH leak with selective loss of ADH suppression and continued secretion when P_{osm} is low but normal suppression and secretion when P_{osm} is normal (≈30% of cases).
- *Type C:* Reset osmostat with normal relationship of ADH to P_{osm} but with a lower threshold for ADH release (e.g., 250-260 mOsm/kg; ≈30% of cases).
- *Type D:* ADH-dissociated antidiuresis at low P_{osm} with appropriately low or undetectable ADH (possibly from increased renal sensitivity to ADH or unknown ADH-like substance; ≈10% of cases).

33. Define polyuria and list its main causes.

Polyuria is a urine output greater than 3.0 L/day. Four main disorders cause polyuria: central neurogenic DI (defect in ADH secretion), nephrogenic DI (defect in ADH action on the kidney), psychogenic polydipsia (psychosis), and dipsogenic DI (defect in thirst center). All forms of DI may be partial or complete. In general, patients with DI have U_{osm} less than P_{osm} and often the U_{osm} is lower than 100 mOsm/kg. Polyuria also may occur from osmotic diuresis in such conditions as diabetes mellitus (glucose), recovery from renal failure (urea), and IV infusions (saline, mannitol). In the last cases, the diagnosis is usually clear from the history and U_{osm} is greater than P_{osm}. See Table 24-2 for drugs and conditions that decrease ADH secretion and action. Causes of acquired nephrogenic DI include chronic renal disease, electrolyte abnormalities (hypokalemia, hypomagnesemia, hypercalcemia), drugs (lithium, demeclocycline, cisplatinum), sickle-cell disease (damaged medullary interstitium), diet (increased water and decreased solute—beer, starvation), and inflammatory or infiltrative renal disease (multiple myeloma, amyloidosis, sarcoidosis). DI may be associated with specific genetic abnormalities. Hereditary central DI is usually autosomal dominant and expresses itself in childhood rather than at birth. Wolfram's syndrome results from a familial defect on the short arm of chromosome 4 and has associated central DI, diabetes mellitus, optic atrophy, and deafness (DIDMOAD). Congenital nephrogenic DI results from abnormalities of V2-R or AQP2 channels, and symptoms of polyuria and dehydration appear in the first week of life. Most cases of nephrogenic DI (90%) are related to abnormalities of the V2-R and are X-linked and therefore almost always limited to expression in males. More than 150 mutations are noted to cause DI related to V2-R abnormalities. Nephrogenic DI related to abnormalities of AQP2 (10%) may be autosomal dominant or recessive. When recessive and in a female, the DI is likely due to a mutation on chromosome 12.

34. How do you distinguish polyuric patients with the various forms of DI from patients with excessive water drinking?

In excessive water drinking, the P_{Na}, BUN, and uric acid are relatively low. In DI, the P_{Na} and uric acid are relatively high, and the BUN is relatively low. Central DI often has an abrupt onset resulting from loss of a critical amount of AVP due to destruction of more than 80% to 90% of the ADH-secreting hypothalamic neurons at a critical point in time. Affected patients also have a preference for ice-cold water. Often the cause of polyuria is clear from the history and basic lab values. If the diagnosis is in

doubt, a water restriction test (WRT) can be performed. Other names for the WRT are dehydration test and water deprivation test. The test may take 6 to 18 hours, depending on the initial state of hydration.

35. How is the WRT performed?

1. Office testing is acceptable unless the patient cannot be watched closely, in which case hospitalization may be required.
2. Measure baseline weight, P_{osm}, P_{Na}, P_{BUN}, $P_{glucose}$, U_{volume}, U_{osm}, U_{Na}, and U_K. Measure hourly weight and U_{osm}.
3. Allow no food or water.
4. Watch the patient closely for signs of dehydration and surreptitious water drinking.
5. End the WRT when U_{osm} has not increased more than 30 mOsm/kg for 3 consecutive hours, P_{osm} has reached 295 to 300 mOsm/kg, or the patient has lost 3% to 5% of body weight. If weight loss exceeds 3% to 5% of body weight, further dehydration is unsafe.
6. At P_{osm} of 295 to 300 mOsm/kg, endogenous ADH levels should be 5 pg/mL or greater, and the kidney should respond with maximal urinary concentration.
7. Repeat all baseline measurements toward and at the end of the WRT.
8. Give 5 units of aqueous AVP or 2 μg of desmopressin (DDAVP) subcutaneously.
9. Repeat the baseline tests at 30, 60, and 120 minutes.
10. Calculate U_{osm}/P_{osm} and $[U_{Na} + UK]/P_{Na}$ as a check on measured U_{osm}/P_{osm}.

36. How do you interpret the results of the WRT?

Table 24-5 summarizes the expected results of the WRT. The WRT stimulates maximal endogenous ADH release by increasing P_{osm} and evaluates the kidneys' concentrating ability by measuring U_{osm}. Giving exogenous ADH allows evaluation of the renal concentrating response to ADH if dehydration-induced ADH production is impaired. Baseline and end-test plasma samples should be saved and frozen for later ADH measurement if the WRT results are equivocal. Expected normal values for PADH are less than 0.5 pg/mL for P_{osm} less than 280 mOsm/kg, and more than 5 pg/mL for P_{osm} more than 295 mOsm/kg.

37. What are the expected plasma ADH concentrations and urinary osmolality in polyuric patients after water restriction?

See Table 24-6.

TABLE 24-5. VALUES BEFORE AND AFTER WATER RESTRICTION

	BEFORE RESTRICTION		AFTER RESTRICTION		
	P_{osm}	P_{Na}	U_{osm}/P_{osm}	U_{osm}/P_{osm} + ADH†	P_{ADH}
Normals	NL	NL	> 1	> 1 (< 10%)	↑
Psychogenic polydipsia/ dipsogenic DI	↓	↓	> 1	> 1 (< 10%)	↑ or NL
Complete central DI	↑	↑	< 1	> 1 (> 50%)	—
Partial central DI	↑	↑	> 1	> 1(10–50%)	↓
Complete nephrogenic DI	↑	↑	< 1	< 1 (< 10%)	↑↑
Partial nephrogenic DI	↑	↑	> 1	> 1 (< 10%)	↑↑

*Recall that when $U_{osm} > P_{osm}$, there is antidiuresis, and the kidney is retaining free water. The same is true when $[U_{Na} + U_K] > P_{Na}$, and these measurements are more easily obtainable. When $U_{osm} < P_{osm}$ or $[U_{Na} + U_K] < P_{Na}$, there is net loss of free water with little net clinical ADH effect.

ADH, antidiuretic hormone; DI, diabetes insipidus; ↓, low-normal; ↑↑, high; ↑, high normal; and—, undetectable.

†The values in parentheses indicate the percentage changes in U_{osm} (not the U_{osm}/P_{osm} ratios) after 5 units of subcutaneous aqueous vasopressin or 2 μg of desmopressin acetate.

TABLE 24–6. EXPECTED VALUES FOR ADH AND U_{osm} AFTER WATER RESTRICTION

CAUSE OF POLYURIA	ADH (PG/ML)	U_{OSM} (MOSM/KG)
Normal	> 2	> 800
Primary polydipsia	< 5	> 500
Complete central DI	Undetectable	< 300
Partial central DI	< 1.5	300-800
Nephrogenic DI	> 5	300-500

ADH, antidiuretic hormone; DI, diabetes insipidus.

38. How should you approach the patient with hypernatremia?

Hypernatremia is uncommon in comparison with hyponatremia, occurring in less than 1% of general hospitalized patients. Indeed, unless patients have an abnormality of thirst or do not have access to water, they usually maintain near-normal P_{Na} by drinking water in proportion to losses. However, as many as 5% to 10% of ICU patients may have some degree of hypernatremia. Loss of water is the usual cause of hypernatremia, and almost all patients require water for treatment (Table 24-7). As in questions 28 and 29, the patient's volume status must be assessed carefully. After lab studies are obtained, the patient should be approached as outlined in Table 24-8. If the patient has polyuria, the approach described in questions 33 and 34 should be included.

TABLE 24–7. CAUSES OF HYPERNATREMIA*

PATHOPHYSIOLOGY	ASSOCIATED CONDITION
Renal H_2O loss > Na loss, U_{Na} > 20 mEq/L	Osmotic diuretics
	Loop diuretics
	Renal disease
	Postobstructive diuresis
Non-renal H_2O loss > Na loss, U_{Na} < 20 mEq/L	Osmotic diarrhea
	Vomiting
	Sweating
	Diarrhea
	Burns
Excess Na > H_2O, U_{Na} > 20 mEq/L	Cushing's syndrome
	Primary hyperaldosteronism
	Excessive intake of NaCl or $NaHCO_3$
	Hypertonic saline and bicarbonate
	Hypertonic dialysis
Renal H_2O loss, U_{Na} > 20 mEq/L	Central diabetes insipidus
	Nephrogenic diabetes insipidus
Non-renal H_2O loss U_{Na} < 20 mEq/L	Increased sensible loss
	No access to H_2O

*Hypernatremia always means too little plasma water relative to Na. With access to water, hypernatremia usually does not occur or is mild. However, unattended patients who are too old, too young, or too sick may not have adequate access to water, and hypernatremia may be severe. Thorough volume assessment is crucial. Volume loss (hypovolemic) usually means renal or nonrenal saline (H_2O > salt) loss and is usually treated with 0.9% to 0.45% saline to correct the volume deficit, followed by water. Volume excess (hypervolemic) usually means saline (salt > H_2O) excess with high total body Na and is treated with water and restriction of salt. A loop diuretic may also be necessary to treat volume overload. Euvolemic hypernatremia results from water loss and is treated with free water replacement, and vasopressin is used if water loss is caused by diabetes insipidus.

TABLE 24–8. APPROACH TO HYPERNATREMIA

CONDITION	POSTURAL SIGNS	EDEMA	U_{NA} (MEQ/L)	U_{OSM}	TREATMENT*
Renal H_2O > Na loss	Yes	No	> 20	↓–	0.9%-0.45% saline
Nonrenal H_2O > Na loss	Yes	No	< 20	↑	0.9%-0.45% saline
Na excess	No	Yes/No	> 20	↑–	Free H_2O/diuretics
Renal H_2O loss	No	No	> 20	↓↑–	Free H_2O
Nonrenal H_2O loss	No	No	< 20	↑	Free H_2O

*Free H_2O = 5% dextrose in water infusion or water orally. Infuse saline to restore the volume deficit when patients show signs of severe volume depletion, such as hypotension or postural changes in blood pressure and pulse. This is appropriate when isotonic (0.9%) saline with an osmolality of 308 mOsm/kg is lower than plasma osmolality. This corrects both the volume deficit and the hypernatremia. After the volume deficit has improved, switch to 0.45% saline and eventually 5% dextrose in water. Loop diuretics are used to treat Na excess.
↑, hypertonic; ↓, hypotonic; –, isosmotic.

39. How should you diagnose and manage the patient with DI?

Patients with DI have excessive renal water loss owing to decreased ADH secretion (central DI) or renal unresponsiveness to ADH (nephrogenic DI). The hallmark of DI is polyuria with hypotonic urine. Mild hypernatremia, low BUN, and relatively high uric acid are suggestive of DI. ADH and oxytocin neurosecretory vesicles are responsible for the normal finding of a high-signal-intensity posterior pituitary lobe that appears as a bright spot on T1-weighted magnetic resonance images. In patients with idiopathic central DI, this normal posterior pituitary bright spot is absent. However, the posterior pituitary bright spot also decreases with age and may be absent in a majority of elderly patients without DI. Abrupt onset of polyuria is also suggestive of central DI. Little ADH is necessary for urinary concentration, and therefore 80% to 90% of the ADH-secreting neurons must be lost before polyuria develops. As described in questions 33 and 34, DI must first be distinguished from primary polydipsia and identified as being central or nephrogenic. Water should then be given to prevent dehydration until further evaluation suggests definitive therapy. Mild cases of DI require no treatment other than adequate fluid intake. A patient with DI will probably self-treat with water unless there is a thirst deficit or there is no access to water. Central DI is treated with DDAVP as a nasal spray or oral tablet. DDAVP is available for oral use (0.1 or 0.2 mg tablets) with a starting dose of 0.05 mg once or twice daily, and increasing to a maximum of 0.4 mg every 8 hours as necessary. The tablet is 5% absorbed, and absorption is further decreased as much as 50% with meals. At least one dose should be given at bedtime. Oral DDAVP is preferred for patients with sinusitis from the nasal preparation. DDAVP nasal spray (100 μg/mL solution) is given every 12 to 24 hours as needed for thirst and polyuria. It may be administered by metered-dose nasal inhaler (0.1 mL/spray) or by a plastic calibrated tube. The starting dosage is 0.05 to 0.1 mL once or twice daily, and the dosage is titrated to an acceptable urine output. Parenteral DDAVP (4 μg/mL) may be given intravenously, intramuscularly, or subcutaneously at 1 to 2 μg every 12 to 24 hours to hospitalized patients. Nephrogenic DI may be partial or incomplete and therefore may respond to DDAVP. If possible, the underlying cause should be corrected or ameliorated (see question 33).

A low-sodium and low-protein diet that does not compromise nutritional needs should be advised. Regular voiding to avoid overdistending the bladder and bladder dysfunction should be emphasized. Both central DI and nephrogenic DI respond partially to hydrochlorothiazide (25 mg once or twice daily). Amiloride 5 to 10 mg once or twice daily may be additive to thiazides and is especially useful for lithium nephrotoxicity. Nephrogenic DI may respond to combination therapy if one agent is ineffective. Combinations may include indomethacin with hydrochlorothiazide, indomethacin with DDAVP,

or indomethacin with amiloride. Although oral indomethacin 25 to 50 mg every 8 hours has been effective, other NSAIDs (tolmetin and ibuprofen) may be less effective.

40. How quickly should you correct states of water excess or deficiency?

The main concern in therapy for abnormal TBW is to prevent devastating neurologic complications. Understanding brain adaptation to changes in TBW, as outlined in questions 25 and 26, emphasizes the need for urgent therapy only in the symptomatic patient. The three useful rules in treating disturbances of water (measured by changes in P_{Na}) are as follows:

1. Return the P_{Na} to normal at a speed relative to that by which it became abnormal. If the change in P_{Na} was slow (days), correct it slowly (days). If the change was rapid (minutes to hours), correct it rapidly (minutes to hours).
2. If there are no symptoms of water or Na imbalance (see question 24), there is no immediate urgency. If there are symptoms, there is urgency. Questions 25 and 26 outline the brain adaptations to altered tonicity that may cause devastating changes in brain volume. These adaptations also cause the patient's symptoms. Thus symptoms should drive the clinician to correct the altered tonicity rapidly.
3. The degree of rapid P_{Na} correction should be *toward* normal (until symptoms abate), not *to* normal.

These concepts—speed, symptoms, and degree of P_{Na} correction—apply for both hyponatremia and hypernatremia (see question 47).

41. What is the significance of the $[U_{Na} + U_K]/P_{Na}$ ratio?

The ratio $[U_{Na} + U_K]/P_{Na}$ allows the calculation of electrolyte-free water excreted per day and is useful in deciding how much water can be consumed without lowering the P_{Na}. If $[U_{Na} + U_K]/P_{Na}$ is greater than 1, the patient is excreting no free water. Thus, all water given to the patient is being retained, and free water clearance is negative. Any water consumed would lower P_{Na}. If the ratio is less than 1, the patient is excreting free water and may consume some free water without decreasing P_{Na}. For example, if patient A makes 2 L of urine daily and has a U_{Na} value of 20 mEq/L, a U_K value of 20 mEq/L, and a P_{Na} value of 135 mEq/L, the patient excretes 1.4 L of electrolyte-free urine. If insensible loss is 800 mL, then patient A could consume 1.4 L + 0.8 L = 2.2 L without a change in the P_{Na}. If patient A had a 1000-mL fluid restriction, the net fluid balance would be 1000 mL – 2200 mL = 1200 mL lost.

However, if patient B makes 2 L of urine and has a U_{Na} value of 130 mEq/L, a U_K value of 60 mEq/L, and a P_{Na} value of 125 mEq/L, patient B makes −1.04 L or retains free water—no free water loss. If patient B has the same insensible loss of 800 mL, patient B would retain 204 mL if no additional fluid were allowed. Given the same 1000-mL fluid restriction, patient B would have 1000 mL + 204 mL = 1204 mL net gain in fluid. This net free water retention would make the hyponatremia worse. The calculations for free water clearance in patient A and B are as follows.

The formula for free water clearance is $C_{H_2O} = V\left(1 - \frac{[U_{Na} + U_K]}{P_{Na}}\right)$.

Patient A:

$$C_{H_2O} = 2\,L\left(1 - \frac{[20 + 20]}{135}\right) = 2\,L(1 - 0.30) = 2\,L \times 0.70 = 1.4\,L$$

Patient B:

$$C_{H_2O} = 2\,L\left(1 - \frac{[130 + 60]}{125}\right) = 2\,L(1 - 1.52) = 2\,L(1 - 1.52) = 2\,L \times (-0.52) = -1.04\,L$$

42. What are vasopressin receptor antagonists, and when would you use them for hyponatremia therapy?

The conventional treatment of hyponatremia, water restriction or saline administration, is still appropriate therapy for most patients with hyponatremia. Conivaptan is a first-in-class vasopressin

receptor antagonist (VRA) available for treatment of hospitalized patients with hyponatremia and normal extracellular fluid volume (SIADH). Conivaptan prevents AVP binding to V1a and V2 receptors located within the vasculature and renal tubules, respectively. Blocking the V2-R decreases free water reabsorption and increases excretion. Blocking the V1a receptor may cause vasodilatation, reducing afterload in CHF, but also may cause negative hemodynamics in cirrhosis. Conivaptan is available in 20-mg/5-mL glass ampules. The recommended dosage is a 20-mg loading dose administered intravenously over 30 minutes followed by 20 mg infused continuously over 24 hours for an additional 1 to 3 days. If the serum sodium fails to rise at the desired rate, the dosage is increased to 40 mg/day by continuous infusion. The infusion should not exceed 4 days in duration. Tolvaptan is a pure V2-R antagonist available in 15-mg and 30-mg tablets for once-daily oral dosing. The dose can be increased by 15 to 30 mg daily to a maximum dose of 60 mg daily. Like conivaptan, tolvaptan produces selective water diuresis with no effect on Na and K excretion. The term "aquaretic drugs" (aquaretics) has been coined for these medications to highlight the fact that they have different mechanisms of action from those of the saluretic diuretic furosemide. They are proven to be beneficial in SIADH and in hyponatremic patients with CHF and cirrhosis. Blocking the ADH effect may allow rapid correction of hyponatremia to occur; therefore, judicious monitoring of P_{Na} changes is important to prevent excessively rapid correction of P_{Na}.

43. What is the appropriate P_{Na} correction factor for hyperglycemia?

The standard correction factor is a 1.6-mEq/L decrease in P_{Na} for each 100-mg/dL increase in plasma glucose concentration above 100 mg/dL. For glucose values greater than 400 mg/dL, data now suggest a correction factor as high as a 4.0-mEq/L decrease in P_{Na} for each 100-mg/dL increase in plasma glucose and an average correction factor of 2.4 mEq/L.

CLINICAL PROBLEMS IN WATER METABOLISM

44. A 75-year-old woman presents with confusion but no focal neurologic signs. She has type 2 diabetes mellitus. Blood pressure is 110/54 mm Hg. Pulse is 96 beats/min. Neck veins are not visualized in the supine position. $P_{glucose}$ = 900 mg/dL, P_{Na} = 135 mEq/L, plasma creatinine = 3.0 mg/dL, BUN = 50 mg/dL, U_{Na} = 40 mEq/L; urine glucose is 4+ and urine ketones 3+. Describe her fluid and volume status and treatment.

Glucose remains in the ECF because of insulin deficiency and increases ECF tonicity. Greater tonicity pulls water from the ICF to the ECF, concentrating the ICF and diluting the ECF until ICF and ECF osmolalities are equal. The osmotic pressure of 900 mg/dL glucose (900/18 = 50 mOsm/kg) is the driving force for water movement from ICF to ECF. Water movement from ICF to ECF dilutes the ECF and decreases P_{Na} (translocation hyponatremia). Each 100-mg/dL rise in $P_{glucose}$ above 100 mg/dL decreases the P_{Na} by 1.6 mEq/L. In this patient, the predicted decrease in P_{Na} = (900 − 100)/100 × 1.6 = 13 mEq/L. The predicted P_{Na} would be 140 − 13 = 127 mEq/L. However, a more accurate correction factor for the elevated glucose would be 2.4 mEq/L (see question 43). Thus the predicted decrease in P_{Na} would be (900 − 100)/100 × 2.4 = 19 mEq/L. The predicted P_{Na} would be 140 − 19 = 121 mEq/L. But this patient's P_{Na} is 135 mEq/L, suggesting that there has been further water loss from osmotic diuresis and significant dehydration. The P_{osm}—2(135) + 900/18 + 56/2.8 = 340 mOsm/kg—is compatible with hyperosmolar coma. Because this woman has decreased TBW, decrease blood pressure, and a BUN/Creatinine ratio that suggests prerenal azotemia, you might expect her to have low U_{Na} and high U_{osm}. However, osmotic diuresis caused by urine glucose, ketones, and urea increases urinary Na and water, making U_{Na} and U_{osm} less useful markers of dehydration. Flatness of neck veins in the supine position is usually due to intravascular volume depletion. Rapid lowering of her glucose to 100 mg/dL will quickly decrease P_{osm}, shift water to the ICF, increase P_{Na} by 13 to 19 mEq/L, and potentially cause cerebral edema and cardiovascular collapse. Thus therapy is normal saline to replace volume and judicious lowering of $P_{glucose}$ with IV insulin.

45. You admit a 35-year-old schizophrenic patient because of a change in mental function and excessive urine output. U_{osm} = 70 mOsm/kg. P_{osm} = 280 mOsm/kg, 24-hour urine output = 12 L/day. How much free water is the patient excreting each day?

Free water clearance (C_{H_2O}) is the amount of solute-free water excreted per day. Osmolar clearance (C_{osm}) is the amount of urine excreted per day that contains all the solute that is isosmotic to plasma. When the urine is hypotonic to plasma, the total urine volume consists of two components: one part that is free of solute (C_{H_2O}) and the other that is isosmotic to plasma (C_{osm}). To measure how much of the urine is pure (free) water, calculate the C_{H_2O}. To do so, you need to know the C_{osm} and the urine volume (V). The formula for clearance of any substance (including osmoles) is always the same:

$$C = \frac{UV}{P}$$

where C is volume of plasma cleared of the substance per unit time, U is urinary concentration of the substance, P is plasma concentration of the substance, and V is total urinary volume per unit time. The calculations for this patient follow:

1. $V = C_{osm} + C_{H_2O}$
2. $C_{H_2O} = V - C_{osm}$
3. $C_{osm} = \frac{U_{osm}V}{P_{osm}}$
4. $C_{osm} = \frac{(70\ \text{mOsm/kg} \times 12\ \text{L/day})}{280\ \text{mOsm/kg}} = 3.0\ \text{L/day}$
5. $C_{H_2O} = V - C_{osm} = 12\ \text{L/day} - 3\ \text{L/day} = 9\ \text{L/day}$

Manipulation of formula (2) offers another means of calculating free water clearance, as follows:

1. $C_{H_2O} = V\left(1 - \frac{U_{osm}}{P_{osm}}\right)$
2. $C_{H_2O} = 12\ \text{L/day}\left(1 - \frac{70}{280}\right) = 9\ \text{L/day}$

Thus the patient's daily urine output contains 9 L/day of pure (free) water, and 3 L/day that is isotonic to plasma. This information does not distinguish primary polydipsia from DI. However, the low P_{osm}, 280 mOsm/kg, suggests primary polydipsia.

46. A 45-year-old-man with a 30-pack-year history of smoking presents with cough, dyspnea, fatigue, and a 15-lb weight loss. Chest x-ray shows mediastinal adenopathy and right atelectasis with pleural effusion. P_{osm} = 270 mOsm/kg, P_{Na} = 125 mEq/L, U_{osm} = 470 mOsm/kg, U_{Na} = 130 mEq/L, U_K = 60 mEq/L, and urine volume = 1 L/day. How much free water is the patient excreting each day? What is the likely pulmonary lesion?

Urine is hypertonic to plasma if the U_{osm} exceeds P_{osm} or the $U_{[Na + K]}$ exceeds P_{Na}. Urine hypertonic to plasma contains two parts: the volume that would be required to contain all solute and remain isosmotic to plasma is the osmolar clearance (C_{osm}); the volume of free water that was removed from the isotonic glomerular filtrate to make U_{osm} higher than P_{osm} or $U_{[Na + K]}$ higher than P_{Na} is the negative free water clearance ($T^{C_{H_2O}}$; see next paragraph). There are two ways to calculate free water clearance: one method uses osmolality, as in question 45; the other uses electrolytes (Na and K). Electrolyte-free water clearance more accurately estimates free water clearance and negative free water clearance, especially when urine contains large numbers of nonelectrolyte osmolytes, such as urea, that increase osmolality unrelated to free water clearance. To calculate electrolyte free-water clearance, the urinary Na and K concentrations and the plasma Na are used. Because $U_{[Na + K]}$ is greater than P_{Na}—(130 + 60) > 130—the net urinary excretion of free water is negative, and therefore free

water clearance is negative. Calculations for osmolar and electrolyte-free water clearances in this patient follow:

Calculations for classic osmolar (negative) free water clearance:

1. $V = C_{osm} - T^{CH_2O}$
2. $T^{CH_2O} = C_{osm} - V$
3. $C_{osm} = 1\ \text{L/day}\left[\frac{470}{270}\right] = 1.74\ \text{L/day}$
4. $T^{CH_2O} = 1.74\ \text{L/day} - 1\ \text{L/day} = 0.74\ \text{L/day}$

Manipulation of formula 2 offers another means of calculating negative free water clearance, as follows:

1. $T^{CH_2O} = V\left[\frac{U_{osm}}{P_{osm}} - 1\right]$
2. $T^{CH_2O} = 1\ \text{L/day}\left[\frac{470}{270} - 1\right] = 0.74\ \text{L/day}$

Calculations for electrolyte-free water clearance (negative free water clearance) are as follows:

1. $T^{CH_2O} = C_{[Na+K]} - V$
2. $C_{[Na+K]} = \left[\frac{U_{[Na+K]}}{P_{Na}} \times V\right]$
3. $C_{[Na+K]} = \left[\frac{190\ \text{mEq/L}}{125\ \text{mEq/L}} \times 1\ \text{L/day}\right] = 1.52\ \text{L/day}$
4. $T^{CH_2O} = 1.52\ \text{L/day} - 1\ \text{L/day} = 0.52\ \text{L/day}$

Thus the patient's kidneys add (by water reabsorption) a net of 520 to 740 mL of free water to plasma each day. With a low P_{osm}, it is usually inappropriate to retain water in excess of output. This finding suggests SIADH. One must exclude volume depletion, adrenal insufficiency, and hypothyroidism before making the diagnosis of SIADH. This patient had small cell carcinoma of the lung with ectopic ADH secretion. SIADH develops in 15% of patients with small cell carcinoma of the lung. This tumor is highly associated with smoking and accounts for 15% to 25% of lung cancer. Other lung cancers rarely secrete ADH.

47. A 34-year-old, 60-kg woman presents 12 hours after discharge following cholecystectomy. She has headache, confusion, muscle cramps, weakness, lethargy, agitation, nausea, and vomiting. She had no symptoms at discharge. P_{Na} was 110 mEq/L. What has caused the hyponatremia? How quickly should you treat it?

According to this history, hyponatremia developed rapidly and was symptomatic. Treatment is ICU admission and administration of 3% saline and furosemide at rates sufficient to increase P_{Na} 1.5 to 2.0 mEq/L/h for 2 to 4 hours on the basis of symptom resolution. P_{Na} should be measured every 2 to 4 hours to follow progress and guide therapy. U_{Na} and U_K measurements should be ordered as needed if P_{Na} is not changing at the expected rate, to guide replacement of urine water and electrolyte losses. After serious signs and symptoms improve, the rate of correction should be decreased to 0.5 to 1.0 mEq/L/h until symptoms further improve or the P_{Na} is at least 120 mEq/L. A net increase in P_{Na} greater than 10 mEq/L in the first 24 hours and 18 mEq/L over 48 hours must be avoided. For chronic hyponatremia without symptoms, the appropriate rate of correction is 0.5 mEq/L/h or less with similar net daily increases in P_{Na}. Acute symptomatic hyponatremia requires expeditious correction of the P_{Na} because the symptomatic patient has cerebral edema caused by "normal" brain-cell solute content that pulls water from the hypotonic ECF into the brain. Acute raising of the P_{Na} increases ECF tonicity, pulls water out of the swollen brain, and reduces the brain volume toward normal. The brain has no room in the skull to swell more than 8% to 10% before herniation. Therefore, there is no benefit to acute correction of the Na more than 8%—in this case to a P_{Na} greater than 119 mEq/L. Conversely, the patient

with chronic asymptomatic hyponatremia has adapted by loss of brain solute and has near-normal brain volume. Increasing such a patient's P_{Na} too rapidly (> 0.5 mEq/L/h) would shrink the brain and predispose to the osmotic demyelination syndrome (previously called central pontine myelinolysis). The risks of not correcting acute symptomatic hyponatremia include increased cerebral edema, seizures, coma, tentorial herniation, and death. Calculations for water excess and for 3% saline necessary to correct the P_{Na} to 120 mEq/L are as follows"

$$\begin{aligned}\text{Water excess} &= \left(\frac{\text{normal } P_{Na} - \text{observed } P_{Na}}{\text{normal } P_{Na}}\right) \times \text{TBW} \\ &= \left(\frac{140 - 110}{140}\right) \times 0.5 \times 60 \text{ kg} \\ &= 0.21 \times 30 \text{ L} \\ &= 6.3 \text{ L excess in TBW}\end{aligned}$$

$$\begin{aligned}\text{Na deficit} &= (\text{desired } P_{Na} - \text{observed } P_{Na}) \\ &= (120 - 110) \times 0.5 \times 60 \text{ kg} \\ &= 10 \text{ mEq/L} \times 30 \text{ L} \\ &= 300 \text{ mEq Na}\end{aligned}$$

Knowing the Na deficit is useful clinically because it can be replaced at a controlled rate to improve the hyponatremia. The Na in 3% saline is 513 mEq/L:

$$\frac{300 \text{ mEq Na}}{513 \text{ mEq/L}} = 0.585 \text{ L}$$

Thus, assuming no Na or water loss, giving 585 mL of 3% saline will correct the P_{Na} to 120 mEq/L. Make a similar calculation for 3% saline to infuse over 3 to 4 hours to increase the P_{Na} by 6 mEq/L. The answer is 350 mL. However, the patient will lose sodium and water during the infusion. If P_{Na} does not correct at the desired rate, one may need to measure P_{Na}, U_{Na}, and U_K to estimate loss and gain of Na and water during therapy and to replace those losses. An empiric rate of 3% saline infusion for rapid treatment of symptomatic hyponatremia is 2 mL/kg/h. Ideal body weight should be used unless the patient weighs less than ideal body weight, in which case actual weight is preferable. In this patient, 3% saline infusion would be 60 kg × 2 mL/kg/h or 120 mL/h × 4 h = 480 mL.

48. An 80-year-old woman who rarely leaves her home is brought to the hospital after being found confused. Three weeks ago, she saw her physician, who started a diuretic for systolic hypertension. On arrival, her P_{Na} is 110 mEq/L. What is the cause of her hyponatremia?

As a consequence of aging, elderly patients lose GFR, concentrating ability, and diluting ability. Thus an 80-year-old woman may have a normal (for age) renal-concentrating range of 100 to 700 mOsm/kg. However, maximal U_{osm} in the elderly may be as low as 350 mOsm/kg. This woman's average diet may generate only 600 mOsm/day. Her normal range of urine output would then be 0.9 to 6.0 L/day. If her dietary intake fell to 300 mOsm/day, her maximal urine output would fall to 3 L/day, calculated as follows:

$$300 \text{ mOsm/day} \div 100 \text{ mOsm/kg} = 3 \text{ L/day}$$

Given free access to water and a thiazide diuretic, which impairs urinary dilution, she could easily become water intoxicated and hyponatremic. The mechanism of hyponatremia in beer potomania and the "tea-and-toast diet" is low total osmolar intake and relatively increased water intake. The decreased osmotic load for excretion limits the amount of water excreted. This patient's hyponatremia is probably chronic; however, she is symptomatic. Thus, it is not clear whether the hyponatremia is truly chronic or acute. Therefore, how to proceed with therapy in this severely hyponatremic patient is unclear. Computed tomography (CT) or magnetic resonance imaging may help by showing the presence or absence

of cerebral edema. If cerebral edema is present, treatment for acute hyponatremia is necessary. If cerebral edema is absent, judicious treatment for chronic hyponatremia is appropriate. Symptoms, signs, and P_{Na} should be assessed frequently. Remember: Elderly women taking thiazide diuretics, alcoholics, and malnourished, hypokalemic, or burned patients are at particular risk for the demyelination syndrome.

WEBSITES

American Academy of Family Physicians: *Hyponatremia and hypernatremia in the elderly.* http://www.aafp.org/afp/20000615/3623.html.

EMedicine: *SIADH review.* http://www.emedicine.com/ped/topic2190.htm.

EMedicine: *Hyponatremia review.* http://www.emedicine.com/med/topic1130.htm.

EMedicine: *Lithium nephropathy review.* http://www.emedicine.com/med/topic1313.htm.

EMedicine: *Diabetes insipidus review.* http://www.emedicine.com/med/topic543.htm.

BIBLIOGRAPHY

Adrogue HJ, Madias NE: Hypernatremia, *N Engl J Med* 342:1493–1499, 2000.

Adrogue HJ, Madias NE: Hyponatremia, *N Engl J Med* 342:1581–1589, 2000.

Berl T, Schrier RW: Disorders of water metabolism. In Schrier RW, editor: *Renal and Electrolyte Disorders*, ed 7, Philadelphia, 2010, Lippincott Williams & Wilkins, p 1.

Chawla A, Sterns RH, Nigwekar SU, et al: Mortality and serum sodium: do patients die from or with hyponatremia? *Clin J Am Soc Nephrol* 6:960–965, 2011.

Decaux G, Soupart A, Vassart G: Non-peptide arginine-vasopressin antagonists: the vaptans, *Lancet* 371:1624–1632, 2008.

Ellison DH, Berl T: The syndrome of inappropriate antidiuresis, *N Engl J Med* 356:2064–2072, 2007.

Gutierrez OM, Lin HY: Refractory hyponatremia, *Kidney Int* 71:79–82, 2007.

Hannon MJ, Finucane FM, Sherlock M, et al: Disorders of water homeostasis in neurosurgical patients, *J Clin Endocrinol Metab* 97:1423–1433, 2012.

Hillier TA, Abbott RD, Barrett EJ: Hyponatremia: evaluating the correction factor for hyperglycemia, *Am J Med* 106:399–403, 1999.

Hoorn EJ, van der Lubbe N, Zietse R: SIADH and hyponatraemia: why does it matter? *NDT Plus 2* [Suppl 3]:iii5–iii11, 2009.

Liamis G, Milionis H, Elisaf M: A review of drug-induced hyponatremia, *Am J Kidney Dis* 52:144–153, 2008.

Loh JA, Verbalis JG: Disorders of water and salt metabolism associated with pituitary disease, *Endocrinol Metab Clin N Am* 37:212–234, 2008.

Piper GL, Lewis JK: Fluid and electrolyte management for the surgical patient, *Surg Clin N Am* 92:189–205, 2012.

Robinson AG, Verbalis JG: Posterior pituitary. In Melmed S, Polonsky KS, Larsen PR, et al., editors: *Williams Textbook of Endocrinology*, ed 12, Philadelphia, 2011, Elsevier Saunders, p 291.

Rosner MH, Kirven J: In-depth review. Exercise-associated hyponatremia, *Clin J Am Soc Nephrol* 2:151–161, 2007.

Sanghvi SR, Kellerman PS, Nanovic L: Beer potomania: an unusual cause of hyponatremia at high risk of complications from rapid correction, *Am J Kidney Dis* 50:673–680, 2007.

Schrier RW: Review. Body water homeostasis: clinical disorders of urinary dilution and concentration, *J Am Soc Nephrol* 17:1820–1832, 2006.

Shea AM, Hammill BG, Curtis LH, et al: Medical costs of abnormal serum sodium levels, *J Am Soc Nephrol* 19:764–770, 2008.

Sherlock M, O'Sullivan E, Agha A, et al: The incidence and pathophysiology of hyponatraemia after subarachnoid haemorrhage, *Clin Endocrinol (Oxf)* 64:250–254, 2006.

Singer I, Oster JR, Fishman LM: The management of diabetes insipidus in adults, *Arch Intern Med* 157:1293–1301, 1997.

Sterns RH, Hix JK, Silver S: Treating profound hyponatremia: a strategy for controlled correction, *Am J Kidney Dis* 56:774–779, 2010.

Verbalis JG: Disorders of water balance. In Taal MW, Chertow GM, Marsden PA, et al., editors: *Brenner & Rector's The Kidney*, ed 9, Philadelphia, 2011, Elsevier Saunders, p 540.

Wald R, Jaber BL, Price LL: Impact of hospital-associated hyponatremia on selected outcomes, *Arch Intern Med* 170:294–302, 2010.

Yee AH, Burns JD, Wijdicks EFM: Cerebral salt wasting: pathophysiology, diagnosis, and treatment, *Neurosurg Clin N Am* 21:339–352, 2010.

Zeidel ML: Hyponatremia: mechanisms and newer treatments. *Endocr Pract* 16:882–887, 2010.

DISORDERS OF GROWTH

Philip Zeitler

1. Summarize normal growth velocity for children until the pubertal growth spurt.

- First 6 months: 16 to 17 cm
- Second 6 months: approximately 8 cm
- Second year: just over 10 cm
- Third year: approximately 8 cm
- Fourth year: 7 cm
- Later childhood until puberty (5 to 10 years): growth averages 5 to 6 cm/year

2. Summarize growth velocity during the pubertal growth spurt.

Maximum growth rate is 11 to 13 cm/year.

In girls, growth spurt occurs early in puberty (breast Tanner stage II).

Growth spurt is later in boys (pubic hair Tanner stage III-IV, testicular volume 12-15 mL).

Some children may experience a transient period of slow growth just before the onset of puberty.

3. How is height measured accurately?

- The most essential tool for the detection of growth abnormalities is the ability to obtain accurate and reproducible measurements. This requires the availability of appropriate equipment as well as proper positioning of the patient.
- At all ages, children should be measured at full stretch with a straight spine, because this is the only position that will be reproducible.
- Children should be shoeless, and hair decorations or braids may need to be removed.
- Scales with floppy arms are unreliable.

4. What technique is used for infants up to 2 years of age?

Supine length should be measured in infants. Accurate measurement requires a supine stadiometer, a boxlike structure with a headboard and movable footplate. Two people are needed, with one holding the infant's head against the headboard while the other straightens the legs and places the ankles at 90 degrees against the movable footplate. The length is read from the attached measuring device, or marks are made for measurement by tape measure.

5. Describe the technique for children 2 years of age and older.

1. Standing height is measured. Accurate measurement requires a stadiometer with a rigid headboard, footplate, and backboard.
2. The child stands against the backboard, with heels, buttocks, thoracic spine, and head touching.
3. The measurer exerts upward pressure on the patient at the angle of the jaw to bring the spine into full stretch, and the headboard is lowered until it touches the top of the head. A counter reads the measurement.
4. If a stadiometer is not available, the child should stand against a wall in the same position as used for a stadiometer. A rigid right angle is moved downward to touch the top of the head, and a mark is made and measured.
5. Weight and head circumference (when appropriate) should be recorded.

6. How is height recorded?

The second critical tool for evaluation of growth is the standardized growth curve, and all measurements should be plotted rather than just recorded in the chart. A carefully constructed and up-to-date growth curve is critical to the recognition of growth abnormalities. Furthermore, the more points that are plotted on the curve, the greater the understanding of the child's growth. Thus efforts should be made to obtain growth measurements at all patient contacts, including illness visits, because well-child visits are infrequent during the middle childhood years when growth abnormalities are most common.

7. List the common errors in plotting growth charts.

Errors in plotting of growth points are a frequent cause of apparent growth abnormalities. Common errors include:

- Plotting the wrong height (e.g., plotting inches instead of centimeters)
- Not plotting the patient's height at the exact chronologic age (height should be plotted to the nearest month or decimal age)
- Use of an inappropriate growth chart

8. What is meant by "appropriate growth chart"?

A number of growth charts are available, and careful consideration should be given to the appropriate chart for a particular patient at a particular time. Commonly available growth charts include:

- Charts for plotting supine length (the 0- to 36-month charts in common use)
- Charts for plotting stature (i.e., standing height) (2- to 18-year charts)

Other specific growth charts are available and should be used when appropriate. These include:

- Ethnic-specific charts
- Growth charts specific for common syndromes (e.g., Turner's syndrome, Down syndrome, achondroplasia) should be used when appropriate

9. How do age and position affect growth measurements?

- A patient measured supine is slightly longer than the same patient measured standing up.
- Charting of a standing patient on a supine chart gives the erroneous impression of decreased growth velocity. This is a common cause of apparent growth abnormality in children aged 2 to 3 years who are measured standing up for the first time but whose measurements continue to be plotted on the supine chart.

10. What historic information is necessary for interpreting a growth chart?

- Birth history and birth weight
- Attainment of developmental milestones
- History of chronic illnesses
- Long-term medication use
- History of surgery or trauma
- Current symptoms
- Height of biological parents and family history of significant short stature
- Timing of parental puberty and family history of significant pubertal delay

11. What physical examination findings help interpret a growth chart?

- Signs of chronic illness
- Stigmata of a syndrome
- Specific signs of hormonal abnormality (thyroid deficiency, growth hormone [GH] deficiency, glucocorticoid excess)

12. How does radiologic imaging help interpret a growth chart?

- A bone-age film can provide important information about skeletal maturity. The degree of skeletal maturity is an important determinant of remaining growth potential and can help estimate expected height in children developing more slowly or more rapidly than their peers.

KEY POINTS 1: GENERAL GROWTH

1. Proper evaluation of growth depends on accurate measurement of height and correct plotting of measurements on the appropriate growth curve.
2. Common errors in plotting include plotting the wrong height, not plotting the patient's height at the exact chronologic age, and use of an inappropriate growth chart.
3. An abnormal growth velocity for age generally distinguishes growth abnormalities from normal growth variants.
4. Apparent abnormalities in growth are most frequently due to normal growth variants. Poor growth secondary to chronic medical illness is the next most frequent cause. Hormonal causes are less frequent.

- A radiograph of the left hand and wrist is obtained in children aged over 2 years, and maturation of epiphyseal centers is compared with available standards.

13. Explain the significance of parental target height or "midparental height."

Parental height helps determine expected adult height on the basis of genetic potential. Add the parents' heights in centimeters; add 13 cm if the child is male, and subtract 13 cm if the child is female; then divide by two. The resulting midparental height ± 5 cm gives the 10th to 90th percentile for offspring of those parents.

14. What is the most important factor in identifying an abnormal growth curve?

An abnormal growth velocity for age generally distinguishes growth abnormalities from normal growth variants. Although there are many causes of short stature, including genetic, short normal children grow normally, whereas children with a problem almost always have an abnormal growth velocity. For example, a child with stature in the fifth percentile who is growing with a normal growth velocity is less worrisome than the child whose stature has fallen from the 90th to the 75th percentile, even though the latter is taller than the former. Growth velocity abnormalities may, however, be subtle.

15. What causes abnormal growth in children?

Abnormalities in growth are most frequently due to either normal growth variants (familial short stature or constitutional delay of growth and puberty) or underlying chronic medical illness, either recognized or unrecognized. Hormonal causes are less frequent.

16. Which syndromes are associated with abnormal growth?

- Down syndrome
- Prader-Willi syndrome
- Turner's syndrome
- Noonan's syndrome
- Other chromosomal abnormalities

17. List nonendocrine diseases and treatments that may be associated with poor growth.

- Malnutrition
- Pulmonary disease (cystic fibrosis, asthma)
- Cardiac disease
- Rheumatologic disease
- Gastrointestinal disease (Crohn's disease, inflammatory bowel disease)
- Neurologic disease (ketogenic diet, stimulant medications)

- Renal disease
- Anemia
- Neoplasia
- Long-term glucocorticoid use

18. Using the tools of growth curve, bone age, and height, how does one distinguish between familial (genetic) short stature and other causes?

Children with familial short stature grow at a normal velocity for age but with stature below the normal curve. They also grow within the expected target height percentile (i.e., they are as tall as expected for their genetic potential). If a child's projected height (by extrapolation of the growth curve) falls within the target range, the likelihood is high that current height is explained by genetic factors. Children with familial short stature also have a bone age approximately equal to chronologic age.

19. Give an example of distinguishing familial short stature from other causes of short stature.

A 5-year-old whose height is below the third percentile, whose growth has traced a line parallel to the third percentile, whose height projects within the parental target range, and whose bone age is also 5 years is likely to have familial short stature. However, if the growth velocity is abnormal or projected height falls below the predicted range, other factors may be involved in the short stature (Figs. 25-1 and 25-2).

20. Other than familial short stature, what is the most common cause of short stature?

Constitutional delay of growth (constitutional short stature), which affects up to 2% of children, is characterized by short stature and delayed bone age and represents a normal growth pattern simply shifted to a later age. Affected children typically have a period of subnormal growth between 18 and 30 months of age, followed by normal growth velocity throughout the remainder of childhood. In accord with the delayed developmental pattern, bone age is delayed. The continuing growth delay also results in a delay in pubertal development and physical maturity. Such children (often boys) generally have a family history of a similar growth pattern and may have a more dramatic deceleration of growth velocity before they enter puberty than normal children. They complete their growth at a later age, reaching an adult height within the expected genetic potential (Fig. 25-3).

21. How is the diagnosis of constitutional delay of growth made?

The diagnosis of constitutional delay of growth based on the following criteria does not require further laboratory support:

- Period of slowed growth in the second year of life with downward crossing of percentile.
- Normal growth velocity during childhood but with stature below the expected percentile for family
- Delayed bone age
- Height prediction appropriate for family (Plot the current height at the patient's bone age and follow the resulting percentile to adult height. In constitutional delay, this generally leads to a projected height within the parental target range.)
- Positive family history, delayed dentition, and delayed puberty in adolescence

22. What is the effect of testosterone therapy on boys with constitutional delay of growth?

Short-term testosterone therapy for boys with constitutional delay (75-100 mg of long-acting testosterone esters given once a month for 6 months) accelerates growth and stimulates pubertal development without compromising final adult height or advancing bone age. Clinically the boys experience pubertal changes, including genital enlargement (but not testicular growth), growth of pubic and axillary hair, deepening of voice, body odor, and acne. There may be personality changes characteristic of early puberty as well.

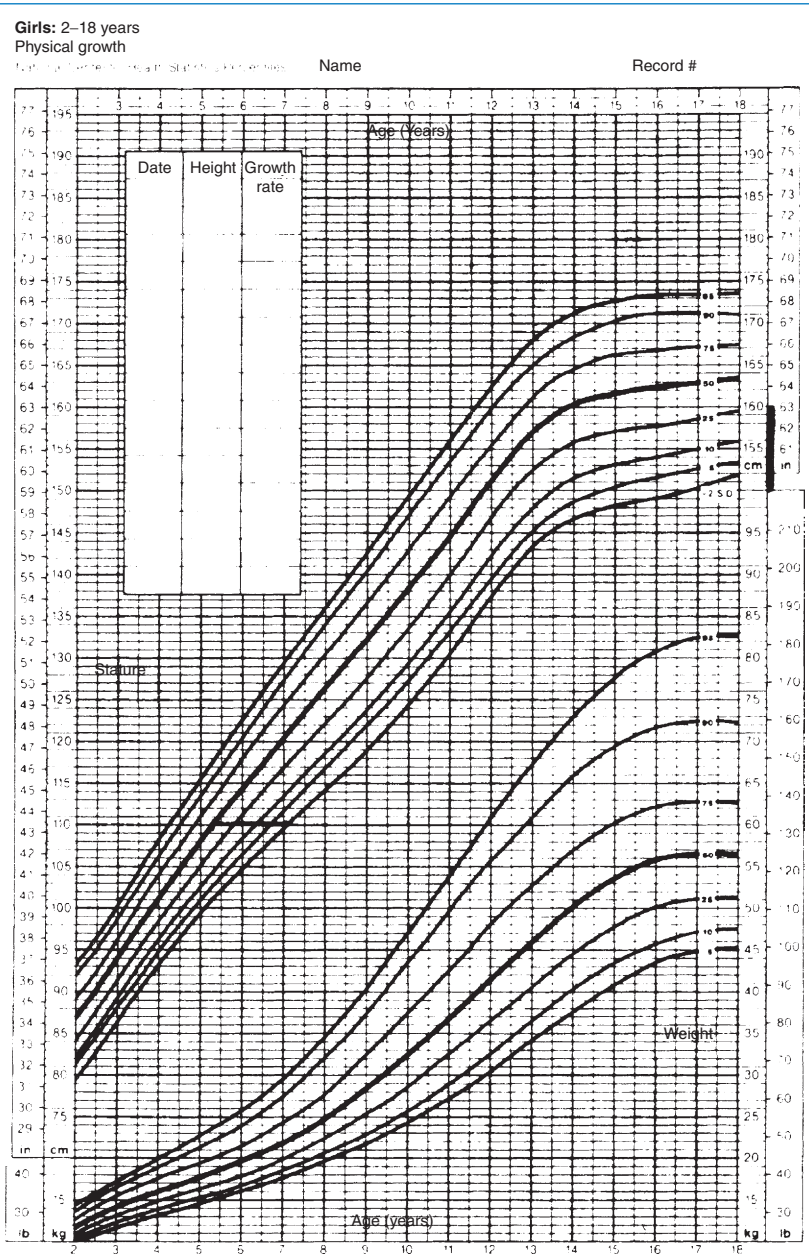


Figure 25-1. Growth chart for a 7-year-old girl with a height of 110 cm. Height age = 5 years, 3 months; bone age = 7 years; father's height = 65 inches (165 cm); mother's height = 62 inches (157 cm); corrected midparental height (± 1 SD) = 155 ± 5 cm; predicted adult height = 60 inches. The child has a predicted adult height within genetic potential and a bone age equal to chronologic age. She has genetic or familial short stature.

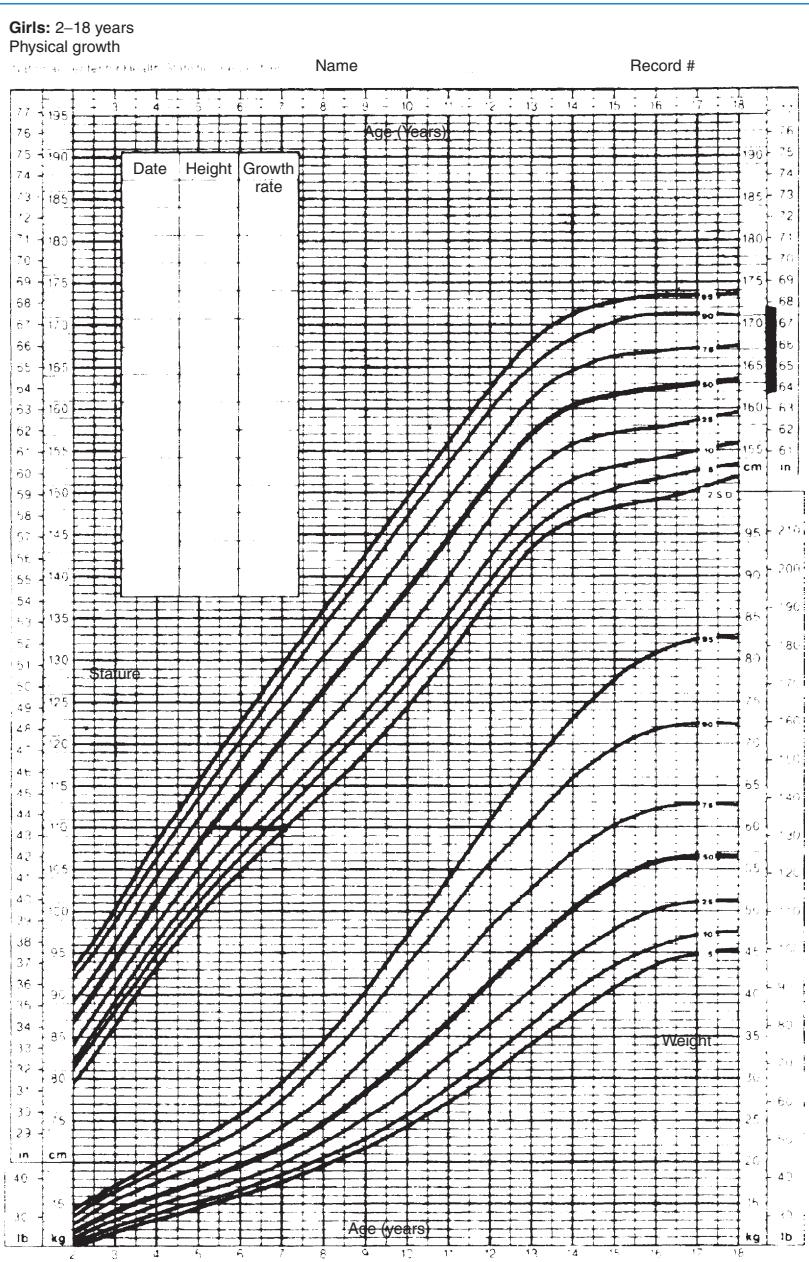


Figure 25-2. Growth chart for a 7-year-old girl with a height of 110 cm. Height age = 5 years, 3 months; bone age = 5 years; father's height = 70 inches (178 cm); mother's height = 66 inches (168 cm); corrected midparental height (± 1 SD) = 167. 5 ± 5 cm. The child is growing below the fifth percentile, but extrapolation of her growth curve to adult height gives a final height below genetic potential. Clearly her height cannot be attributed to genetic short stature alone.

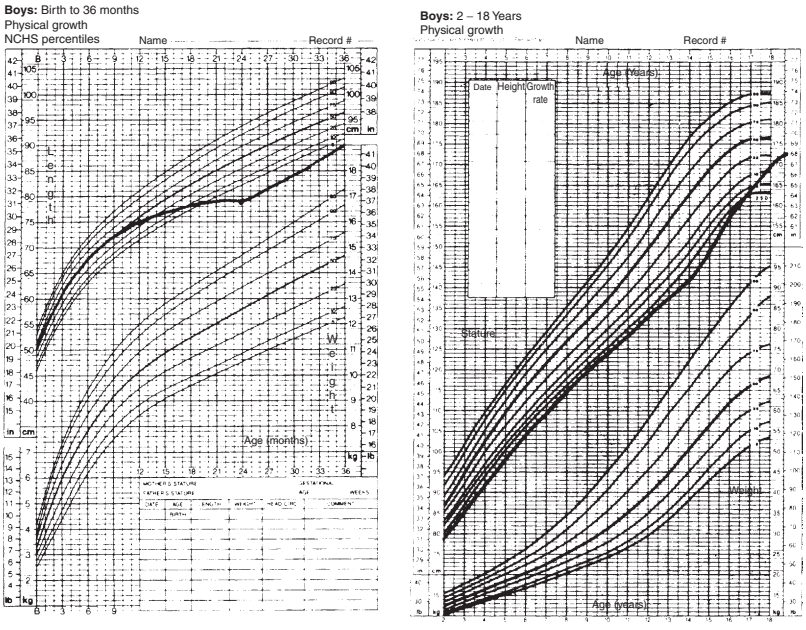


Figure 25-3. Growth charts for a patient with constitutional delay of growth. Subnormal velocity during the second year of life (left chart) followed by normal velocity through childhood and a prolonged growth period with eventual achievement of normal adult height (right chart).

23. List the endocrine causes for short stature in children, in order of prevalence.

- Hypothyroidism: congenital or acquired
- GH deficiency
- Glucocorticoid excess: iatrogenic or endogenous (less common)
- Pseudohypoparathyroidism

24. What laboratory measurements should be considered in evaluating a patient for short stature?

Laboratory tests should be designed to achieve two goals: (1) exclusion of undiagnosed chronic illness and (2) exclusion of specific disorders associated with poor growth.

25. Which laboratory tests help exclude undiagnosed chronic illness?

- Electrolyte measurements
- Blood urea nitrogen/creatinine measurement
- Liver transaminase measurements
- Complete blood count
- Erythrocyte sedimentation rate (ESR) measurement

26. Which laboratory tests help exclude gastrointestinal disorders associated with poor growth?

Because symptoms may be limited, the following tests are recommended:

- Celiac antibody (anti-tissue transglutaminase) test
- Inflammatory bowel disease screen if child has an elevated ESR or anemia

27. List the laboratory tests for genetic disorders associated with poor growth.

- Karyotype (Turner's syndrome): consider in all short girls
- Fluorescence in situ hybridization (FISH), for Prader-Willi syndrome
- Genetic test for PTPN11 mutation, for Noonan's syndrome

28. Which hormonal disorders should be excluded by laboratory results?

- Thyroid deficiency (thyroid-stimulating hormone [TSH] and total or free thyroxine [T_4])
- GH deficiency (see question 30)

29. Describe the causes of GH deficiency.

Most cases of GH deficiency are isolated and idiopathic. Idiopathic GH deficiency affects as many as 1:10,000 to 1:15,000 children. It is sporadic in the great majority of cases, but a rising number of specific gene mutations involved in the synthesis of GH or the regulation of its secretion is being reported. The other important underlying causes are listed in the following sections.

30. How is GH deficiency diagnosed?

The diagnosis of GH deficiency is primarily a clinical one, aided by laboratory support, rather than a diagnosis based on definitive testing. Most important is identifying the patient in whom such a diagnosis would be appropriate. Children with subnormal growth should be evaluated for GH deficiency only after a thorough search fails to reveal any other cause for growth delay.

31. List the components of the laboratory evaluation for GH deficiency.

- Measurement of the serum level of insulin-like growth factor 1 (IGF-1).
- Measurement of IGF-binding protein 3 may be useful in limited specific clinical situations (infancy, poor nutritional state), because IGF-1 may be low for reasons other than GH deficiency in these circumstances.
- Measurement of GH level.

32. Why is the serum level of IGF-1 important?

IGF-1 is a GH-dependent protein that is produced in target tissues in response to GH. Serum level of IGF-1 reflects production of the protein by the liver and gives an indirect indication of GH secretion. The following characteristics of IGF-1 should be kept in mind when its serum level is assessed:

- The concentration of IGF-1 remains constant during the day, unlike the GH level.
- The concentration of IGF-1 varies with age, and the reported value must be compared with appropriate age-specific and pubertal stage-specific norms available from performing laboratories.
- A low serum level of IGF-1 ($>$ 2 SD below the mean for age) is 70% to 80% predictive of low values on more rigorous tests of GH secretion.

33. Does a normal level of IGF-1 exclude GH deficiency?

A normal IGF-1 level is reassuring but does not rule out partial GH deficiency in the appropriate clinical context.

34. Does a low serum level of IGF-1 confirm the diagnosis of GH deficiency?

No. Poor nutrition, chronic disease, and hypothyroidism suppress IGF-1 concentrations. In addition, before the age of 6 years, the IGF-level is low, and the overlap between normal and GH-deficient levels renders its measurement highly insensitive.

35. How is GH testing done?

Because secretion of GH is episodic, random measurements are not helpful for the diagnosis of GH deficiency. GH must be formally measured in response to a series of stimuli. Various pharmacologic agents are used, but there is no consensus about which is optimal. The child must have fasted overnight, must be euthyroid, and must have no underlying chronic disease. In addition, at least two tests using different stimulating agents are generally performed.

36. How are the results of GH testing interpreted?

The normal GH response to stimulation testing depends on the stimulation test and the type of GH assay used. Failure of response to all tests with values equal to or greater than those expected for normal children is consistent with the diagnosis of classic GH deficiency.

Criteria for the diagnosis of partial GH deficiency and of neurosecretory dysfunction (normal pituitary response to stimuli, but low IGF-1, suggesting that endogenous GH secretion is impaired) are less well established.

37. How is idiopathic GH deficiency diagnosed?

GH deficiency can be isolated or associated with other pituitary hormone deficiencies. It can be congenital or can result from trauma or an intracranial neoplasm. All patients diagnosed with GH deficiency should undergo cranial imaging, unless the cause of the deficiency is previously known. Isolated GH deficiency without identifiable etiology is considered idiopathic.

38. How is GH deficiency treated?

GH for administration is available through recombinant DNA technology; the majority of children are treated with 6 or 7 daily shots per week at a total weekly dose of approximately 0.30 mg/kg administered subcutaneously. Because the effect of GH wanes after several years of therapy, it is common to see dramatic catch-up growth ($\approx$10-12 cm/year) in the first or second year of therapy, followed by velocities ranging from normal to 1.5 times normal in subsequent years.

39. What is the prognosis for adult height in treated children with GH deficiency?

Although nearly all treated children reach an adult height significantly better than predicted before therapy is initiated, many do not reach their predicted genetic potential. Children diagnosed and treated at earlier ages have better height prognoses than those whose therapy is initiated later. Similarly, the more mature the skeleton at diagnosis, the poorer the final outcome.

40. When is GH therapy discontinued?

In children with GH deficiency, the point of diminishing benefit of therapy correlates with skeletal maturity rather than chronologic age or duration of therapy. Therapy often is discontinued at a bone age of 15 years (96% of growth) to 16 years (98% of growth) in boys and 14 years (98% of growth) in girls. However, given what is now known about the effects of GH deficiency in adulthood, some patients with severe deficiencies may require lifelong hormonal replacement.

41. What other syndromes are considered indications for GH therapy?

GH is now approved by the U.S. Food and Drug Administration (FDA) for the treatment of short stature in the following conditions:

1. Chronic renal insufficiency before transplant
2. Turner's syndrome (45,XO or mosaic variants)
3. Acquired immunodeficiency syndrome–related wasting syndrome
4. Prader-Willi syndrome
5. Noonan's syndrome
6. Short stature due to intrauterine growth retardation in the absence of catch-up growth
7. Idiopathic short stature in boys with predicted adult height less than 63 inches and girls with predicted height less than 59 inches (normal GH secretion)

Indications 2 through 6 do not require demonstration of GH deficiency. The use of GH for treatment of idiopathic short stature remains controversial among pediatric endocrinologists.

42. What is the prognosis for girls with Turner's syndrome treated with GH?

Girls with Turner's syndrome generally demonstrate a significant increase in predicted adult height, with an average increase of 8.8 cm. The overall effectiveness of therapy, like that in GH deficiency, depends on chronologic age and bone age at initiation of treatment and on duration of treatment. Because GH therapy in Turner's syndrome normalizes height in younger girls,

estrogen replacement therapy can be initiated at an age similar to the age of puberty of the patient's peers.

43. What are the potential risks of GH therapy?

The side effects of GH therapy can be divided into three categories: (1) common but clinically unimportant, (2) uncommon with potential clinical importance, and (3) rare or theoretical.

44. List the common but clinically unimportant side effects of GH therapy.

- Acute correction of body water deficit after initiation of GH in deficient patients may lead to transient peripheral edema, headache, and joint aches and stiffness.
- Increased average glucose concentration.
- Increased systolic blood pressure.

45. List the uncommon side effects with potential clinical importance.

- Pseudotumor cerebri
- Slipped capital femoral epiphysis
- Glucose intolerance
- Worsening of underlying scoliosis

46. What rare or theoretical side effects may be associated with GH therapy?

- Increased risk for development of a secondary neoplasm: Reports now suggest a small increase in the long-term risk of secondary development of meningioma in childhood cancer survivors treated with GH.
- Analysis of large European databases has suggested a possible increase in cancer-related mortality in adults treated with GH as children. These reports are not yet confirmed.

47. Should children with idiopathic short stature (without GH deficiency) be treated with GH?

The FDA has approved the use of GH in children with idiopathic short stature with a predicted adult height less than 63 inches for boys and less than 59 inches for girls. However, the use of GH in children in whom no hormonal abnormality can be demonstrated continues to be intensely controversial among pediatric endocrinologists. Short-term studies involving small cohorts have demonstrated a consistent increase in growth velocity with GH therapy in such children. Several studies that monitored children to final height disagreed about the overall effectiveness of therapy. However, most studies agree that the increase in final adult height is limited and can be obtained only at significant financial cost. The decision to use GH in such children should be carefully considered and requires a thoughtful dialogue among child, family, and an experienced pediatric endocrinologist who knows the child well.

48. How does the pattern of growth in children with excessive glucocorticoids differ from the pattern in children with exogenous obesity?

Glucocorticoid excess, whether iatrogenic (common) or intrinsic (rare), results in impairment of linear growth. The mechanism reflects increased protein catabolism, increased lipolysis, and a decline in collagen synthesis. Glucocorticoids also suppress the pulsatile release of GH from the pituitary gland and the production of IGF-1 at the target organ. The net result is that children with steroid excess are frequently short. They also have an increased weight-to-height ratio and appear obese. Children with exogenous obesity, on the other hand, generally show accelerated linear growth; thus, they are not only obese but also tall for age.

49. What conditions are associated with excessive growth in childhood?

Relatively few conditions result in overgrowth during childhood. These include familial tall stature (stature appropriate for parental target), constitutional advanced growth, hormonal causes, and genetic syndromes.

50. Explain constitutional advanced growth.

Constitutional advanced growth is associated with advanced bone age, accelerated growth, and early puberty, with predicted adult height appropriate for parental target (see question 21). Obesity and familial factors may be involved.

51. List the hormonal causes of excessive growth.

- Hyperthyroidism
- Androgen excess
- GH excess (pituitary gigantism)
- Estrogen excess

52. Summarize the characteristics of GH excess in childhood.

GH excess is rare in children, in whom it causes tall stature (gigantism) rather than the bony overgrowth seen in adults (acromegaly). Diagnosis is based on the following laboratory results:

- Elevated values on random measurements of GH
- Extremely high levels of IGF-1
- Lack of suppression of GH during a standard glucose tolerance test

53. With what findings is androgen excess associated?

- Precocious puberty in boys
- Congenital adrenal hyperplasia
- Androgen-producing tumors

54. With what findings is estrogen excess associated?

- Precocious puberty in girls
- Estrogen-producing tumors

55. List the genetic syndromes associated with excessive growth.

- Klinefelter's syndrome (47,XXY): tall stature, small testes, delay of puberty
- Connective tissue disorders
- Marfan's syndrome: tall stature, arachnodactyly, joint laxity, lens displacement
- Stickler's syndrome
- Soto's syndrome (cerebral gigantism): macrocephaly, progressive macrosomia, dilated ventricles, retardation, advanced bone age
- Beckwith-Wiedemann syndrome: macroglossia, umbilical hernia, hypoglycemia, macrosomia in infancy
- Homocystinuria: arachnodactyly, retardation, homocystine in urine

KEY POINTS 2: GROWTH VARIANTS

1. Children with familial short stature grow at a normal velocity for age and within their expected target height percentile and have a bone age approximately equal to chronologic age.
2. Children with constitutional delay of growth have a period of slow growth in the second year of life but then grow with a normal growth velocity.
3. Children with constitutional delay of growth also have delayed bone age, height prediction appropriate for family, and delayed entry into puberty.
4. The diagnosis of a growth variant does not require laboratory confirmation, but growth should be followed over time to confirm the initial impression.

KEY POINTS 3: GROWTH HORMONE DEFICIENCY

1. GH deficiency is a clinical diagnosis.
2. Other causes of poor growth should be excluded.
3. Laboratory testing is supportive and confirmatory.
4. Laboratory measures include measurement of serum IGF-1 and GH stimulation testing.

BIBLIOGRAPHY

Carel JC: Management of short stature with GnRH agonist and co-treatment with growth hormone: a controversial issue, *Mol Cell Endocrinol* 254:226–233, 2006.

Clayton PE, Cianfarani S, Czernichow P, et al: Management of the child born small for gestational age through to adulthood: a consensus statement of the International Societies of Pediatric Endocrinology and the Growth Hormone Research Society, *J Clin Endocrinol Metab* 92:804–810, 2007.

Cytrynbaum CS, Smith AC, Rubin T, et al: Advances in overgrowth syndromes: clinical classification to molecular delineation in Sotos syndrome and Beckwith-Wiedemann syndrome, *Curr Opin Pediatr* 17:740–746, 2005.

Davenport ML: Evidence for early initiation of growth hormone and transdermal estradiol therapies in girls with Turner syndrome, *Growth Horm IGF Res* 16:591–597, 2006.

Lee MM: Clinical practice. Idiopathic short stature, *N Engl J Med* 354:2576–2582, 2006.

Myers SE, Carrel AL, Whitman BY, et al: Sustained benefit after 2 years of growth hormone on body composition, fat utilization, physical strength and agility, and growth in Prader-Willi syndrome, *J Pediatr* 137:42–49, 2000.

Quigley CA: Growth hormone treatment of non-growth hormone deficient disorders, *Endocrinol Metab Clin North Am* 36:131–186, 2007.

Rosenbloom AL, Connor EL: Hypopituitarism and other disorders of the growth hormone-insulin like growth factor-1 axis. In Lifshitz F, editor: *Pediatric endocrinology*, vol. 2, New York, 2007, Informa Healthcare, pp 65–100.

Zeitler PS, Meacham LR, Allen DB, et al: *Principles and Practice of Pediatric Endocrinology*, Springfield (IL), 2005, Charles C Thomas, pp 857–910.

GROWTH HORMONE USE AND ABUSE

Vanya D. Wagler, Samir J. Patel, and Homer J. LeMar Jr.

Growth hormone plays an essential role in human growth and development; deficiency results in short stature and other defects, whereas high levels can cause excessive growth and acromegaly. In addition to recognized medical indications for replacement, growth hormone has come to public attention because of its use by athletes to enhance performance (doping). This chapter covers the latest evidence about growth hormone physiology, therapeutic use, abuse, and detection.

1. What is growth hormone?

Growth hormone (GH) is the most abundant hormone in the anterior pituitary gland; it is a single-chain peptide hormone produced and secreted by somatotroph cells in the anterior pituitary gland in two molecular forms; 22-kilodalton (kDa) GH is more abundant than the 20-kDa form, but their biologic activities are similar. Measuring individual GH isoforms plays a key role in detection of doping by athletes. Endogenous GH production is highest during puberty, decreasing by middle age to only about 15% of peak levels.

2. How does GH secretion occur?

GH is secreted in a pulsatile fashion, mostly at night. Factors that increase secretion include sleep, exercise, trauma, and sepsis. Obesity and increasing age reduce GH secretion.

3. How is the release of GH regulated?

GH secretion is stimulated by GH-releasing hormone (GH-RH) and inhibited by somatostatin, both from the hypothalamus. Ghrelin, a gastric peptide, also stimulates GH release. Another major regulator of GH production is insulin-like growth factor-1 (IGF-1), which acts at the pituitary to directly inhibit GH production and at the hypothalamus to inhibit the production of GH-RH and to stimulate somatostatin.

4. List the actions of GH.

As its name implies, GH stimulates both linear growth and growth of internal organs (Table 26-1).

5. Does GH exert all of its effects directly?

No. Many of the effects are mediated by IGF-1, which is also called somatomedin C. GH stimulates the production of IGF-1 in peripheral tissues, particularly the liver. In patients with GH resistance, which is often due to GH receptor mutations, some effects of GH can be achieved by IGF-1 administration; IGF-1 has been approved for treatment of GH-resistant patients.

6. What causes excessive GH secretion, and what are the consequences?

The major cause of excessive GH secretion is a GH-producing pituitary tumor. GH excess during childhood results in gigantism. Numerous historical examples have been noted, including Robert Wadlow, the "Alton giant," who reached a height of just over 8 feet 11 inches and wore size 37AA shoes. GH excess after epiphyseal closure results in acromegaly.

7. What conditions are associated with GH deficiency?

GH deficiency can be congenital (genetic mutations) or may result from damage to the pituitary gland by intracranial tumors, surgery, radiation therapy, trauma, and a variety of infiltrative and infectious diseases. Adult-onset GH deficiency is much less common than onset during infancy and childhood and is often related to a preceding event such as radiation exposure or trauma.

TABLE 26-1. ACTIONS OF GROWTH HORMONE AT SPECIFIC SITES

TARGET SYSTEM	ACTIONS
Liver and muscle	Increases nitrogen retention, amino acid uptake, and protein synthesis
Cardiovascular	Increases cardiac muscle mass and cardiac output at rest and during maximal exercise
Hematologic	Increases plasma volume and red cell mass
Skeletal tissue	Increases bone mineral density and bone turnover
Connective tissue	Increases collagen turnover at nonskeletal sites, including tendons
Metabolism	Increases rates of sweating and thermal dispersion during exercise
Endocrine:	
Acute	Increases the uptake and utilization of glucose by muscle; antagonizes the lipolytic effect of catecholamines on adipose tissue
Chronic	Reduces glucose utilization, enhances lipolysis, and increases lean body mass

8. What are some common signs and symptoms of GH deficiency?

GH deficiency in childhood results in short stature; similar effects are seen in GH resistance. GH deficiency in adults causes greater adiposity and decreases in lean body mass, bone density, extracellular water, cardiac function, muscle force and strength, and exercise performance. Patients have reduced exercise capacity and strength levels and often complain of lethargy and fatigue. Quality of life may be diminished, with manifestations of depression, anxiety, mental fatigue, and decreased self-esteem. Excessive intraabdominal fat is associated with an increased risk of cardiovascular disease, which is the predominant cause of death in GH-deficient patients.

9. Where do we get the GH used therapeutically?

Historically, GH was derived from human cadavers; however, modern techniques have allowed for abundant production of biosynthetic GH, which is identical to the endogenous form.

10. Besides availability, what problem was associated with GH derived from human cadavers?

Creutzfeldt-Jakob disease, an uncommon, rapidly progressive, and fatal spongiform encephalopathy, has been reported to result from iatrogenic transmission through human cadaver pituitary tissue. More than 30 young adults who received human cadaver pituitary products have died of this disease, and at least 60 to 70 cases of Creutzfeldt-Jakob disease have been identified in recipients.

11. List the uses of GH approved by the U.S. Food and Drug Administration (FDA).

Historically, the only approved indication for GH therapy was treatment of short stature in children with GH deficiency. Currently, GH is also approved for treatment of short stature that is idiopathic or is associated with Turner syndrome, Prader-Willi syndrome, Noonan syndrome, or progressive chronic renal insufficiency in children. GH is also approved for treatment of wasting in patients with acquired immunodeficiency syndrome (AIDS) and for replacement in GH-deficient adults.

12. List the potential uses of GH.

GH has potential uses in the following conditions: (1) Russell-Silver syndrome, (2) chondrodysplasia in children, (3) steroid-induced growth suppression, (4) short stature associated with myelomeningocele, (5) any severe wasting state (e.g., wounds, burns, cancer), (6) normal aging, (7) non–islet cell tumor hypoglycemia, (8) gonadal dysgenesis, (9) Down syndrome, (10) short stature associated with neurofibromatosis, (11) human immunodeficiency virus (HIV)–associated adipose redistribution syndrome, and (12) osteoporosis.

13. How does GH help GH-deficient adults?

The reported beneficial effects in GH-deficient adults are an increase in muscle mass and function, reduction of total body fat mass, and increased plasma volume as well as improved peripheral blood flow. Reductions in serum total and low-density lipoprotein (LDL) cholesterol, reduction in diastolic blood pressure, a trend toward reduction in systolic blood pressure, and beneficial effects on bone metabolism and skeletal mass have also been documented. In addition, an improvement in psychological well-being and quality of life can occur with GH replacement.

14. How is GH administered?

GH is administered by subcutaneous injection. In children, the dose can be divided into twice-weekly, thrice-weekly, or daily regimens. Daily injections appear to give greater growth velocity than less frequent administration. In adults with GH deficiency, replacement is usually given daily.

15. Why is GH used as an ergogenic aid by athletes?

Some athletes have used GH in an effort to improve performance. Supraphysiologic doses of GH have been reported to increase lean body mass and reduce body fat in trained athletes. However, most studies suggest that GH administration has no beneficial effects on muscle strength, growth, or exercise performance in non–GH-deficient adults except for very modest gains in anaerobic exercise capacity. In general, GH appears to have less significant impact on performance than androgenic steroids. The possibility for modest gains with low likelihood of being caught may be the reason some athletes have used GH in the past.

16. What developments have been made in testing for GH abuse?

Prior to 2004, there was no reliable method to detect exogenous GH administration because of difficulties distinguishing it from endogenous hormone. After years of study and international collaboration, scientists developed a test that has been endorsed by the World Anti-Doping Association (WADA). In February 2010, the test identified the first GH doper, a British rugby player who was banned from competition for 2 years for the infraction. The test was used experimentally in 2004, and became widely available by 2010. The test's limitations include requiring a blood sample and the inability to detect GH use more than 1 or 2 days prior to testing.

17. Why was GH abuse so difficult to detect in the past?

GH was difficult to detect in the past because exogenously administered GH is identical in structure to endogenous hormone, so simply detecting GH in a blood sample was not evidence of doping. Additionally, endogenous GH is secreted in a pulsatile manner; therefore, detection of an increased level on random testing could simply reflect a natural peak, because GH secretion is stimulated by acute exercise. Cadaveric GH has also been used for doping purposes and is difficult to detect because of normal ratios of GH isomers.

18. How can GH abuse in athletes be detected?

GH doping can be detected by two distinct methods. The first method measures the ratio of the two isoforms of GH, and the second method measures the markers of GH action such as IGF-1 and procollagen III *N*-terminal propeptide (P-III-NP).

19. How prevalent is GH use among athletes?

The prevalence is not known, but GH use is thought to be widespread. Use of GH is probably not as extensive as use of anabolic-androgenic steroids. One limiting factor is the expense. Even a 1-month supply may cost several thousand dollars, depending on dosages.

20. What are the adverse effects of the therapeutic use of GH in adults?

Fluid retention causing edema and carpal tunnel syndrome are common in adults but not in children. Arthralgias, myalgias, paresthesias, and worsening glucose tolerance are also common and may be

present in up to one third of patients taking GH. Other potential side effects include gynecomastia, pancreatitis, behavioral changes, worsening of neurofibromatosis, scoliosis and kyphosis, and hypertrophy of tonsils and adenoids.

21. What are the adverse effects of GH in children?

Intracranial hypertension has been reported in children; this is most common in children with renal disease, although it has also been observed in children with GH deficiency and in girls with Turner syndrome. GH therapy is associated with an increased risk of slipped capital femoral epiphysis in the same three groups of children. Children with GH deficiency due to deletion of the GH gene may develop antibodies to GH, with secondary growth deceleration; this phenomenon is rare in other children.

22. What adverse effects occur in athletes using GH?

Little is known about side effects of GH use in athletes. Chronic abuse of supraphysiologic GH doses may lead to features of acromegaly, osteoarthritis, irreversible bone and joint deformities, increased vascular, respiratory, and cardiac abnormalities, hypertrophy of other organs, hypogonadism, diabetes mellitus, abnormal lipid metabolism, increased risk of breast and colon cancer, and muscle weakness due to myopathy. Use of GH in combination with anabolic androgenic steroids may increase left ventricular mass and cause cardiac remodeling.

23. Can GH reverse the natural aging process?

No. However, alternative medicine companies promote products alleged to stimulate increased production of GH in hopes of reversing normal aging. This theory has been sustained partly by a study suggesting that diminished secretion of GH is responsible for the effects of aging, including increased adipose tissue, decreased lean body mass, and thinning of the skin. Although GH replacement has a role in deficient individuals, no studies have shown that supplemental GH can reverse physiologic aging.

KEY POINTS 1: GROWTH HORMONE USE AND ABUSE

1. Growth hormone secretion is stimulated by exercise, stress, trauma, and signaling by growth hormone–releasing hormone and grehlin. Inhibition occurs by feedback from somatostatin and IGF-1.
2. Growth hormone abuse to enhance performance is thought to be prevalent in athletes, but little evidence supports meaningful performance enhancement, except for some increase in anaerobic exercise capacity.
3. Detection of GH doping has become possible on a large scale, including at the Olympic Games. Current testing relies on either altered GH isoform ratios or altered markers of GH action.
4. Long-term effects of supratherapeutic doses of GH in athletes are not known, but there is concern about multiple possible negative effects.

WEBSITES

Human Growth Foundation: http://www.hgfound.org.

Mayo Clinic: *Performance-enhancing drugs: know the risks*. http://www.mayoclinic.com/health/performance-enhancing-drugs/HQ01105.

World Anti-Doping Agency: http://www.wada-ama.org.

BIBLIOGRAPHY

Berrgren A, Ehrnborg C, Rosén T, et al: Short-term administration of supraphysiological growth hormone does not increase maximum endurance exercise capacity in healthy, active young men and women with normal GH-insulin-like growth factor I axes, *J Clin Endocrinol Metab* 90:3268–3273, 2005.

Bildlingmaier M, Manolopoulou J: Detecting growth hormone abuse in athletes, *Endocrinol Metab Clin N Am* 39:25–32, 2010.

Blackman M, Sorkin J, Munzer T, et al: Growth hormone and sex steroid administration in healthy aged women and men: a randomized controlled trial, *JAMA* 288:2282–2292, 2002.

Bouillanne O, Raenfray M, Tissandier O, et al: Growth hormone therapy in elderly people: an age-delaying drug? *Fundam Clin Pharmacol* 10:416–430, 1996.

Cooke DW, Divall SA, Radovick S: Normal and aberrant growth. In Melmed S, Polonsky KS, Larsen PR, et al, editors: *Williams textbook of endocrinology*, ed 12, Philadelphia, 2011, Saunders, pp 935–1053.

Cummings DE, Merriam GR: Growth hormone therapy in adults, *Annu Rev Med* 54:513–533, 2003.

Dean H: Does exogenous growth hormone improve athletic performance? *Clin J Sport Med* 12:250–253, 2002.

Holt RIG: Detecting growth hormone abuse in athletes, *Anal Bioanal Chem* 401:449–462, 2011.

Hurel SJ, Koppiker N, Newkirk J, et al: Relationship of physical exercise and aging to growth hormone production, *Clin Endocrinol* 51:687–691, 1999.

Jenkins PJ: Growth hormone and exercise, *Clin Endocrinol* 50:683–689, 1999.

Karila TA, Karjalainen JE, Mantysarri MJ, et al: Anabolic androgenic steroids produce dose-dependent increase in left ventricular mass in power athletes, and this effect is potentiated by concomitant use of growth hormone, *Int J Sports Med* 24:337–343, 2003.

Laron Z: Laron syndrome (primary growth hormone resistance or insensitivity): the personal experience 1958–2003, *J Clin Endocrinol Metab* 89:1031–1044, 2004.

Meinhardt U, Nelson AE, Hansen JL, et al: The effects of growth hormone on body composition and physical performance in recreational athletes, *Ann Intern Med* 152:568–577, 2010.

Melmed S, Jameson JL: Disorders of the anterior pituitary and hypothalamus. In Longo D, Fauci A, Kasper D, et al, editors: *Harrison's principles of internal medicine*, ed 18, pp 2876–2902, 2011. McGraw-Hill Professional

Melmed S, Kleinberg D, Ho K: Pituitary physiology and diagnostic evaluation. In Melmed S, Polonsky KS, Larsen PR, et al, editors: *Williams textbook of endocrinology*, ed 12, Philadelphia, 2011, Saunders, pp 175–228.

Molitch ME, Clemmons DR, Malozowski S, et al: Evaluation and treatment of adult growth hormone deficiency: an Endocrine Society clinical practice guideline, *J Clin Endocrinol Metab* 91:1621–1634, 2006.

Murray RD, Skillicorn CJ, Howell SJ, et al: Influences on quality of life in growth hormone-deficient adults and their effect on response to treatment, *Clin Endocrinol* 51:565–573, 1999.

Rodrigues-Arnao J, Jabbar J, Fulcher K, et al: Effects of growth hormone replacement on physical performance and body composition in growth hormone-deficient adults, *Clin Endocrinol* 51:53–60, 1999.

Rudman D, Feller A, Nagraj H, et al: Effects of growth hormone in men 60 years old, *N Engl J Med* 323:1–6, 1990.

Travis J: Pharmacology: growth hormone test finally nabs first doper, *Science* 327:1185, 2010.

Wallace JD, Cuneo RC: Growth hormone abuse in athletes: a review, *Endocrinologist* 10:175–184, 2000.

Weber MM: Effects of growth hormone on skeletal muscle, *Hormone Res* 58 (Suppl 3), 43–48, 2002.

CHAPTER 27

PRIMARY ALDOSTERONISM

Arnold A. Asp

1. Define primary aldosteronism.

Primary aldosteronism (PA) is a generic term for a group of disorders in which excessive production of aldosterone by the zona glomerulosa of the adrenal cortex occurs independently of normal renin-angiotensin stimulation. These primary disorders of the adrenal system are distinct from forms of secondary hyperaldosteronism due to excessive renin (renal artery stenosis, renin-producing tumors). The four most important clinical entities constituting PA are bilateral hyperplasia of the zona glomerulosa (commonly termed idiopathic hyperaldosteronism [IHA]), solitary aldosterone-producing adenoma (APA), adrenal carcinoma, and glucocorticoid-remediable aldosteronism. IHA and APA are the most important causes of PA.

2. How common are these disorders?

The most common manifestation of excess aldosterone secretion is hypertension. Cross-sectional and prospective studies indicate that up to 12% of the hypertensive population may have PA.

3. Aside from hypertension, what are the common clinical manifestations of primary aldosteronism?

Aldosterone normally acts at the renal distal convoluted tubule to stimulate reabsorption of sodium ions (Na), as well as secretion of potassium (K) and hydrogen ions (H) and at the cortical and medullary collecting ducts to cause direct secretion of H. Excess secretion of aldosterone in PA results in hypertension, potassium loss, and metabolic alkalosis; hypomagnesemia may also occur (Fig. 27-1). Spontaneous hypokalemia ($K < 3.5$ mmol/L), however, is an uncommon presenting manifestation of PA, occurring in only 9% to 37% of cases of PA. Therefore, normokalemic hypertension is the most common presentation. Vague symptoms are manifestations of hypokalemia: weakness, muscle cramping, paresthesias, headaches, hyperglycemia (insulinopenia), palpitations, polyuria, and polydipsia.

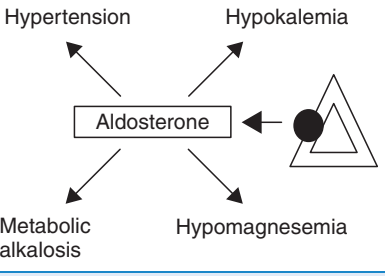


Figure 27-1. Primary aldosteronism. Triangles represent the adrenal gland with the outer layer being the adrenal cortex. The closed circle represents a tumor. The arrow represents hormone secretion.

4. Who should be screened for primary aldosteronism?

Hypertension affects 29% of the adult U.S. population; screening for PA must be judicious. Case detection should be targeted to four groups of patients:

- Patients with moderate to severe hypertension: Joint National Commission (JNC) stage 2 (BP 160-179 systolic/100-109 diastolic mm Hg) or stage 3 (> 180/> 110 mm Hg); PA prevalence 8% to 13%.
- Patients with resistant hypertension: BP higher than 140/90 mm Hg despite treatment with three antihypertensive medications; PA prevalence 17% to 23%.
- Hypertensive patients with spontaneous or diuretic-induced hypokalemia; PA prevalence 50%.
- Patients with adrenal incidentalomas who have hypertension; PA prevalence 1% to 10%.

Hypertension due to aldosterone excess causes enhanced perivascular inflammation and myocardial fibrosis; end-organ damage is therefore more severe than in essential hypertension. Screening and confirmation of the diagnosis are described in questions 14 and 16.

5. What is the most common form of primary aldosteronism?

Of the four causes mentioned in question 1, IHA is most common, accounting for up to 70% of cases in most series. IHA, also known as bilateral adrenal hyperplasia, is characterized by bilateral hyperplasia (diffuse and focal) of the zona glomerulosa layer of both adrenal glands. The most likely cause is supranormal sensitivity of the zona glomerulosa in affected adrenal glands to physiologic concentrations of angiotensin II.

6. What is the second most common cause of primary aldosteronism?

APAs account for up to 30% of cases of PA. APAs are small (< 2 cm), occur more commonly in the left adrenal gland, and are composed of zona glomerulosa cells, zona reticularis cells, and hybrid cells with characteristics of both layers. APAs are also known as Conn's syndrome.

7. Why differentiate between IHA and APA?

APAs are a surgically curable form of PA; IHA is not. APAs produce greater amounts of aldosterone than other forms of PA; consequently, the degrees of hypertension and biochemical abnormalities tend to be more severe. APAs demonstrate partial autonomy of function, secreting aldosterone in response to stimulation by corticotropin (ACTH) but not by angiotensin II. Aldosterone synthesis by these tumors, therefore, parallels the normal circadian rhythm of ACTH secretion, with the highest serum aldosterone concentrations occurring in the mornings and the lowest in the evenings.

8. How do symptoms of IHA differ from symptoms of APA?

Aldosterone is produced in smaller amounts in IHA than in APA; therefore the degree of hypertension, hypokalemia, hypomagnesemia, and metabolic alkalosis is less dramatic. Serum aldosterone levels tend to rise during upright posture, perhaps owing to greater sensitivity to angiotensin II.

9. How commonly does adrenal cancer cause primary aldosteronism?

Adrenal carcinoma as a cause of PA is rare. The tumors are very large (> 6 cm) and commonly metastatic at the time of diagnosis. All cases of PA should be imaged with computed tomography (CT) to exclude this rare cause of PA.

10. What is glucocorticoid-remediable aldosteronism?

In this rare cause of PA, production of mineralocorticoid is stimulated solely by ACTH. The disorder is inherited in an autosomal-dominant fashion.

11. How is aldosterone synthesis normally regulated in the zona glomerulosa?

Humans possess two mitochondrial 11β-hydroxylase isoenzymes that are responsible for cortisol and aldosterone synthesis (designated CYP11B1 and CYP11B2). Both are encoded on chromosome 8. CYP11B1, which is responsible for conversion of 11-deoxycortisol to cortisol, is expressed only in the zona reticularis. CYP11B2, which is responsible for the conversion of corticosterone to aldosterone, is expressed only in the zona glomerulosa. CYP11B1 activity is stimulated by ACTH, whereas CYP11B2 is stimulated by angiotensin II or hyperkalemia.

12. Explain the genetic basis of glucocorticoid-remediable aldosteronism.

Glucocorticoid-remediable aldosteronism results from a heritable mutation that causes the fusion of the promoter region of the CYP11B1 gene with the structural region of the CYP11B2 gene. The resulting chimeric gene responds to ACTH with overproduction of aldosterone, as well as precursors 18-hydroxycortisol and 18-oxocortisol. These metabolites of the cortisol C-18 oxidation pathway are biochemical markers that facilitate identification of affected kindreds. Excessive aldosterone secretion may be inhibited by administration of glucocorticoids that suppress ACTH secretion by the pituitary.

13. How is primary aldosteronism diagnosed?

The diagnosis of PA is based on the demonstration of inappropriately elevated plasma aldosterone concentration (PAC) with concomitantly suppressed plasma renin activity (PRA). Although hypokalemia is suggestive of PA, normokalemic hypertension is the most common presentation.

14. How are patients screened for primary aldosteronism?

The most sensitive screening test is the aldosterone/renin ratio (ARR). Concomitant PAC and PRA values are obtained from a specimen collected in the office (PAC in ng/dL; PRA in ng/mL/h) from a patient who has been out of bed for at least 2 hours and seated for 5 to 15 minutes. Preparation prior to screening includes correction of hypokalemia to more than 3.5 mmol/L, a sodium-unrestricted diet, and withdrawal of medications proven to alter the ARR (spironolactone, eplerenone, amiloride, triamterene, potassium wasting diuretics) for 4 weeks. ARR greater than 30 with PAC exceeding 15 ng/dL raises the possibility of PA.

15. Will antihypertensive agents alter the ARR results?

Nearly every patient screened for PA has begun therapy with one or more antihypertensives. Medications mentioned in question 14 must be withdrawn. Potentially, beta-adrenergic blockers, central alpha-2-receptor agonists, and renin inhibitors all greatly reduce PRA and slightly reduce PAC. Potentially, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and dihydropyridine calcium channel blockers all greatly increase PRA and slightly reduce PAC. These commonly used medications rarely alter the results of ARR, but if a nondiagnostic result is encountered, alternative antihypertensive drugs may be substituted for the potential offending agents for 2 weeks, and the test repeated. The following medications have little effect on the ARR and may be substituted for temporary control during ARR testing: verapamil–slow release, hydralazine, prazosin, doxazosin, and terazosin.

16. How is the diagnosis of primary aldosteronism confirmed?

Several tests confirm PA. The most commonly used is the oral sodium loading test. Intravascular volume expansion should normally suppress aldosterone secretion. In the oral sodium loading test, the patient consumes more than 200 mmol (6 g) of dietary sodium for 3 days, and then from day 3 through day 4, a 24-hour urine collection for aldosterone and sodium is collected. Urinary excretion of aldosterone (high-performance liquid chromatography–tandem mass spectrometry) that exceeds 12 μg/day confirms a diagnosis of PA. Urinary sodium excretion of at least 200 mmol/day ensures adequacy of the test. An alternative test is acute volume expansion by intravenous administration of 2 L of normal saline over 4 hours with measurement of PAC at baseline and at the end of the saline infusion. Failure of the PAC at 4 hours to fall to less than 50% of the baseline PAC also confirms the diagnosis.

17. After confirmation of primary aldosteronism, why is it important to differentiate APA from IHA?

APA is amenable to surgical resection of the involved adrenal gland, whereas IHA is usually treated medically.

18. Does CT or magnetic resonance imaging (MRI) aid in differentiation?

To a limited extent, both localizing procedures may aid in identifying the cause of PA. A large APA may be discernible on high-resolution CT, which at some institutions can identify adenomas as small as 5 mm.

MRI at present performs as well as CT in identifying APA but involves higher cost and longer scan time. The diagnostic accuracy of MRI or CT in preoperatively localizing an APA has been reported to be 70% to 85%, but accuracy declines in older populations, in whom incidental hormonally inactive adrenal masses are more common. Some experts believe that biochemically silent adrenal masses are so rare in patients younger than 40 years that no further evaluation is necessary. In patients older than 40 years, adrenal venous sampling (AVS) must be performed to verify unilateral aldosterone production (see question 19). Adrenal carcinoma, a rare cause of PA, is easily identified with either CT or MRI. See also Chapter 29 for more on this topic.

19. Which localizing test is required if CT or MRI suggests an APA in a patient older than 40 years?

A more invasive localizing procedure to differentiate a normal adrenal gland from one containing an adenoma is AVS. Many institutions believe AVS should be performed before surgical intervention for an APA is considered. In this procedure, catheters are introduced into the left and right adrenal veins and the inferior vena cava. Levels of PAC are determined from these sites, along with concomitant cortisol levels following infusion of cosyntropin (synthetic ACTH). Cortisol levels are determined to ensure that the adrenal veins are properly catheterized. PAC/cortisol is referred to as "cortisol-corrected" aldosterone. APAs produce large amounts of aldosterone; the normal adrenal vein PAC is 100 to 400 ng/dL, whereas APAs may generate concentrations of 1000 to 10,000 ng/dL. The ratio of PAC/cortisol produced on the affected side versus the unaffected side always exceeds 4:1. When compared with CT scan results, discordant AVS results are found in up 30% of cases.

20. Explain the difficulty with adrenal venous sampling.

Collection of an aldosterone and cortisol specimen from the left adrenal gland is relatively simple, because the venous effluent drains directly into the left renal vein. The venous flow from the right adrenal, however, goes directly into the inferior vena cava. Catheterization of the right adrenal vein is difficult because of the few angiographic landmarks. Contrast material used to localize the right adrenal gland can cause corticomedullary hemorrhage during the procedure.

21. How accurate is adrenal venous sampling?

Overall, the procedure is over 90% accurate in localizing APA.

22. How is the patient with APA managed?

The patient undergoes screening tests, as described in question 15. The diagnosis of PA is confirmed with 24-hour urine collection for aldosterone measurement during oral salt loading, as described in question 16. AVS reveals a 4:1 gradient between the adenoma and the "normal" adrenal, and surgical resection of the affected adrenal is considered.

23. What should be done after the APA is localized?

After the APA is localized, unilateral adrenalectomy is performed. Laparoscopic resection is now widely available and is preferable to the open posterior approach. One year postoperatively, 70% of patients so treated are normotensive. By the fifth postoperative year, only 53% remain normotensive. Normal potassium balance tends to be permanent.

24. Do all patients with APA require surgery?

No. Although surgical resection is preferred, patients who have other comorbid conditions that preclude surgery may be successfully treated medically as described in question 28.

25. How is a patient with IHA managed?

The patient undergoes screening and confirmatory tests, as described in questions 15 and 16. CT does not reveal unilateral enlargement of the adrenals, and AVS does not show a unilateral abnormality. After the diagnosis of IHA is made, the patient is scrupulously sequestered from surgical colleagues.

KEY POINTS 1: PRIMARY ALDOSTERONISM

1. Spontaneous hypokalemia in a hypertensive patient should suggest the possibility of primary or secondary aldosteronism—but normokalemic hypertension is the most common presentation.
2. Primary aldosteronism may be due to bilateral hyperplasia or a small adrenal adenoma.
3. The best screen for primary aldosteronism is a PAC/PRA ratio greater than 30, with PAC greater than 15 ng/dL.
4. Primary aldosteronism is confirmed with a 24-hour urine aldosterone level greater the 12 μg/day after salt loading.
5. Because computed tomography and magnetic resonance imaging are often unable to distinguish adenomas from hyperplasia, adrenal venous sampling may be necessary to localize the lesion.
6. Adenomas are treated surgically; bilateral hyperplasia is treated pharmacologically.

26. What is the agent of choice for pharmacologic treatment of IHA?

Pharmacologic therapy is effective. The agent of choice is spironolactone (25-200 mg bid), a competitive mineralocorticoid receptor antagonist. Hypokalemia corrects dramatically, whereas hypertension responds after 4 to 8 weeks. Unfortunately, spironolactone also interferes with the action of androgens, causing decreased libido, impotence, and gynecomastia in men and menstrual irregularities in women. Eplerenone (50 mg b.i.d.) is a selective mineralocorticoid receptor antagonist with 60% of the potency of spironolactone, but without many of the side effects of the latter. Eplerenone is more costly and there are fewer long-term data available for this agent.

27. What other pharmacologic options are available?

In patients intolerant of the agents discussed in question 26, amiloride (5-15 mg b.i.d.) corrects hypokalemia within several days. A concomitant antihypertensive agent is usually necessary to reduce blood pressure. Success also has been reported in IHA treated with calcium channel blockers (calcium is involved in the final common pathway for aldosterone production) and angiotensin-converting enzyme inhibitors (IHA appears to be sensitive to low concentrations of angiotensin II).

28. How is a patient with glucocorticoid-remediable aldosteronism managed?

This disorder is discussed in questions 11 and 13. Therapy with low dosages of dexamethasone (0.75 mg/day) or any of the agents used for therapy of IHA (see questions 25 and 26) may be effective.

BIBLIOGRAPHY

Dluhy RG, Lifton RP: Glucocorticoid-remediable aldosteronism, *J Clin Endocrinol Metab* 84:4341–4344, 1999.

Fardella CE, Mosso L, Gomez-Sanchez C, et al: Primary hyperaldosteronism in essential hypertensives: prevalence, biochemical profile, and molecular biology, *J Clin Endocrinol Metab* 85:1863–1867, 2000.

Funder JW, Carey RM, Fardella CE, et al: Case detection diagnosis, and treatment of patients with primary aldosteronism: an Endocrine Society Clinical Practice Guideline, *J Clin Endocrinol Metab* 93:3266–3281, 2008.

Jossart GH, Burpee SE, Gagner M: Surgery of the adrenal glands, *Endocrinol Metab N Am* 29:57–68, 2000.

Liftin RP, Dluhy RG, Powers M, et al: A chimaeric 11-hydroxylase/aldosterone synthetase gene causes glucocorticoid-remediable aldosteronism and human hypertension, *Nature* 355:262–265, 1992.

Lim PO, Young WF, MacDonald TM: A review of the medical treatment of primary aldosteronism, *J Hypertens* 19:353–361, 2001.

Magill SB, Raff H, Shaker JL, et al: Comparison of adrenal vein sampling and computed tomography in the differentiation of primary aldosteronism, *J Clin Endocrinol Metab* 86:1066–1071, 2001.

Milliez P, Girerd X, Plouin PF, et al: Evidence for an increased rate of cardiovascular events in patients with primary aldosteronism, *J Am Coll Cardiol* 45:1243–1248, 2005.

Mulatero P, Rabbia F, Milan A, et al: Drug effects on aldosterone/plasma renin activity ratio in primary aldosteronism, *Hypertension* 40:897–902, 2002.

Mulatero P, Stowasser M, Loh K, et al: Increased diagnoses of primary aldosteronism, including surgically correctable forms, in centers from five continents, *J Clin Endocrinol Metab* 89:1045–1050, 2004.

Rossi G, Bernini G, Desideri G, et al: Renal damage in primary aldosteronism: results of the PAPY study, *Hypertension* 48:232–238, 2006.

Rossi P: Diagnosis and treatment of primary aldosteronism, *Endocrinol Metab N Am* 40:313–332, 2011.

Schwartz GL: Screening for adrenal-endocrine hypertension: overview of accuracy and cost-effectiveness, *Endocrinol Metab Clin N Am* 40:279–294, 2011.

Schwartz GL, Turner ST: Screening for primary aldosteronism in essential hypertension: diagnostic accuracy of the ratio of plasma aldosterone concentration to plasma renin activity, *Clin Chem* 51:386–394, 2005.

Tan YY, Ogilvie JB, Triponez E, et al: Selective use of adrenal venous sampling in the lateralization of aldosterone-producing adenomas, *World J Surg* 30:879–885, 2006.

Tanabe A, Naruse M, Takagi S, et al: Variability in the renin/aldosterone profile under random and standardized sampling conditions in primary aldosteronism, *J Clin Endocrinol Metab* 88:2489–2492, 2003.

Tiu SC, Choi CH, Shek CC, et al: The use of aldosterone-renin ratio as a diagnostic test for primary hyperaldosteronism and its test characteristics under different conditions of blood sampling, *J Clin Endocrinol Metab* 90:72–78, 2005.

CHAPTER 28

PHEOCHROMOCYTOMA

Arnold A. Asp

1. What is a pheochromocytoma?

A pheochromocytoma is an adrenal medullary tumor composed of chromaffin cells and capable of secreting biogenic amines and peptides, including epinephrine, norepinephrine, and dopamine. These tumors arise from neural crest–derived cells, which also give rise to portions of the central nervous system and the sympathetic (paraganglion) system. Because of this common origin, neoplasms of the sympathetic ganglia, such as neuroblastomas, paragangliomas, and ganglioneuromas, may produce similar amines and peptides.

2. How common are pheochromocytomas?

Pheochromocytomas are relatively rare. Data from the Mayo Clinic indicate that pheochromocytomas occur in 2 to 8 per million people per year; autopsy data from the same institution reflect an incidence of 0.3% (3/1000 autopsies), indicating that many pheochromocytomas go undetected during life. The incidence of pheochromocytoma from other countries, such as Japan, is lower, 0.4 cases per million people per year.

3. Where are pheochromocytomas located?

Nearly 90% of tumors arise within the adrenal glands, whereas approximately 10% are extra-adrenal and therefore classified as paragangliomas. Sporadic, solitary pheochromocytomas are located more commonly in the right adrenal gland, but familial forms (10% of all pheochromocytomas) are bilateral and multicentric. Bilateral adrenal tumors raise the possibility of multiple endocrine neoplasia 2A or 2B (MEN-2A or MEN-2B) syndromes (see Chapter 51).

4. Where are paragangliomas found?

Paragangliomas occur most commonly within the abdomen but also have been described along the entire sympathetic paraganglia chain from the base of the brain to the testicles. The common locations for paragangliomas are the organ of Zuckerkandl, the aortic bifurcation, and the bladder wall; the mediastinum, heart, carotid arteries, and glomus jugulare bodies are less frequent.

5. Can pheochromocytomas metastasize?

Yes. Demonstration of a metastatic focus in tissue normally devoid of chromaffin cells is the only accepted indication that a pheochromocytoma is malignant. Metastasis occurs in 3% to 14% of cases. The most common sites of metastases are regional lymph nodes, liver, bone, lung, and muscle.

6. What is the rule of 10s for pheochromocytomas?

Approximately 10% are extra-adrenal, 10% bilateral, 10% familial, and 10% malignant.

7. What are the common clinical features of a pheochromocytoma?

The signs and symptoms of a pheochromocytoma are variable. The classic triad, consisting of sudden severe headaches, diaphoresis, and palpitations, carries a high degree of specificity (94%) and sensitivity (91%) for pheochromocytoma in a hypertensive population. The absence of all three symptoms reliably excludes the condition. Hypertension occurs in 90% to 95% of cases and is paroxysmal in 25% to 50% of these (Fig. 28-1). Orthostatic hypotension occurs in 40% of cases because of hypovolemia and impaired arterial and venous constriction responses. Tremor, pallor, and anxiety may also be accompanying signs, whereas flushing is uncommon.

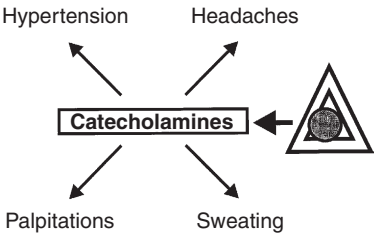


Figure 28-1. Classic manifestations of pheochromocytoma. Triangles represent the adrenal gland with the inner layer being the adrenal medulla. The closed circle represents a tumor. The arrow represents hormone secretion.

8. What are some of the nonclassic manifestations of pheochromocytomas?

Signs and symptoms of other endocrine disorders may dominate the presentation of a pheochromocytoma. Tumors may elaborate corticotropin (ACTH) with resultant manifestations of Cushing's syndrome and hypokalemic alkalosis. Vasoactive intestinal peptide (VIP) may be produced, resulting in severe diarrhea and hypokalemia. Hyperglycemia, resulting from catecholamine-associated antagonism of insulin release, and hypercalcemia, resulting from adrenergic stimulation of the parathyroid glands or elaboration of parathyroid hormone–related peptide (PTHrP), have also been encountered. Lactic acidosis may occur as a result of catecholamine-associated decrements in tissue oxygen delivery.

9. Discuss the cardiovascular manifestations of pheochromocytomas.

Cardiovascular manifestations of pheochromocytomas include arrhythmias and catecholamine-induced congestive cardiomyopathy. Atrial and ventricular fibrillations commonly result from precipitous release of catecholamines during surgery or from therapy with tricyclic antidepressants, phenothiazines, metoclopramide, and naloxone. Although cardiogenic pulmonary edema may result from cardiomyopathy, noncardiogenic pulmonary edema may also occur as a result of transient pulmonary vasoconstriction and increased capillary permeability.

10. Describe the intracerebral symptoms related to pheochromocytoma.

Seizures, altered mental status, and cerebral infarctions may occur as a result of intracerebral hemorrhage or embolization.

11. What do pheochromocytomas elaborate?

Most pheochromocytomas secrete norepinephrine. Tumors that produce epinephrine are more commonly intra-adrenal, because the extra-adrenal sympathetic ganglia do not contain phenylethanolamine-*N*-methyltransferase (PNMT), which converts norepinephrine to epinephrine. Dopamine is most commonly associated with malignant tumors.

12. Why is the blood pressure response among patients with pheochromocytomas so variable?

- Pheochromocytomas elaborate different biogenic amines. Epinephrine, a beta-adrenergic stimulatory vasodilator that causes hypotension, is secreted by some intra-adrenal tumors, whereas norepinephrine, an alpha-adrenergic stimulatory vasoconstrictor that causes hypertension, is produced by most intra-adrenal and all extra-adrenal tumors.
- Tumor size indirectly correlates with plasma catecholamine concentrations. Large tumors (> 50 g) manifest slow turnover rates and release catecholamine degradation products, whereas small tumors (< 50 g) with rapid turnover rates elaborate active catecholamines.

- Tissue responsiveness to ambient catecholamine concentrations does not remain constant. Prolonged exposure of tissue to increased plasma catecholamines causes downregulation of alpha-1 receptors and tachyphylaxis. Plasma catecholamine levels therefore do not correlate with mean arterial pressure.

13. How is a pheochromocytoma diagnosed?

The diagnosis of pheochromocytoma depends on the demonstration of excessive plasma or urine catecholamine levels or urine degradation products. The plasma free metanephrine (PMN) test is probably the best screening method; specificity exceeds that of urinary metanephrine measurement (89% vs. 69%, respectively). Normal PMN values usually reliably exclude pheochromocytoma. Fourfold elevations of PMN values are associated with nearly 100% probability of a pheochromocytoma. The PMN specimen should be drawn with the patient supine for 15 minutes following an overnight fast.

14. How is pheochromocytoma differentiated from essential hypertension?

Confirmation of elevated PMNs involves measurement of urinary metanephrine, normetanephrine (NMN), vanillylmandelic acid (VMA), and free catecholamines produced in a 24-hour period. The ability of such measurements to differentiate pheochromocytomas from essential hypertension varies among institutions: for VMA, sensitivity is 28% to 56% and specificity is 98%; for MN and NMN, sensitivity is 67% to 91% and specificity is 100%; and for free catecholamines, sensitivity is 100% and specificity is 98%. Renal failure may falsely elevate values. Many groups advocate 24-hour urinary levels of metanephrine and catecholamines as good screening tests. Yield is improved when urine is collected after a paroxysmal episode of symptoms.

15. What conditions may alter the diagnostic tests discussed earlier?

Older assays for VMA were sensitive to dietary vanillin and phenolic acids, requiring patients to restrict their intake of such substances. High-pressure liquid chromatography assays have eliminated most false-positive results due to diet and drugs that alter the metabolism of catecholamines.

16. Which drugs alter the metabolism of catecholamines?

- Drugs that reduce plasma and urine concentrations: alpha-2-receptor agonists, calcium channel blockers (long-term therapy), angiotensin-converting enzyme inhibitors, bromocriptine
- Drugs that decrease VMA and increase catecholamines and MN: methyldopa, monoamine oxidase inhibitors
- Drugs that increase plasma or urine catecholamines: alpha-1-receptor blockers, beta-blockers, labetalol
- Drugs that produce variable changes in any test: phenothiazines, tricyclic antidepressants, levodopa

17. What other medications may interfere with test results?

- Methylglucamine in radiocontrast agents (decreases metanephrine)
- Methenamine mandelate (decreases urinary catecholamines)
- Clofibrate (decreases VMA)
- Nalidixic acid (increases VMA)

18. List two other conditions that may interfere with test results.

- Stimulation of endogenous catecholamines: physiologic stress (ischemia, exercise), drug withdrawal (alcohol, clonidine), vasodilator therapy (nitroglycerin, acute calcium channel blocker administration)
- Administration of exogenous catecholamines: appetite suppressants, decongestants

19. What other biochemical tests are available?

Cases in which screening tests are equivocal may warrant a clonidine suppression test. This test employs a centrally acting alpha-2-receptor agonist that, in patients without a pheochromocytoma, suppresses neurogenically mediated release of catecholamines through the sympathetic nervous system. Blood samples to assess plasma catecholamines (norepinephrine and epinephrine) are drawn through an indwelling venous catheter; clonidine, 0.3 mg, is administered orally; plasma catecholamines are sampled again at 1, 2, and 3 hours. Plasma catecholamine values decrease to less than 500 pg/mL in patients with essential hypertension but exceed this level in patients with pheochromocytomas.

20. Compare computed tomography and magnetic resonance imaging for localization of pheochromocytomas.

The majority of tumors are larger than 3 cm, rendering them detectable by computed tomography (CT) or magnetic resonance imaging (MRI). CT, with special attention to the adrenal glands and pelvis, is advocated as the initial localizing procedure (97% are intra-abdominal). CT is the most cost-effective means of localization. Many authorities also recommend MRI as an adjunctive localizing modality. Advantages of MRI include the lack of radiation exposure and a characteristic hyperintensity on T_2-weighted image. The hyperintense image allows definition of tumor size, differentiation from vascular structures, and identification of unsuspected metastases. Also see Chapter 29 for a discussion of adrenal imaging.

KEY POINTS 1: PHEOCHROMOCYTOMA

1. Episodic headache, diaphoresis, and palpitations in a hypertensive patient suggest pheochromocytoma.
2. Ten percent of pheochromocytomas are bilateral, 10% extra-adrenal, 10% familial, and 10% malignant.
3. The best screening assay for pheochromocytoma is measurement of plasma free metanephrines.
4. Confirmation of the diagnosis of pheochromocytoma is elevated 24-hour urine levels of metanephrines and catecholamines.
5. Tumor localization is accomplished with computed tomography (most cost-effective) or magnetic resonance imaging (T_2-weighted phase).
6. Therapy is surgical resection after administration of alpha-adrenergic blockade followed by beta-adrenergic blockade.

21. What other modalities are useful for localization of pheochromocytomas?

Scintigraphic localization with meta-iodobenzylguanidine I 123 (MIBG) may also reveal unsuspected metastases. MIBG is actively concentrated by sympathomedullary tissue and is subject to interference by drugs that block reuptake of catecholamines (tricyclic antidepressants, guanethidine, labetalol).

22. Summarize the performance criteria of each localizing procedure.

See Table 28-1.

23. How are pheochromocytomas treated?

Surgical resection is the only definitive therapy.

24. Why is preoperative preparation with alpha-adrenergic blockade recommended?

Alpha-adrenergic blockade reduces the incidence of intraoperative hypertensive crisis and postoperative hypotension. The most commonly used agent is phenoxybenzamine, a long-acting, noncompetitive

TABLE 28-1. PERFORMANCE OF LOCALIZING TESTS FOR PHEOCHROMOCYTOMAS

	CT	MRI	MIBG
Sensitivity (%)	98	100	78
Specificity (%)	70	67	100
Positive predictive value (%)	69	83	100
Negative predictive value (%)	98	100	87

antagonist (10-20 mg 2-3 times/day, advanced to 80-100 mg/day), or prazosin, a short-acting competitive antagonist (1 mg t.i.d., advanced to 5 mg t.i.d.). Therapy may be limited by hypotension, tachycardia, and dizziness. Goals of therapy include blood pressure less than 160/90 mm Hg, an electrocardiogram (ECG) free of ST- and T-wave changes over 2 weeks before surgery, and no more than one premature ventricular contraction within 15 minutes. Opinions about the duration of preparation vary between 7 and 28 days before surgery.

25. Discuss the role of beta-blockers and other agents in the preoperative period.

Beta-adrenergic blockade to control tachycardia is added only after alpha-adrenergic blockade has been instituted to prevent unopposed alpha stimulation. Other agents used in the preoperative period include labetalol and calcium channel blockers. Intraoperative hypertension associated with tumor manipulation may be controlled with either phentolamine or nitroprusside. Postoperative hypotension may be minimized by preoperative volume expansion with crystalloid.

26. How are malignant pheochromocytomas treated?

Although evidence of malignancy may be discovered at the time of surgery, metastases from slow-growing pheochromocytomas may remain inapparent for several years. Therapy is rarely curative, because the tumors respond poorly to radiation therapy and chemotherapy; treatment is therefore palliative. Surgical debulking is the therapy of choice, followed by use of alpha-methyltyrosine. This drug is a "false" catecholamine precursor that inhibits tyrosine hydroxylase (the rate-limiting enzyme in catecholamine synthesis) and reduces excessive production of catecholamines.

27. Discuss the role of chemotherapy and MIBG ablation.

Combination chemotherapy with cyclophosphamide, vincristine, and dacarbazine may slow tumor growth, as may ablation with MIBG I 131. Unfortunately, neither of these therapeutic measures has resulted in cure. Also see Chapter 29 for further discussion.

28. What is the prognosis for malignant pheochromocytoma?

The prognosis is not dismal. Cases of 20-year survival have been reported, and the 5-year survival rate with malignant pheochromocytomas is 44%.

29. What syndromes are associated with pheochromocytomas?

- Multiple endocrine neoplasia 2A: hyperparathyroidism, medullary thyroid carcinoma (MTC), pheochromocytoma
- Multiple endocrine neoplasia 2B: medullary thyroid carcinoma, pheochromocytoma, mucosal neuromas, marfanoid habitus
- Carney's triad: paragangliomas, gastric epithelial leiomyosarcomas, benign pulmonary chondromas (females) or Leydig cell tumors (males)
- Neurofibromatosis: café-au-lait spots in 5% of patients with pheochromocytoma; 1% of patients with neurofibromatosis have pheochromocytomas
- von Hippel–Lindau syndrome: retinal and cerebellar hemangioblastomas; about 10% have pheochromocytomas
- Succinate dehydrogenase mutations: paragangliomas with increased malignancy risk

BIBLIOGRAPHY

Eisenhofer G: Editorial: biochemical diagnosis of pheochromocytoma—is it time to switch to plasma free metanephrines? *J Clin Endocrinol Metab* 88:550–552, 2003.

Jossart GH, Burpee SE, Gagner M: Surgery of the adrenal glands, *Endocrinol Metab Clin North Am* 29:57–68, 2000.

Krane NK: Clinically unsuspected pheochromocytomas: experience at Henry Ford Hospital and a review of the literature, *Arch Intern Med* 146:54–57, 1986.

Kudva YC, Sawka AM, Young WF: The laboratory diagnosis of adrenal pheochromocytoma: the Mayo Clinic experience, *J Clin Endocrinol Metab* 88:4533–4539, 2003.

Lenders JW, Pacak K, Walther MM, et al: Biochemical diagnosis of pheochromocytoma: which test is best? *JAMA* 287:1427–1434, 2002.

Pacak K: 2007 Preoperative management of the pheochromocytoma patient, *J Clin Endocrinol Metab* 92:4069–4079, 2007.

Prys-Roberts C: Phaeochromocytoma—recent progress in management, *Br J Anaesth* 85:44–57, 2000.

Sawka AM, Jaeschke R, Singh RJ, et al: A comparison of biochemical tests for pheochromocytoma: measurement of fractionated plasma metanephrines compared with the combination of 24-hour urinary metanephrines and catecholamines, *J Clin Endocrinol Metab* 88:553–558, 2003.

Schwartz GL: Screening for adrenal-endocrine hypertension: overview of accuracy and cost-effectiveness, *Endocrinol Metabol N Am* 40:279–294, 2011.

Wittles RM, Kaplan EL, Roizen MF: Sensitivity of diagnostic and localization tests for pheochromocytoma in clinical practice, *Arch Intern Med* 160:2521–2524, 2000.

Xekouki P, Stratakis CA: Pheochromocytoma, *Translational Endocrinology Metabolism* 2:77–127, 2011.

Zuber SM, Kantorovich V, Pacak K: Hypertension in pheochromocytoma: characteristics and treatment, *Endocrinol Metab N Am* 40:295–311, 2011.

CHAPTER 29

ADRENAL MALIGNANCIES

Michael T. McDermott

1. What types of cancers occur in the adrenal glands?

Carcinomas may arise in the adrenal cortex (adrenocortical carcinoma [ACC]) or the adrenal medulla (malignant pheochromocytomas). Metastatic cancer from other sites may also be seen.

2. Do adrenocortical carcinomas produce hormones?

Approximately 60% secrete steroid hormones; about 40% are nonfunctioning.

3. What are the clinical features of functioning adrenocortical carcinomas?

A functioning ACC secretes cortisol, androgens, estrogens, or aldosterone—alone or in combination. Cortisol overproduction is most common (~45%) and results in Cushing syndrome. Androgen secretion (~25%) causes hirsutism and virilization in women and precocious puberty in children but is often asymptomatic in men. Estrogen production causes menstrual disturbances in women and gynecomastia and hypogonadism in men. Excess aldosterone secretion causes hypertension and hypokalemia (Conn syndrome) (Fig. 29-1).

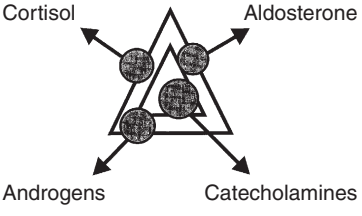


Figure 29-1. Functioning adrenal tumors. Circles represent adrenal tumors. Arrows point to the various hormones adrenal tumors may secrete.

4. What are the clinical features of nonfunctioning adrenocortical carcinomas?

A nonfunctioning ACC manifests clinically as abdominal or flank pain or as an adrenal mass discovered on physical examination or incidentally during an imaging procedure.

5. What imaging procedure is best for evaluating an adrenal mass?

Computed tomography (CT) is the method of choice to determine the size and physical characteristics of the mass. Features that most strongly suggest ACC are size greater than 6 cm, heterogeneity, calcifications, irregular borders, local invasion, lymphadenopathy, and decreased lipid content. The last feature is assessed by signal attenuation, expressed in Hounsfield units (HU). An adrenal mass CT protocol is employed in many institutions; this consists of a non-contrast CT, a contrast-enhanced CT, a delayed contrast-enhanced CT, and calculation of the relative washout percentage (RWP) of enhancement. Table 29-1 shows the typical CT findings for some commonly seen adrenal masses. MRI can also be used to assess the size, features, and lipid content of adrenal masses but is more expensive. Fluorodeoxyglucose (^{18}F) positron emission tomography (FDG-PET) or PET-CT fusion scanning may also be useful, especially for masses with high HU or low RWP on CT. High sensitivities and specificities have been reported with this technique using a standard uptake value (SUV) cutoff of 3.1. Other PET tracers, such as metomidate ^{11}C, may offer even better sensitivity in the future.

TABLE 29-1. EVALUATION OF AN INCIDENTAL ADRENAL MASS BY CT

MASS	NONCONTRAST CT ATTENUATION VALUE (HU)	CONTRAST-ENHANCED CT*	DELAYED CONTRAST-ENHANCED CT† ATTENUATION VALUE (HU)	RELATIVE WASHOUT PERCENTAGE
Adenoma	10	Enhances	< 30	> 50
Carcinoma	> 20	Indeterminate	> 30	< 50
Pheochromocytoma	< 20	Indeterminate	> 30	< 50
Metastatic cancer	> 20	Indeterminate	> 30	< 50

*60 seconds after injection.
†10-15 minutes after injection.
CT, computed tomography; HU, Hounsfield unit(s).

6. What hormone tests should be used to evaluate an adrenal mass?

The goal is to determine whether the mass is producing hormones that may cause symptoms or that may be indicative of malignancy (androgens). Many experts recommend a focused evaluation consisting of an overnight 1-mg dexamethasone suppression test, measurement of plasma free metanephrines or fractionated urinary catecholamines and metanephrines, and, for hypertensive patients, measurement of plasma aldosterone and renin. Tests currently recommended by the European Network for the Study of Adrenal Tumors (ENSAT) are shown in Table 29-2.

TABLE 29-2. HORMONAL EVALUATION OF THE INCIDENTAL ADRENAL MASS PROPOSED BY ENSAT

Cortisol testing (3 of 4 tests)	Dexamethasone suppression test (1-mg)
	Urine cortisol (24-hour)
	Serum cortisol, basal
	Plasma ACTH, basal
Sex steroid testing (all)	Serum testosterone
	Serum dehydroepiandrosterone sulfate (DHEA-S)
	Serum androstenedione
	Serum 17-OH progesterone
	Serum estradiol (men, postmenopausal women)
Aldosterone testing (if hypertension present)	Plasma aldosterone
	Plasma renin activity
	Serum potassium
Pheochromocytoma testing (1 or 2 tests)	Plasma metanephrines
	Urine metanephrines (24-hour)

Adapted from Lacroix A: Approach to the patient with adrenocortical carcinoma. *J Clin Endocrinol Metab* 95: 4812-4822, 2010
ENSAT (European Network for the Study of Adrenal Tumors).

7. How should the incidentally discovered adrenal mass be managed?

Surgery is often recommended for tumors larger than 4 cm, for those showing significant growth on follow-up, and for those with evidence of excessive cortisol, androgen, estrogen, aldosterone, or catecholamine secretion. Nonfunctioning adrenal masses smaller than 4 cm should be reassessed in 6 months and then annually thereafter.

8. Describe a useful staging system for adrenocortical carcinoma.

See Table 29-3.

TABLE 29-3. STAGING SYSTEM FOR ADRENOCORTICAL CARCINOMA PROPOSED BY ENSAT IN 2008

STAGE	TNM
I	T1, N0, M0
II	T2, N0, M0
III	T1-2, N1, M0
	T3-4, N0-1, M0
IV	T1-4, N0-1, M1

Adapted from Lacroix A: Approach to the patient with adrenocortical carcinoma. *J Clin Endocrinol Metab* 95:4812–4822, 2010

ENSAT (European Network for the Study of Adrenal Tumors).

T1, tumor $<$ 5 cm; T2, tumor $>$ 5 cm; T3, tumor infiltrating surrounding tissues; T4, tumor invading adjacent organs; N0, no positive lymph nodes; N1, positive lymph nodes; M0, no distant metastases; M1, distant metastases present.

9. Describe the initial treatment for an adrenocortical carcinoma.

Surgery is the initial treatment of choice for ACC. If the tumor resection is complete, adjuvant therapy with mitotane, an adrenocorticolytic agent, is recommended because of the high recurrence rate (~60%). After an incomplete resection, adjuvant mitotane alone or combined with streptozotocin is recommended. Adjuvant tumor bed radiation therapy is also advised by some investigators. Follow-up imaging, with or without tumor marker measurement, should be performed every 3 months for 1 year, then every 6 months for 5 years, and then annually thereafter. In patients receiving mitotane, serum mitotane levels should be monitored and maintained in the 14 to 20 μg/mL range; concomitant glucocorticoid with or without mineralocorticoid replacement therapy is necessary in all patients except those with hypercortisolism. Patients with persistent hypercortisolism despite mitotane use may need additional therapy with an enzyme inhibitor (ketoconazole, metyrapone).

10. How should advanced, metastatic, and recurrent adrenal cortical carcinoma be managed?

Aggressive surgery, when possible, and radiation therapy may offer benefit, although usually only temporarily. Chemotherapy regimens using either mitotane plus etoposide, doxorubicin, and cisplatin (EDC) or mitotane plus streptozotocin have shown benefit, but superior response rates and better progression-free survival have been reported with mitotane-EDC. Targeted therapies utilizing tyrosine kinase inhibitors and growth factor receptor (insulin-like growth factor 1 receptor, epidermal growth factor receptor) inhibitors also show some promise. Targeted radionuclide therapy with iodometomidate ^{131}I offers a novel approach with encouraging results reported thus far.

11. What is the prognosis for patients with adrenocortical carcinoma?

The mean survival is 15 months. The 5-year survival rate is less than 30%. Prognosis is improved by young age, small tumor size, localized disease, complete tumor resection, and nonfunctioning of the tumor. Table 29-4 shows 5-year disease-free survival rates by disease stage.

TABLE 29-4. FIVE-YEAR DISEASE-FREE SURVIVAL FOR ADRENOCORTICAL CARCINOMA ACCORDING TO ENSAT 2008 STAGING SYSTEM

STAGE	5-YEAR DISEASE-FREE SURVIVAL
I	82%
II	61%
III	50%
IV	13%

Adapted from Lacroix A: Approach to the patient with adrenocortical carcinoma. *J Clin Endocrinol Metab* 95:4812-4822, 2010
ENSAT (European Network for the Study of Adrenal Tumors).

12. How often are pheochromocytomas malignant?

Approximately 10% to 15% of pheochromocytomas are malignant.

13. What are the clinical features of a malignant pheochromocytoma?

Pheochromocytomas, whether benign or malignant, usually cause hypertension, headaches, sweating, and palpitations. They are diagnosed biochemically by the finding of increased levels of metanephrine or catecholamines in the plasma or urine. Malignant pheochromocytomas often do not differ clinically or histologically at presentation from those that are benign.

14. What clues suggest that a pheochromocytoma is malignant?

Malignancy is most strongly suggested by tumor size greater than 6 cm, evidence of extra-adrenal spread (usually to the lymph nodes, liver, lungs, or bones) and disproportionately increased plasma or urine levels of dopamine. Because malignant pheochromocytomas cannot be distinguished from benign ones histologically, the malignant character of some tumors may not become apparent until metastatic disease appears.

15. Which of the familial pheochromocytoma syndromes is most commonly associated with malignant pheochromocytomas?

Table 29-5 lists the four well-recognized familial pheochromocytoma and paraganglioma syndromes. Only the succinate dehydrogenase B mutation, an autosomal-dominantly inherited condition, is associated with malignant pheochromocytomas and paragangliomas.

TABLE 29-5. GENETIC SYNDROMES ASSOCIATED WITH PHEOCHROMOCYTOMAS AND/OR PARAGANGLIOMAS

SYNDROME	GENE MUTATION
Multiple endocrine neoplasia 2	Ret
Von Hippel–Lindau syndrome	VHL
Neurofibromatosis 1	NF-1
Succinate dehydrogenase B mutation	SDH

16. What are the best tests to localize metastatic pheochromocytomas?

CT or magnetic resonance imaging (MRI) localizes about 80% to 90% of metastatic pheochromocytomas. When these have negative results or are not feasible, functional imaging with metaiodobenzylguanidine (MIBG) ^{123}I scintigraphy, octreotide scintigraphy (OctreoScan), and PET with [^{18}F] fluorodeoxyglucose (FDG-PET) are the best current options. Other highly specific functional PET imaging agents, such as 6-[^{18}F] fluorodopamine and 6-[^{18}F] fluorodopa are in development but are not yet generally available.

17. What is the treatment for a malignant pheochromocytoma?

Surgery is the treatment of choice, when possible. Preoperatively, alpha-adrenergic blocking agents (phenoxybenzamine, prazosin) or calcium channel blockers are given to control blood pressure and to replete intravascular volume. Beta-blockers may then be added for reflex tachycardia or persistent hypertension. If surgery is not possible or successful, other available therapies are only palliative. Alpha-blockers, calcium channel blockers, and the catecholamine synthesis inhibitor α-methyltyrosine can provide blood pressure and symptom control. Therapies for which partial tumor responses have been reported include chemotherapy with cyclophosphamide, vincristine, and dacarbazine, and radionuclide therapy with ^{131}I MIBG.

18. What is the prognosis for malignant pheochromocytoma?

The 5-year survival rate for malignant pheochromocytoma is about 40%.

19. What tumors metastasize to the adrenal glands?

The vascular adrenal glands are a common site of bilateral metastatic spread from cancers of the lung, breast, stomach, pancreas, colon, and kidney and from melanomas and lymphomas.

20. What is the clinical significance of metastatic disease to the adrenal glands?

Acute adrenal crises are rare. However, up to 33% of patients may have subtle adrenal insufficiency manifested by nonspecific symptoms and an inadequate response (peak cortisol level < 20 μg/dL) to a 250-μg cosyntropin stimulation test. These patients may experience improvement in well-being when given physiologic glucocorticoid replacement.

KEY POINTS 1: ADRENAL MALIGNANCIES

1. Adrenal cortical carcinoma manifests with features of excess cortisol, androgens, estrogens, or aldosterone; with abdominal or flank pain; or as an incidentally discovered adrenal mass.
2. Malignant pheochromocytomas often manifest with features similar to those of benign pheochromocytomas (hypertension, headaches, palpitations, sweating).
3. Features suggesting that an adrenal tumor is malignant are size > 6 cm, heterogeneity, calcifications, irregular borders, local invasion, lymphadenopathy, decreased lipid content (Hounsfield units > 20), or elevations of serum androgens or urinary or plasma dopamine.
4. Surgery is the treatment of choice for all malignant adrenal tumors; mitotane $\pm$ tumor bed radiation therapy is the recommended adjuvant therapy for adrenocortical carcinomas.
5. Incidentally discovered adrenal masses should be evaluated for evidence of malignancy (size > 6 cm or progressive growth) and excess hormone secretion (cortisol, androgens, estrogens, aldosterone, catecholamines).

BIBLIOGRAPHY

Abiven G, Coste J, Groussin L, et al: Clinical and biological features in the prognosis of adrenocortical cancer: poor outcome of cortisol-secreting tumors in a series of 202 consecutive patients, *J Clin Endocrinol Metab* 91: 2650–2655, 2006.

Allolio B, Fassnacht M: Clinical review: Adrenocortical carcinoma: clinical update, *J Clin Endocrinol Metab* 91:2027–2037, 2006.

Assie G, Antoni G, Tissier F, et al: Prognostic parameters of metastatic adrenocortical carcinoma, *J Clin Endocrinol Metab* 92:148–154, 2007.

Fassnacht M, Hahner S, Polat B, et al: Efficacy of adjuvant radiotherapy of the tumor bed on local recurrence of adrenocortical carcinoma, *J Clin Endocrinol Metab* 91:4501–4504, 2006.

Fassnacht M, Johanssen S, Fenske W, et al: Improved survival in patients with stage II adrenocortical carcinoma followed up prospectively by specialized centers, *J Clin Endocrinol Metab* 95:4925–4932, 2010.

Fassnacht M, Terzolo M, Allolio B, et al: Combination chemotherapy in advanced adrenocortical carcinoma, *N Engl J Med* 366:2189–2197, 2012.

Groussin L, Bonardel G, Silvera S, et al: 18F-Fluorodeoxyglucose positron emission tomography for the diagnosis of adrenocortical tumors: a prospective study in 77 operated patients, *J Clin Endocrinol Metab* 94:1713–1722, 2009.

Hahner S, Kreissl MC, Fassnacht M, et al: 131-I Iodometomidate for targeted radionuclide therapy of advanced adrenocortical carcinoma, *J Clin Endocrinol Metab* 97:914–922, 2012.

Hermsen IG, Fassnacht M, Terzolo M, et al: Plasma concentrations of o,p′DDD, o,p′DDA, and o,p′DDE as predictors of tumor response to mitotane in adrenocortical carcinoma: results of a retrospective ENSAT Multicenter Study, *J Clin Endocrinol Metab* 96:1844–1851, 2011.

Kirschner LS: Review: Emerging treatment strategies for adrenocortical carcinoma: a new hope, *J Clin Endocrinol Metab* 91:14–21, 2006.

Lacroix A: Approach to the patient with adrenocortical carcinoma, *J Clin Endocrinol Metab* 95:4812–4822, 2010.

Leboulleux S, Dromain G, Bonniaud G, et al: Diagnostic and prognostic value of 18-fluorodeoxyglucose positron emission tomography in adrenocortical carcinoma: a prospective comparison with computed tomography, *J Clin Endocrinol Metab* 91:920–925, 2006.

Mackie GC, Shulkin BL, Ribiero RC, et al: Use of [F18] fluorodeoxyglucose positron emission tomography in evaluating locally recurrent and metastatic adrenocortical carcinoma, *J Clin Endocrinol Metab* 91:2665–2671, 2006.

Pacak K, Eisenhofer G, Ahlman H, et al: Pheochromocytoma: recommendations for clinical practice from the First International Symposium, *Nat Clin Pract Endocrinol Metab* 3:92–102, 2007.

Terzolo M, Angeli A, Fassnacht M, et al: Adjuvant mitotane treatment for adrenocortical carcinoma, *N Engl J Med* 356:2372–2380, 2007.

Young WF: The incidentally discovered adrenal mass, *N Engl J Med* 356:601–610, 2007.

CHAPTER 30

ADRENAL INSUFFICIENCY

Emily Schroeder and Cecilia C. Low Wang

1. What is adrenal insufficiency, and how is it categorized?

"Adrenal insufficiency" is the term used to describe inadequate production of glucocorticoids, mineralocorticoids, or both by the adrenal glands. It can occur because of dysfunction or complete destruction of the adrenal cortex (primary adrenal insufficiency), inadequate adrenocorticotropic hormone (ACTH) production by the pituitary (secondary adrenal insufficiency), or inadequate corticotropin-releasing hormone (CRH) production by the hypothalamus (tertiary adrenal insufficiency).

2. What are common causes of adrenal insufficiency?

Autoimmune adrenalitis (Addison's disease) is the most common cause of primary adrenal insufficiency and is associated with increased levels of 21-hydroxylase antibodies. Addison's disease can occur in isolation or in combination with other endocrine deficiencies as part of an autoimmune polyglandular syndrome. The most common cause of central (secondary/tertiary) adrenal insufficiency is withdrawal of glucocorticoids after long-term use. Central adrenal insufficiency can also occur as part of panhypopituitarism from large pituitary tumors or their treatment with surgery and/or radiation therapy. See Table 30-1 for other causes of adrenal insufficiency.

3. What are common symptoms of adrenal insufficiency?

Most patients report nonspecific symptoms such as weakness, fatigue, and anorexia. Many also complain of gastrointestinal symptoms such as nausea, vomiting, vague abdominal pain, and constipation. Psychiatric symptoms and symptoms of orthostatic hypotension, arthralgias, myalgias, and salt craving are also reported.

4. How does adrenal insufficiency usually present?

Weight loss is a common presenting sign. Hyperpigmentation, particularly of the buccal mucosa and gums, is noted in most patients with primary adrenal insufficiency. Patients should be examined for darkening of the palmar creases, nail beds, and scars forming after onset of ACTH excess. Hyperpigmentation occurs because production of proopiomelanocortin (POMC), a prohormone that is cleaved into ACTH, melanocyte-stimulating hormone (MSH), and other hormones is increased and leads to increased melanin production. Orthostasis is common in both primary and central adrenal insufficiency.

5. What laboratory abnormalities can be found in adrenal insufficiency?

The classic laboratory abnormalities are hyponatremia and hyperkalemia. The hyperkalemia is due to mineralocorticoid deficiency, whereas the hyponatremia occurs mainly because of glucocorticoid deficiency. Hyponatremia is the result of elevated vasopressin values with free water retention, shift of extracellular sodium into cells, and decreased delivery of filtrate to the diluting segments of the nephron due to decreased glomerular filtration rate. Azotemia can be seen because of hypovolemia. Patients often demonstrate a normocytic normochromic anemia and may have eosinophilia and lymphocytosis. Mild to moderate hypercalcemia may occur. Fasting blood glucose is usually low-normal, but occasionally patients can have fasting or postprandial hypoglycemia. Patients with coexisting type 1 diabetes mellitus and adrenal insufficiency may experience greater frequency and severity of hypoglycemic episodes.

TABLE 30–1. CAUSES OF ADRENAL INSUFFICIENCY

Primary	Autoimmune
	Bilateral adrenal hemorrhage or thrombosis: coagulopathy, meningococcal sepsis
	Metastases: lymphoma, lung, breast, renal, gastrointestinal
	Infectious: tuberculosis, human immunodeficiency virus, cytomegalovirus, fungal (*Histoplasma, Coccidioides*)
	Adrenoleukodystrophy and other congenital disorders
	After adrenalectomy
	Infiltrative: hemochromatosis, amyloidosis
	Congenital adrenal hyperplasia
	Adrenal enzyme deficiency
	Drugs (see text)
Secondary	Withdrawal of long-term suppressive glucocorticoid therapy
	Pituitary tumors including craniopharyngioma
	Metastases to the pituitary
	Pituitary surgery or irradiation
	Lymphocytic hypophysitis
	Infiltrative diseases: hemochromatosis, sarcoidosis, histiocytosis X
	Infection (e.g., tuberculosis, histoplasmosis)
	Sheehan syndrome (massive blood loss leading to shock in the peripartum period)
	Severe head trauma disrupting the pituitary stalk or otherwise affecting the pituitary
Tertiary	Withdrawal of long-term suppressive glucocorticoid therapy
	Hypothalamic tumors
	Metastases to the hypothalamus
	Infiltrative diseases affecting the hypothalamus
	Cranial irradiation
	Trauma
	Infections (e.g., tuberculosis)

6. How do the clinical presentations of primary and central forms of adrenal insufficiency differ?

Hyperpigmentation and hyperkalemia are not observed in secondary/tertiary adrenal insufficiency. Otherwise, the clinical presentations are similar.

7. How is adrenal insufficiency usually diagnosed biochemically?

In the outpatient setting, a low morning cortisol value (< 3 μg/dL) is sufficient to diagnose adrenal insufficiency, and a high morning cortisol value (> 20 μg/dL) excludes the diagnosis. In most instances, a dynamic test, the cosyntropin stimulation test, is also performed. This test determines whether the adrenals are able to respond to maximal stimulation by synthetic ACTH. This test can also be used in the diagnosis of central adrenal insufficiency, as long as sufficient time has elapsed for the adrenal cortex to atrophy in response to lack of ACTH stimulation.

The standard cosyntropin test is performed by collecting a specimen for measurement of a baseline serum cortisol level, administration of 250 μg of cosyntropin (brand name Cortrosyn, Synacthen) intravenously (IV) or intramuscularly (IM), and then collecting specimens for serum cortisol measurement 30 and 60 minutes later. An abnormal result is defined as a stimulated cortisol level at either 30 or 60 minutes of less than 18 to 20 μg/dL ($<$ 450-500 nmol/L). This test can be performed at any time during the day. If an individual is receiving glucocorticoid therapy, the dose should be withheld (12 hours for hydrocortisone, 24 hours for prednisone) before the test is performed to avoid detection of synthetic glucocorticoids in the cortisol assay.

Other dynamic testing includes the insulin tolerance test, metyrapone test, glucagon stimulation test, and CRH stimulation test. The insulin tolerance test evaluates the hypothalamic-pituitary-adrenal (HPA)

axis in response to insulin-induced hypoglycemia (blood glucose level < 40 mg/dL). This test should be performed in experienced centers only by trained staff, and should not be performed if the individual has significant coronary artery disease or an uncontrolled seizure disorder.

8. What about the low-dose cosyntropin stimulation test?

It has been argued that mild cases of primary adrenal insufficiency may be missed with the standard-dose cosyntropin stimulation test because the dose of ACTH administered in this test is quite supraphysiologic. Data from studies examining the potential role of low-dose cosyntropin stimulation testing, in which 1 μg cosyntropin is administered, do not clearly establish that the low-dose test is better than the standard test. There are several potential problems with performing the test, including false-positive results because of inaccurate or irreproducible dilution of cosyntropin, the need for IV administration, and the need for carefully timed sampling for serum cortisol levels. It is unclear whether abnormal results from this test are clinically relevant. Therefore the standard-dose test should be used in most instances.

9. What testing can be used to distinguish primary from central adrenal insufficiency?

In primary adrenal insufficiency, ACTH is elevated, whereas ACTH is "abnormally normal" (i.e., not elevated in response to low cortisol) or frankly low in central adrenal insufficiency.

10. When can the results of the ACTH stimulation test be misleading?

Partial ACTH deficiency and recent ACTH deficiency are situations that may lead to false-negative results of the cosyntropin stimulation test. Insulin-induced hypoglycemia (insulin tolerance testing) or metyrapone testing may be used in these situations.

11. When are imaging tests appropriate?

After the biochemical diagnosis of adrenal insufficiency, imaging may be performed in certain instances to help determine the cause. In cases of central adrenal insufficiency, magnetic resonance imaging (MRI) of the pituitary and hypothalamus is indicated if exogenous glucocorticoids have not been implicated. If a primary adrenal process is suspected, abdominal computed tomography (CT) can be performed with thin slices through the adrenals. Imaging should not be performed before a biochemical diagnosis is made because of the high incidence of incidental imaging findings that are without clinical significance.

12. When should the diagnosis of adrenal crisis be considered?

Adrenal crisis should be suspected in patients with unexplained catecholamine-resistant hypotension or other severe signs or symptoms consistent with adrenal insufficiency. Symptoms of adrenal crisis are often nonspecific—weakness, fatigue, nausea, vomiting, abdominal pain, fever, and altered mental status. Acute adrenal hemorrhage should be suspected if there is a constellation of abdominal/flank pain, hypotension/shock, fever, and hypoglycemia in a deteriorating patient. Adrenal crisis is more common in primary than in central adrenal insufficiency.

13. How is adrenal crisis managed?

If adrenal crisis is suspected, it should be treated aggressively because, if left untreated, adrenal crisis is fatal. A formal diagnosis of adrenal insufficiency can be performed later. The patient can receive a dose of dexamethasone initially (4 mg IV) while the basal cortisol measurement and the cosyntropin stimulation test are performed; empiric treatment with IV hydrocortisone (100 mg IV q8h, with rapid tapering) can then be initiated. In addition, treatment should include intravenous saline and glucose to correct volume depletion, dehydration, and hypoglycemia. Patients often need intensive care unit (ICU)–level supportive care. A search for precipitating factors and the underlying cause needs to be performed.

14. How is adrenal insufficiency diagnosed in the critical care setting?

Because the diurnal rhythm of ACTH and cortisol secretion is disrupted in acute illness, and because severe stress should stimulate cortisol production, a random cortisol specimen can be drawn to

diagnose complete or relative adrenal insufficiency in the critical care setting. In patients who (1) are hemodynamically unstable and unresponsive to vasopressors despite adequate fluid resuscitation or (2) have signs or symptoms suggestive of adrenal insufficiency, random cortisol specimen should be collected, and a cosyntropin stimulation test performed immediately afterward.

The cortisol level at which adrenal insufficiency should be diagnosed (a random level of < 20 μg/dL, some other value such as < 25 μg/dL, and/or an increment of 9 μg/dL after cosyntropin administration) is controversial. The reasons are concerns about the existence of a cortisol-resistant state in critically ill patients due to inflammatory cytokines, reduction in binding affinity to cortisol-binding globulin, and proinflammatory transcription factors. Some authorities in this field believe that a cortisol level that is adequate in an ambulatory setting may not be adequate in the setting of severe stress or prolonged or complicated surgical procedures; this latter inadequacy is referred to as relative adrenal insufficiency.

15. When and how should glucocorticoids be used in the critical care setting?

There is considerable debate about the most appropriate use of glucocorticoids in the critical care setting. Although the results of clinical trials of glucocorticoid treatment for sepsis without proven adrenal insufficiency have been mixed, a systematic review showed that 5 or more days of 300 mg/day or less of hydrocortisone or its equivalent resulted in a significant reduction in 28-day all-cause mortality and hospital mortality. However, there is marked heterogeneity among trial results, and the Corticosteroid Therapy of Septic Shock (CORTICUS) trial failed to show benefit for empiric glucocorticoid treatment.

Some groups advocate using stress-dose steroids empirically in critically ill patients with resistant hypotension, testing for adrenal insufficiency with a random cortisol measurement and cosyntropin stimulation testing, and then stopping stress-dose steroids if the tests for adrenal insufficiency are normal. On the other hand, the American College of Critical Care Medicine, in its Surviving Sepsis Campaign, does not advocate formal testing for adrenal insufficiency, but instead recommends use of glucocorticoids in selected groups of patients: those with vasopressor-dependent septic shock and those with early severe acute respiratory distress syndrome.

If steroids are used, typical hydrocortisone doses in the critical care setting are 50 mg IV every 6 hours or 100 mg IV every 8 hours. These dosages should be tapered quickly as the patient's clinical status improves and the underlying illness resolves.

16. How do I manage chronic adrenal insufficiency, and when should I consider prescribing fludrocortisone?

All patients with chronic adrenal insufficiency require replacement with glucocorticoids, and occasionally with mineralocorticoids. Hydrocortisone is frequently used in primary adrenal insufficiency because it has some mineralocorticoid activity. The usual dosage of hydrocortisone is 10 to 15 mg every morning and 5 to 10 mg in the afternoon. When prednisone is used, typical doses are 2.5 to 5 mg daily. If additional mineralocorticoid effect is necessary for persistent hyperkalemia and/or orthostatic hypotension, fludrocortisone 0.05 to 0.2 mg once a day may be added.

17. What are some deficiencies in the current approach to treating adrenal insufficiency?

Many individuals with adrenal insufficiency experience significantly reduced subjective health status and quality of life, increased fatigue, and depression. The reason for some of these effects may be that current treatment regimens do not replicate the physiologic diurnal cortisol profile or because most female patients do not receive replacement of adrenal androgens. Work is being done to develop sustained-release glucocorticoid formulations that better approximate the natural diurnal cortisol pattern.

18. Should I recommend dehydroepiandrosterone replacement for my adrenally insufficient patient?

Dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEA-S) are the main androgens produced by the adrenals. Both are weak androgens, but they are converted to the more

potent androgens, testosterone and 5α-dihydrotestosterone (DHT), peripherally. This peripheral conversion is a significant source of androgens in women. Oral DHEA supplementation using 25 to 50 mg/day normalizes circulating levels of androgens in women with adrenal insufficiency. A meta-analysis of 10 randomized, placebo-controlled trials showed a small improvement in health-related quality of life and depression after treatment with DHEA, with no significant improvement in anxiety or sexual well-being. The data are insufficient to recommend DHEA therapy for all women with adrenal insufficiency, but it may be tried in women who continue to have significantly impaired well-being despite optimal glucocorticoid and mineralocorticoid treatment. In the United States, DHEA is classified as a dietary supplement and therefore is not subject to the same quality control as medications.

19. What are the relative potencies of available glucocorticoids?

See Table 30-2.

20. How is treatment for chronic adrenal insufficiency monitored?

Adequate treatment for chronic adrenal insufficiency is monitored by taking a focused history regarding overall well-being and symptoms suggestive of orthostasis and obtaining blood pressure, weight, and electrolytes. It is important to avoid the use of excessive dosages of replacement glucocorticoids, which lead to iatrogenic Cushing syndrome, which in turn can result in needless weight gain, osteoporosis, hypertension, hyperglycemia, glaucoma, or avascular necrosis. The goal should be to use the smallest replacement dosage of glucocorticoids possible that maintains normal electrolyte levels and good quality of life. Serum cortisol and plasma ACTH levels are not useful for monitoring treatment of adrenal insufficiency.

21. When do individuals with chronic adrenal insufficiency require "stress-dose" glucocorticoids, and what doses should be used?

Any medical stress, including febrile illnesses, trauma, labor and delivery, and diagnostic or surgical procedures, can precipitate an acute adrenal crisis in the patient with chronic adrenal insufficiency. Supplemental steroids should be used to prevent adrenal crisis, but care should be taken to avoid unnecessary supplemental doses of glucocorticoids. Typically, the usual replacement dose is doubled or tripled for mild to moderate infections and during labor and delivery. Doses should also be doubled or tripled for approximately 24 hours for dental surgery, minor surgery (cataract, laparoscopic), and invasive diagnostic procedures. For moderate surgical stress, patients should be given doses equivalent to hydrocortisone 50 to 75 mg/day in divided doses for 1 to 2 days. For major surgical procedures, severe infections, and severe acute illnesses, patients are typically given hydrocortisone 200 to 300 mg/day for 2 to 3 days in divided doses every 6 to 8 hours.

TABLE 30-2. RELATIVE POTENCIES OF SELECTED STEROID FORMULATIONS

COMPOUND	PHYSIOLOGIC REPLACEMENT DOSE (MG)	GLUCOCORTICOID ACTIVITY,† RELATIVE TO HYDROCORTISONE	MINERALOCORTICOID ACTIVITY, RELATIVE TO HYDROCORTISONE	DURATION OF ACTION
Hydrocortisone*	15-25	1	1.0	Short
Methylprednisolone	4	4	0.5	Short
Prednisone	5	4	0.75	Longer
Prednisolone	5	4	0.75	Longer
Dexamethasone	0.25-0.50	30-50	0.0	Long

*Hydrocortisone is the synthetic form of cortisol.
†Suppression of hypothalamic-pituitary-adrenal axis.

Patients with adrenal insufficiency should wear a medical alert bracelet or necklace identifying them as individuals with adrenal insufficiency, in case they are incapable of providing an adequate history. An alternative form of hydrocortisone or dexamethasone can be provided so that patients are still able to receive glucocorticoids intramuscularly (hydrocortisone or dexamethasone) or per rectum (hydrocortisone) in an emergency situation.

22. What drugs can cause adrenal insufficiency?

The most common cause of central adrenal insufficiency is glucocorticoid therapy. Glucocorticoids can cause exogenous Cushing syndrome, leading to suppression of the HPA axis. Patients may then be unable to mount an adequate cortisol response to stress, or adrenal insufficiency may develop if the steroid dose is abruptly stopped or tapered. Exogenous Cushing syndrome can result from oral, ocular, inhaled, transdermal, rectal, or parenteral glucocorticoids. Some injected glucocorticoids for musculoskeletal disorders can last for weeks to months. Glucocorticoids are also found in some herbal or complementary/alternative therapies. Protease inhibitors and other drugs slow metabolism of glucocorticoids via interactions with the CYP3A4 enzyme. Thus, when protease inhibitors and glucocorticoids are used to together, exogenous Cushing's disease with HPA suppression can result even at low glucocorticoid doses.

High-dose progestins, such as megestrol acetate and medroxyprogesterone acetate, have enough glucocorticoid activity to cause Cushing syndrome. Opioids can also suppress the HPA axis. Drugs that can cause primary adrenal sufficiency include the azole antifungal agents, the anesthetic etomidate, the antiparasitic suramin, and steroid synthesis inhibitors such as aminoglutethimide, metyrapone, and mitotane. Mifepristone, a progesterone antagonist, is a glucocorticoid receptor antagonist.

23. How should steroid dosage be tapered in patients taking pharmacologic doses of steroids to treat nonadrenal diseases?

Patients may be started on glucocorticoids to treat a variety of autoimmune, neoplastic, or inflammatory disorders. Discontinuing glucocorticoid therapy can be challenging because of (1) worsening of the disorder for which the glucocorticoid is being used, (2) suppression of the HPA axis with resulting secondary adrenal insufficiency upon discontinuation of the glucocorticoid, and (3) steroid withdrawal syndrome.

The initial tapering of glucocorticoids from pharmacologic to physiologic doses depends on the underlying illness for which the steroids are being used. If the illness worsens during this period of tapering, the dosage needs to be increased and the higher dosage continued until the symptoms stabilize before another attempt at more gradual tapering. When the patient is taking a near-physiologic dosage, she or he can be switched to a shorter-acting glucocorticoid such as hydrocortisone, and tapering of the dosage can be continued to below physiologic dosages or to alternate-day therapy in certain instances.

Testing should be performed when patients have been receiving physiologic or lower doses for at least 1 month, to ensure that adrenal suppression has resolved and that normal responsiveness of the HPA axis has returned. A morning cortisol specimen should be collected 12 to 24 hours after the last dose of glucocorticoid (12 hours for short-acting synthetic glucocorticoids such as hydrocortisone, and 24 hours for longer-acting ones such as prednisone). A plasma cortisol level less than 3 μg/dL is consistent with adrenal insufficiency, so the glucocorticoid should be continued for 4 to 6 weeks before retesting. A level greater than 20 μg/dL is consistent with return of adrenal function, and glucocorticoids can be discontinued. A level between 3 and 20 μg/dL is equivocal, and further testing is needed, usually with a cosyntropin stimulation test. It may take months for the HPA axis to respond normally to ACTH.

Central adrenal insufficiency should be suspected in individuals who have a clinical presentation suggestive of adrenal insufficiency and who have received the equivalent of 20 mg prednisone for 5 days or physiologic dosages of glucocorticoid for at least 30 days in the past 12 months. These patients should receive stress doses of glucocorticoids during moderate to severe illness or surgery.

KEY POINTS 1: CLASSIFICATION AND DIAGNOSIS OF ADRENAL INSUFFICIENCY

1. Adrenal insufficiency is classified as primary (failure of adrenals to produce cortisol), secondary (failure of pituitary to produce adrenocorticotropic hormone [ACTH]), or tertiary (failure of hypothalamus to produce corticotropin-releasing hormone [CRH]).
2. Adrenal insufficiency should be suspected in outpatients who have received supraphysiologic doses of glucocorticoids for longer than 1 month, in patients in the intensive care unit (ICU) who are hemodynamically unstable despite aggressive fluid resuscitation or have septic shock, and in any patient with signs or symptoms suggesting adrenal insufficiency.
3. Adrenal insufficiency is diagnosed with the finding of a 30- or 60-minute cortisol level less than 18-20 μg/dL on a standard-dose cosyntropin stimulation test.

KEY POINTS 2: TREATMENT OF ADRENAL INSUFFICIENCY

1. Treatment of adrenal insufficiency depends on the condition of the patient.
2. Nonstressed outpatients should be treated with replacement doses of hydrocortisone or prednisone with or without fludrocortisone, depending on the type of adrenal insufficiency.
3. Stressed patients should receive supplemental glucocorticoids tailored to the degree of stress.
4. Adrenal crisis should be treated aggressively using intravenous saline and dextrose, intravenous glucocorticoids (dexamethasone if treatment is being given before random collection of blood for measurement of cortisol and adrenocorticotropic hormone, hydrocortisone if given afterwards), other supportive care, and a search for the precipitating illness.

BIBLIOGRAPHY

Alkatib AA, Cosma M, Elamin MB, et al: A systemic review and meta-analysis of randomized placebo-controlled trials of DHEA treatment effects on quality of life in women with adrenal insufficiency, *J Clin Endocrinol Metab* 94:3676–3681, 2009.

Annane D, Bellissant E, Bollaert P-E, et al: Corticosteroids in the treatment of severe sepsis and septic shock in adults: a systematic review, *JAMA* 301:2362–2375, 2009.

Arafah BM: Hypothalamic pituitary adrenal function during critical illness: limitations of current assessment methods, *J Clin Endocrinol Metab* 91:3725–3745, 2006.

Axelrod L: Perioperative management of patients treated with glucocorticoids, *Endocrinol Metab Clin N Am* 32:367–383, 2003.

Bornstein SR: Predisposing factors for adrenal insufficiency, *N Engl J Medicine* 360:2328–2339, 2009.

Bouillon R: Acute adrenal insufficiency, *Endocrinol Metab Clin N Am* 35:767–775, 2006.

Carroll TB, Aron DC, Findling JW, et al: Glucocorticoids and adrenal androgens. In Gardner DG, Shoback D, editors: *Greenspan's basic and clinical endocrinology*, 9th ed, Chicago, 2011, McGraw-Hill Medical, p 285.

Dorin RI, Qualls CR, Crapo LM: Diagnosis of adrenal insufficiency, *Ann Intern Med* 139:194–204, 2003.

Grossman AB: The diagnosis and management of central hypoadrenalism, *J Clin Endocrinol Metab* 95:4855–4863, 2010.

Hahner S, Allolio B: Therapeutic management of adrenal insufficiency, *Best Pract Res Clin Endocrinol Metab* 23:167–179, 2009.

Hopkins RL, Leinung MC: Exogenous Cushing syndrome and glucocorticoid withdrawal, *Endocrinol Metab Clin N Am* 34:371–384, 2005.

Marik PE, Pastores SM, Annane D, et al: Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care Medicine, *Crit Care Med* 36:1973–1949, 2008.

Meikle AQ, Tyler FH: Potency and duration of action of glucocorticoids: effects of hydrocortisone, prednisone and dexamethasone on human pituitary-adrenal function, *Am J Med* 63:200–207, 1977.

Neary N, Nieman L: Adrenal insufficiency: etiology, diagnosis and treatment, *Curr Opin Endocrinol Diabetes Obes* 17: 217–223, 2010.

Sprung CL, Annane D, Keh D, et al: Hydrocortisone therapy for patients with septic shock, *N Engl J Med* 358:111–124, 2008.

Stewart PM, Krone NP: The adrenal cortex. In Melmed S, Polonsky KS, Larsen PR, et al, editors: *Williams textbook of endocrinology*, 12th ed, Philadelphia, 2011, Saunders, pp 495–496.

CONGENITAL ADRENAL HYPERPLASIA

Jason Daily and Robert A. Vigersky

1. Define congenital adrenal hyperplasia.

Congenital adrenal hyperplasia (CAH) is a group of several autosomal recessive disorders all involving a deficiency or relative defect in cortisol synthesis, aldosterone synthesis, or both resulting in some degree of cortisol deficiency, aldosterone deficiency, or both.

2. What enzyme defects can lead to CAH?

Defects in any of the six enzymes required for the synthesis of cortisol from cholesterol in the adrenal cortex can lead to CAH, including steroidogenic acute regulatory (StAR) protein, which is essential in transporting cholesterol to the mitochondria; 3β-hydroxysteroid dehydrogenase, which converts the Δ5-steroids (pregnenolone, 17-hydroxypregnenolone, DHEA) to the Δ4-steroids (progesterone, 17-hydroxyprogesterone, androstenedione); P450 side-chain cleavage (CYP11A1), which is responsible for cholesterol side-chain cleavage forming progesterone; and three hydroxylases, CYP17A1 (17α-hydroxylase), CYP21A2 (21-hydroxylase), and CYP11B1 (11β-hydroxylase).

3. Describe the functions of the three hydroxylases.

- CYP17A1 (17α-hydroxylase) is essential in converting progesterone to 17-hydroxyprogesterone (17-OHP) and pregnenolone to 17-hydroxypregnenolone. This enzyme also includes a 17,20-lyase activity that converts 17-hyroxypregnenlone to dehydroepiandrosterone.
- CYP21A2 (21-hydroxylase) converts progesterone to deoxycorticosterone (DOC) and 17-OHP to 11 deoxycortisol.
- CYP11B1 (11β-hydroxylase) converts DOC to corticosterone (which then goes on to become aldosterone) and 11-deoxycortisol to cortisol.

4. How is CAH inherited?

All of the enzyme defects leading to CAH are autosomal recessive disorders: therefore, both copies of the involved gene must be abnormal for the condition to occur.

5. What is the most common form of CAH?

By far the most common form is 21-hydroxylase (CYP21A2) deficiency, which accounts for 90% of cases and leads to deficiencies of the salt-retaining hormones DOC and aldosterone in both sexes and/or to virilization of genetic females. Both of these forms are considered “classic” CAH.

6. Which genes encode for 21-hydroxylase?

Two genes encode for 21-hydroxylase: *CYP21A1* (pseudogene) and *CYP21A2,* both of which are located in a 35-kb region on the long arm of chromosome 6 (6p21.3). Both genes are downstream of the gene coding for complement factor 4 (C4A and C4B). *CYP21A1* and *CYP21A2* genes have 98% nucleotide sequence identity, but the former has accumulated several mutations that totally inactivate its gene product. *CYP21A1* is thus an inactive pseudogene, whereas the *CYP21A2* gene encodes for the active 21-hydroxylase enzyme.

7. What causes most of the genetic events responsible for *CYP21A2* deficiencies?

Most of the genetic events responsible for CYP21A2 deficiencies result from the similarity between *CYP21A1* and *CYP21A2* and are due to two types of recombination events between *CYP21A2* and the

pseudogene. Seventy-five percent represent deleterious mutations found in the pseudogene that are transferred to *CYP21A2* during mitosis; this process is termed "gene conversion." Twenty percent are meiotic recombinations producing a nonfunctional chimeric pseudogene. More than 60 additional mutations account for the remaining 5%.

8. What determines the patient's phenotype for 21-hydroxylase deficiency?

Clinical manifestations of the disease are related to the degree of cortisol deficiency, aldosterone deficiency, or both, and the accumulation of precursor hormones. More than 100 *CYP21A2* mutations are known. The patient's phenotype is generally based on the specific genetic alteration of the *CYP21A2* gene, and phenotypes can be grouped into the following four categories:

- Patients with no enzyme activity typically have large deletions or splicing mutations and predominantly have the salt-wasting form of the disorder.
- Patients with a nonconservative amino substitution in exon 4 usually have 1% to 2% of enzyme activity and typically have the simple virilizing form of the disease.
- Patients with a point mutation in exon 7 have 20% to 50% of normal enzyme activity and most often have the nonclassic form of the disease.
- Patients who are heterozygotes have mild abnormalities but no clinically important endocrine disorder.

9. What is the second most common cause of CAH?

The second most common cause of CAH (7% of all cases) is deficiency of the 11β-hydroxylase enzyme (CYP11B1), which is an autosomal recessive defect caused by a mutation on the short arm of chromosome 8 (8q24.3). The result of this deficiency is an increased level of DOC, which may cause hypertension through activation of the mineralocorticoid receptor, leading to sodium retention and hypokalemic alkalosis. The enzyme deficiency also results in increased production of androgens and their precursors, which cause ambiguous genitalia in genetic females.

10. Summarize the rarer forms of CAH.

The rarer forms of CAH are 17α-hydroxylase and 3β-hydroxysteroid dehydrogenase deficiencies. There have been fewer than 200 cases of 17α-hydroxylase deficiency, with 40 described mutations of *CYP17* that span an 8.7-kb region on the short arm of chromosome 10 (10q24.3). The consequence of this deficiency is hypertension due to sodium retention and hypokalemia due to DOC excess (associated with suppression of renin and aldosterone) along with deficiency of androgens and androgen precursors, which causes pseudohermaphroditism in genetic males and delayed puberty in both sexes (see questions 16 and 21).

11. How common is CAH?

CAH is one of the most common inherited diseases. The most common form of CAH, 21-hydroxylase deficiency, has an incidence of 1:10,000 to 1:20,0000 births. The prevalence of this disorder varies greatly among different ethnic groups and is highest among the Ashkenazi Jewish population of Eastern Europe. Nonclassic 21-hydroxylase deficiency occurs in approximately 0.2% of the general Caucasian population but more frequently (1%-2%) in certain populations, such as the Eastern European Ashkenazi Jews.

12. What percentage of the population at large are heterozygote carriers of the 21-hydroxylase defect?

Less than 2% of the population at large is heterozygote carriers of the 21-hydroxylase defect—that is, abnormality of one of the two copies of the 21-hydroxylase gene. Such heterozygote carriers appear normal in all respects but may have elevated 17-OHP with adrenocorticotropic hormone (ACTH) stimulation testing.

13. How common is 11β-hydroxylase deficiency?

The 11β-hydroxylase deficiency, the second most frequent form of CAH, occurs in 1:100,000 births in the general population but in 1:5000 births in Jews of Moroccan descent. CAH due to defects of the other enzymes listed here is extremely rare.

14. Explain why adrenal hyperplasia develops.

The process of adrenal hyperplasia begins in utero. Reduced production of cortisol in the fetus, due to decreased activity of one of the enzymes needed for cortisol synthesis, results in lowered levels of serum cortisol. Cortisol normally acts through a negative feedback loop to inhibit the secretion of ACTH by the pituitary gland and corticotropin-releasing hormone (CRH) by the hypothalamus. Thus, the low serum cortisol levels that occur in a person with CAH increase the secretion of CRH and ACTH in an attempt to stimulate the adrenal glands to overcome the enzyme block and return the serum cortisol level to normal. As this process continues over time, the elevations of serum ACTH stimulate growth of the adrenal glands, leading to hyperplasia. It has been shown that the adrenal volume correlates positively with 17-OHP levels.

15. What is the most serious clinical consequence of CAH?

Adrenal crisis in the newborn period is the most serious consequence of CAH. It usually occurs with genetic defects that result in severe reductions in both aldosterone and cortisol. It is especially insidious in genetic males who do not have ambiguous genitalia as a clue to the diagnosis. Overall, about two thirds of patients with 21-hydroxylase deficiency have this salt-wasting form. These patients have decreased production of DOC and aldosterone but also have increased levels of progesterone and 17-OHP, which may act as mineralocorticoid antagonists, exacerbating the effects of aldosterone deficiency. Aldosterone deficiency leads to hypotension, volume depletion, hyponatremia, hyperkalemia, and increased renin activity. Cortisol deficiency contributes to poor cardiac function, poor vascular response to catecholamines, decreased glomerular filtration rate, and increased secretion of antidiuretic hormone. Both deficiencies lead to hyponatremia, dehydration, and shock.

16. What are other clinical consequences of CAH in females?

Many of the precursors and metabolites that build up behind the blocked enzymes (21-hydroxylase, 11β-hydroxylase, and 3β-hydroxysteroid dehydrogenase) are androgens. They may cause the following conditions:

- Masculinization of the external genitalia of a genetic female fetus, leading to ambiguous genitalia at birth (female pseudohermaphroditism).
- Behaviors more typical of boys during childhood in terms of toy preference, rough play, and aggressiveness. (However, most females are heterosexual and their sexual identity is invariably female.)
- Rapid growth during early childhood with ultimate short stature as an adult due to early closure of epiphyses.
- Infertility in 20% of females with simple virilizing disease and approximately 40% of females with salt-wasting disease.
- Osteopenia in young adulthood in 45% of women with salt wasting.
- Obesity.
- Lower quality-of-life scores in patients with CAH than in age- and sex-matched controls.
- Variable and subtle hyperpigmentation.

17. What are other clinical consequences of CAH in males?

Newborn males with CAH due to deficiency of 21-hydroxylase or 11β-hydroxylase do not have ambiguous genitalia. Because of the typical normal physical appearance, it is often difficult to detect an affected male, especially when symptoms of salt wasting occur after the first week of life.

Later in childhood or early adulthood, males with CAH may present with the following features:

- No overt signs
- Premature puberty
- Variable and subtle hyperpigmentation
- Advanced height in early childhood with ultimate short stature
- Acne
- Testicular enlargement due to adrenal rests, which may produce adrenal-specific hormones
- Oligospermia and/or infertility
- Lower quality-of-life scores than age- and sex-matched controls

18. Are patients with CAH at increased risk for cardiovascular disease?

Studies have shown that patients with CAH have higher body mass index (BMI), higher blood pressures, and more insulin resistance than age-matched controls. They also have endothelial dysfunction similar to that in other obese patients. Further studies are needed to determine whether they have higher rates of cardiovascular events but, given the increased risk factors, patients with CAH should receive lifestyle counseling at an early age.

19. How do patients with 17α-hydroxylase deficiency present?

In 17α-hydroxylase deficiency, the enzyme defect blocks synthesis of androgens, thus precluding masculinization or ambiguity of the external genitalia. Patients present at puberty with the following features:

- Primary (or rarely, secondary) amenorrhea
- Hypertension
- Hypokalemia (because of increased mineralocorticoid production)

20. How do patients with nonclassic CAH present?

Patients with nonclassic CAH (also called late-onset CAH) produce normal amounts of cortisol and aldosterone at the expense of mild to moderate overproduction of sex hormone precursors. The prevalence of nonclassic CAH in women presenting with hyperandrogenic symptoms has been shown to be 2.2%. Thus, a follicular phase 17-OHP test should be included in the evaluation of any female patient with hyperandrogenic symptoms. Usually these patients are asymptomatic, with normal external genitalia, but they may present with the following features:

- Premature puberty
- Severe cystic acne—occurring in 33% of patients
- Hirsutism—most common symptoms occurring in 60% of symptomatic females
- Oligomenorrhea and polycystic ovaries—second most common, occurring in 54% of patients
- Infertility—occurring in 13% of patients

21. Summarize the relationship between adrenal "incidentalomas" and CAH.

Adrenal incidentalomas are more common in patients with CAH and in heterozygotes. Conversely, 60% of patients with incidentalomas have exaggerated 17-OH progesterone responses to ACTH.

22. Describe the presentation of males with CAH due to deficiencies of other enzyme activity.

During fetal development, males with CAH due to deficient activity of 3β-hydroxysteroid dehydrogenase, 17α-hydroxylase, or cholesterol side-chain cleavage enzymes are unable to produce the androgens that are necessary for the formation of male external genitalia. As a consequence, they may have the following features:

- External genitalia at birth are only partially masculinized.
- Normal female appearance (male pseudohermaphroditism).

23. Describe the clinical features that suggest the possibility of CAH.

Adrenal crisis or severe salt wasting in the newborn period suggests the possibility of CAH. CAH also must be considered prominently in the differential diagnosis of any newborn with ambiguous genitalia. Because adrenal crisis and salt loss in CAH may be fatal if not treated, the finding of ambiguous genitalia in a newborn should trigger a rapid attempt to confirm or exclude CAH. Most males with CAH do not have ambiguous genitalia; consequently, many cases go unrecognized at birth, unless there is a documented family history of the disorder.

24. What clinical clues help support or refute the diagnosis of CAH in a newborn with ambiguous genitalia?

The overwhelming majority of genetic males with CAH have unambiguous external genitalia at birth; conversely, CAH is an uncommon cause of ambiguous genitalia in a genetic male. Thus, determination

that the infant with ambiguous genitalia is a genetic male makes CAH unlikely and decreases the diagnostic urgency, because the disorders giving rise to ambiguous genitalia in genetic males are rarely associated with a fatal outcome. For example, the finding of palpable gonads in the scrotal or inguinal area suggests that the infant is a genetic male because such palpable gonads are almost always testes. Conversely, the detection of a uterus in an infant with ambiguous genitalia, on either physical examination or ultrasound, strongly suggests that the infant is a genetic female, thus heightening the possibility of CAH.

25. Discuss the role of molecular biology techniques in the diagnosis of CAH.

Molecular biology techniques can rapidly confirm the genetic sex of a newborn without the prolonged wait for a traditional chromosome analysis. Because of the potentially severe consequences of CAH, it is probably prudent to assume that any genetic female with ambiguous genitalia has CAH until proven otherwise. Furthermore, it is probably best to wait to assign gender until molecular testing is done, because gender misassignment may cause long-term psychological problems for the families of such children. Early diagnosis and appropriate therapy also allow one to avoid the progressive effects of excess adrenal androgens, which cause short stature, gender confusion in girls, and psychosexual disturbances in both boys and girls.

26. How is the diagnosis of CAH confirmed?

Because one does not know which enzyme is deficient in a newborn with suspected CAH (unless the family has a documented history of a particular enzyme defect), serum levels of all steroids that may be in the affected biosynthetic pathway can be measured before and after the administration of 250 μg of synthetic ACTH. Urinary measurement of these steroids by gas chromatography/mass spectroscopy has become economically feasible. Plasma renin activity and aldosterone levels should also be measured to assess the adequacy of aldosterone synthesis. Determination of which steroid levels are supranormal and which are low facilitates localization of the exact enzyme block.

27. How are specific genetic defects confirmed?

Specific genetic defects may be confirmed with molecular genetic testing. Polymerase chain reaction (PCR) amplification for the rapid simultaneous detection of the 10 mutations that are found in approximately 95% of 21-hydroxylase deficiency alleles is used for rapid results. Molecular genetic analysis of CYP21 is not essential for diagnosis but may be helpful to:

- confirm the basis of the defect.
- aide in genetic counseling.
- establish the disease in certain cases.

28. What should be done when nonclassic CAH is suspected in older patients?

When nonclassic CAH is suspected in the preteen, teenage, or adult patient, obtain an early morning 17-OHP measurement, and if the level is greater than 200 ng/dL, proceed with ACTH stimulation testing. ACTH stimulation testing should be done with 250 μg (not 1 μg) of synthetic ACTH; measurement of 17-OHP, 17-OH pregnenolone, and cortisol should be done before and 60 minutes after injection. Stimulated levels of 17-OHP with classic CAH are typically greater than 20,000 ng/dL, whereas patients with nonclassic CAH usually have 17-OHP levels in the range of 1500 to 10,000 ng/dL. Hyperandrogenism can be assessed in women by measuring serum levels of testosterone, androstenedione, and 3α-androstanediol glucuronide.

29. Describe the test used for newborn screening.

The screening process for newborns is divided into first-tier screening and second-tier screening tests. First-tier screening tests for CAH focus on the rapid detection of classic 21-hydroxylase deficiency on Guthrie cards (filter paper on which blood samples are collected, dried, and transported) measured by automated time-resolved dissociation-enhanced lanthanide fluoroimmunoassay. This screening method measures 17-OHP. Basal 17-OHP usually exceeds 10,000 ng/dL in affected infants, whereas the levels in normal infants are below 100 ng/dL. For the test to have a high level of sensitivity, cutoff

values are set low in order to have 1% of all test results reported as positive, thus leading to several false-positive results. Infants who are premature, sick, or stressed have higher levels of 17-OHP. Second-tier testing includes molecular genetic testing or biochemical testing that measures steroid ratios by liquid chromatography followed by mass spectrometry. As of 2009, all 50 states in the United States and at least 12 other countries screen for CAH.

30. What other tests may be used?

If CAH is suspected and newborn filter paper screening is not available, ACTH stimulation with steroid precursor measurements should be done after the first 24 hours of life. Adrenal ultrasonography can also be used as a potential screening test for CAH in neonates with ambiguous genitalia and/or salt-losing crisis by detecting an adrenal limb width greater than 4 mm.

31. How is CAH treated in neonates?

The most important goal of treatment is to prevent salt loss and adrenal crisis in the newborn period. This goal requires the prompt administration of glucocorticoids and, in many cases, mineralocorticoids as well as careful monitoring of salt intake. This treatment not only replaces the deficient hormones but also suppresses serum ACTH elevations, thereby reducing adrenal production of androgenic precursors and metabolites. Such treatment may be given presumptively during the wait for the results of definitive laboratory tests and then discontinued if the results are not confirmatory.

32. What is the appropriate hydrocortisone formulation in infants and children unable to take a tablet?

The hydrocortisone tablet and suspension are not bioequivalent, and the suspension may have uneven distribution. Infants and children unable to take a tablet should take crushed hydrocortisone tablets in liquid.

33. When is surgical correction of ambiguous genitalia carried out?

Surgical correction of ambiguous genitalia in girls consists of genitoplasty of the clitoris and labia and vaginoplasty. Single-stage surgery is now implemented between 2 and 6 months of life. Patients so treated may have variable degrees of impairment of psychosexual functioning as adults, depending on the method and timing of the surgery and the underlying mutation. Evidence has shown that patients with more severe mutations have lower sexual function scores, a lower satisfaction with their sexual lives, and more surgical complications.

34. Describe the treatment of CAH in children.

The preferred glucocorticoid for long-term replacement is hydrocortisone in doses of 10 to 15 mg/m^2/day in three divided doses. Hydrocortisone is preferred because of its short half-life, which minimizes growth suppression. It is sometimes extremely difficult or impossible to find a dosage of glucocorticoid that normalizes production of androgens and maintains normal growth and weight gain. In such situations, mineralocorticoids (fludrocortisone) and/or spironolactone/flutamide (androgen receptor blockers that prevent virilization) in combination with the aromatase inhibitor testolactone (which prevents estrogen-induced epiphyseal fusion) may be useful adjunctive therapy in combination with nonsuppressive replacement doses of glucocorticoids. Rarely, adrenalectomy has been used for difficult-to-control cases, because treatment of adrenal insufficiency is relatively much simpler. All patients with salt-wasting CAH should be treated with fludrocortisone, the recommended dosing being 0.05 to 0.2 mg/day given once or twice a day.

35. How is CAH treated in adolescents and adults?

The use of growth hormone, gonadotropin-releasing hormone analogs (GNRHas), anti-androgens, and aromatase inhibitors—alone or in various combinations—may improve the final predicted height, particularly in those whose predicted height is 2.25 standard deviations or less below normal. However, such treatment should be done under the auspices of an institutional review board (IRB)–approved protocol, because both the necessity and the long-term consequences of such an approach have yet to be determined. Prednisone (5-7 mg daily in two divided doses) or dexamethasone (0.25-0.5 mg daily) may be used once growth has been completed. Because of the potency of dexamethasone, intermediate doses

can be achieved by using liquid dexamethasone (1 mg/mL), which is generally used for other conditions in infants and children. Patients should be monitored carefully for signs of iatrogenic Cushing syndrome, and sonography should be used in males to detect testicular adrenal rests.

36. What is the role of glucocorticoid treatment in nonclassic CAH?

Glucocorticoid therapy has been shown to be effective in improving acne and irregular menstruation. There is also evidence that women with nonclassic CAH undergoing glucocorticoid therapy have a lower miscarriage rate than women not receiving glucocorticoids. Glucocorticoid therapy may therefore benefit women with infertility or those with a history of miscarriage. Testicular adrenal rest tumors are rare in male patients with nonclassic CAH; thus, glucocorticoid therapy is not indicated in males.

37. What factors favor the achievement of predicted adult height?

- Early diagnosis
- Lower doses of hydrocortisone in the first year of life
- Use of hydrocortisone rather than prednisone or dexamethasone during the pubertal growth spurt
- Mineralocorticoid treatment in all patients who are genetically, even if not clinically, determined to have salt wasting

38. What changes in therapy are necessary as a result of medically significant stress?

Patients with CAH who have been undergoing steroid therapy should wear a medical alert bracelet or necklace and should be provided with an emergency kit of hydrocortisone or dexamethasone for intramuscular use. For medically significant stress, the following measures are recommended:

- Triple the oral dose of glucocorticoids.
- Use intramuscular (or intravenous) steroids if the patient is unable to consume oral medications. Hydrocortisone is the preferred glucocorticoid because of its mineralocorticoid properties.
- Sodium chloride, 1-2 g/day, may be necessary in infants.
- Higher doses of fludrocortisone acetate (Florinef) are not recommended during severe stress. The mineralocorticoid effects of hydrocortisone are sufficient.

39. What changes in therapy are necessary during pregnancy in patients with CAH?

- Use hydrocortisone or prednisone instead of dexamethasone, which passes through the placenta unmetabolized.
- Adjust the steroid dose according to the clinical status.
- Keep testosterone and free testosterone values in the normal range for pregnancy.
- Use stress doses of steroids during labor and delivery.

40. How is treatment monitored?

The goals of treatment are to prevent symptoms of adrenal insufficiency and to suppress ACTH and adrenal androgen production. For the second goal, it is most appropriate to monitor the levels of the key precursors immediately behind the blocked enzyme (e.g., 17-OHP and androstenedione in the case of 21-hydroxylase deficiency). The goal is not to normalize the 17-OHP level since this will lead to iatrogenic Cushing syndrome. Monitoring should be done every 3 months initially and then every 4-12 months. The levels of 17-OHP can be kept between 400-1200 ng/dL (normal less than 150 in children) and the androstenedione level should be appropriate for the patient's age and sex.

41. What other monitoring tools may be beneficial?

Androgen levels should be monitored during treatment. These include testosterone, androstenedione, and 3α-androstanediol glucuronide. In addition, plasma renin activity should be monitored in patients with salt-wasting CAH. Children must undergo annual bone age determinations, and their height should be carefully monitored. Because patients with CAH have a higher number of risk factors for cardiovascular disease, they should be routinely monitored and treated for cardiovascular disease, which may begin at an earlier age than normal. Adult men with CAH are prone to development of testicular adrenal

rests and may have reduced fertility. This can be monitored by serial ultrasound and semen analysis, if appropriate.

42. What genetic counseling is appropriate for a couple who previously had a child with CAH?

Because all forms of CAH are autosomal recessive disorders, both parents of a child with CAH are obligate heterozygote carriers of the gene defect. Consequently, the chance that another child of the same couple will have CAH is one in four; 50% of the children will be heterozygote carriers. Genetic counseling should be given to all parents who have a child with CAH. Modern genetic techniques and chorionic villus sampling of fetal DNA at 9 weeks of gestation allow the diagnosis of CAH during the first trimester of pregnancy. The other use for genotypic identification includes the prediction of the phenotype (i.e., severity of the disease). There appears to be a good relationship between genotype and phenotype in classic but not in nonclassic CAH.

43. Are any prenatal treatments available for the fetus with CAH?

Glucocorticoid treatment of the fetus with 21-hydroxylase should be regarded as experimental at this time and only be done in the context of an IRB-approved protocol. Earlier recommendations for such treatment were based on small and uncontrolled studies. The potential adverse effects of glucocorticoid therapy in this setting may outweigh any benefits.

WEBSITE

The Hormone Foundation's Patient Guide to Congenital Adrenal Hyperplasia http://www.hormone.org/Resources/upload/CAH-patient-guide-Web-2.pdf.

KEY POINTS 1: CONGENITAL ADRENAL HYPERPLASIA

1. Congenital adrenal hyperplasia (CAH), the most common inherited disease, is a group of autosomal recessive disorders, the most frequent of which is 21-hydroxylase deficiency.
2. The most serious consequences of CAH are neonatal salt wasting, ambiguous genitalia in females at birth, premature puberty, and, ultimately, short stature.
3. CAH is diagnosed through measurement of cortisol precursors before and 1 hour after the intravenous administration of 250 μg of synthetic corticotropin (ACTH).
4. Predicted adult height can be achieved through early diagnosis, lower doses of corticosteroids in the first year of life and during puberty, and the use of fludrocortisone even in those who have salt wasting on genetic but not clinical grounds.
5. CAH is a rare cause of ambiguous genitalia in a genetic male.
6. The most common symptom in nonclassic CAH in females is hirsutism.
7. Prenatal treatment with dexamethasone and height-enhancing treatment with growth hormone and/or gonadotropin-releasing hormone analogs (GNRHas) should be done only under institutional review board–approved protocols in centers of excellence that are part of multicenter studies.

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BIBLIOGRAPHY

Arlt W, Willis D, Wild S, et al: Health status of adults with congenital adrenal hyperplasia: a cohort study of 203 patients, *J Clin Endocrinol Metab* 95:5110–5121, 2010.

Balsamo A, Cicognani A, Baldazzi L, et al: CYP21 genotype, adult height, and pubertal development in 55 patients treated for 21-hydroxylase deficiency, *J Clin Endocrinol Metab* 88:5680–5688, 2003.

Bidet M, Bellanne-Chantelot C, Galand-Portier M, et al: Fertility in women with nonclassical congenital adrenal hyperplasia due to 21-hydroxylase deficiency, *J Clin Endocrinol Metab* 95:1182–1190, 2010.

Cabrera M, Vogiatzi M, New M: Long term outcome in adult males with classic congenital adrenal hyperplasia, *J Clin Endocrinol Metab* 86:3070–3078, 2001.

Chrousos G, Loriaux D, Mann D, et al: Late-onset 21-hydroxylase deficiency mimicking idiopathic hirsutism or polycystic ovarian disease: an allelic variant of congenital virilizing adrenal hyperplasia with a milder enzymatic defect, *Ann Intern Med* 96:1–43, 1982.

Claahsen-van der Grinten H, Otten B, Sweep F, et al: Testicular tumors in patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency show functional features of adrenocortical tissue, *J Clin Endocrinol Metab* 92:2674–3680, 2007.

Deneux C, Veronique T, Dib A, et al: Phenotype-genotype correlation in 56 women with nonclassical congenital adrenal hyperplasia due to 21-hydroxylase deficiency, *J Clin Endocrinol Metab* 86:207–213, 2001.

Escobar-Morreale H, Sanchón R, Millán J: A prospective study of the prevalence of nonclassical congenital adrenal hyperplasia among women presenting with hyperandrogenic symptoms and signs, *J Clin Endocrinol Metab* 93:527–533, 2008.

Falhammar H, Nyström H, Ekström U, et al: Fertility, sexuality and testicular adrenal rest tumors in adult males with congenital adrenal hyperplasia, *European J Endocrinol* 166:441–449, 2012.

Forest MG, Betuel H, David M: Prenatal treatment in congenital adrenal hyperplasia due to 21-hydroxylase deficiency: update 88 of the French multicenter study, *Endocr Res* 15:277, 1989.

Harrington J, Peña A, Gent R, et al: Adolescents with congenital adrenal hyperplasia due to 21-hydroxylase deficiency have vascular dysfunction, *Clinical Endocrinol (Oxf),* 76:837–842, 2012.

Hirvikoski T, Nordenström A, Lindholm T, et al: Cognitive functions in children ar risk for congenital adrenal hyperplasia treated prenatally with dexamethasone, *J Clin Endocrinol Metab* 92:542–548, 2007.

Hirvikoski T, Nördenstrom A, Wedell A, et al: Prenatal dexamethasone treatment of children at risk for congenital adrenal hyperplasia: the Swedish experience and standpoint, *J Clin Endocrinol Metab* 97:1881–1883, 2012.

King J, Wisniewski A, Bankowski B, et al: Long-term corticosteroid replacement and bone mineral density in adult women with classical congenital adrenal hyperplasia, *J Clin Endocrinol Metab* 91:865–869, 2006.

Levine L: Congenital adrenal hyperplasia, *Pediatric Rev* 21:159–171, 2000.

Lin-Su K, Vogiatzi M, Marshall I, et al: Treatment with growth hormone and luteinizing hormone releasing hormone analog improves final adult height in children with congenital adrenal hyperplasia, *J Clin Endocrinol Metab* 90:3318–3325, 2005.

Lin-Su K, Harbison M, Lekarev O, et al: Final adult height in children with congenital adrenal hyperplasia treated with growth hormone, *J Clin Endocrinol Metab* 96:1710–1717, 2011.

Linder B, Esteban N, Yergey A, et al: Cortisol production rate in childhood and adolescence, *J Pediatr* 117:892, 1991.

Lo J, Schwitzgebel V, Tyrrell J, et al: Normal female infants born of mothers with classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency, *J Clin Endocrinol Metab* 84:930–936, 1999.

Merke D, Keil M, Jones J, et al: Flutamide, testolactone, and reduced hydrocortisone dose maintain normal growth velocity and bone maturation despite elevated androgen levels in children with congenital adrenal hyperplasia, *J Clin Endocrinol Metab* 85:1114–1120, 2000.

Merke D, Bornstein D: Congenital adrenal hyperplasia, *Lancet* 365: 2125–2136, 2005.

Miller W: The syndrome of 17,20 lyase deficiency, *J Clin Endocrinol Metab* 97:59–67, 2012.

Mnif M, Kamoun M, Mnif F, et al: Long-term outcome of patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency, *Am J Med Sci* 344:363–373, 2012.

Mulaikal R, Migeon C, Rock J: Fertility rates in female patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency, *N Engl J Med* 316:178, 1987.

Muthusamy K, Elamin M, Smushkin G, et al: Adult height in patients with congenital adrenal hyperplasia: a systematic review and metaanalysis, *J Clin Endocrinol* 95:4161–4172, 2010.

New M, Carlson A, Obeid J, et al: Prenatal diagnosis for congenital adrenal hyperplasia in 532 pregnancies, *J Clin Endocrinol Metab* 86:5651–5657, 2001.

Nordenskjold A, Holmdahl G, Frisen L, et al: Type of mutation and surgical procedure affect long-term quality of life for women with congenital adrenal hyperplasia, *J Clin Endocrinol Metab* 93:380–386, 2008.

Nordenström A, Frisen L, Falhammar H, et al: Sexual function and surgical outcome in women with congenital adrenal hyperplasia due to CYP21A2 deficiency: clinical perspective and the patients' perception, *J Clin Endocrinol Metab* 95:3633–3640, 2010.

Nordenström A, Servin A, Bohlin G, et al: Sex-typed toy play behavior correlates with the degree of prenatal androgen exposure assessed by CYP21 genotype in girls with congenital adrenal hyperplasia, *J Clin Endocrinol Metab* 87: 5119–5124, 2002.

Pang S: Congenital adrenal hyperplasia, *Endocrinol Metab Clin N Am* 26:853–891, 1997.

Reisch N, Scherr M, Flade L, et al: Total adrenal volume but not testicular adrenal rest tumor volume is associated with hormonal control in patients with 21-hydroxylase deficiency, *J Clin Endocrinol Metab* 95:2065–2072, 2010.

Sherman S, Aston C, Morton N, et al: A segregation and linkage study of classical and nonclassical 21-hydroxylase deficiency, *Am J Hum Genet* 42:830, 1988.

Speiser P, Azziz R, Baskin L, et al: Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society clinical practice guideline, *J Clin Endocrinol Metab* 95:4133–4160, 2010.
Speiser P, White P: Congenital adrenal hyperplasia, *N Engl J Med* 349:776, 2003.
Therrell B Jr, Berenbaum S, Manter-Kapanke V, et al: Results of screening 1.9 million Texas newborns for 21-hydroxylase-deficient congenital adrenal hyperplasia, *Pediatrics* 101:583, 1998.
Trapp C, Oberfiled S: Recommendations for treatment of nonclassic congenital adrenal hyperplasia (NCCAH): an update. *Steroids* 77:342–346, 2012.
Urban M, Lee P, Migeon C: Adult height and fertility in men with congenital virilizing adrenal hyperplasia, *N Engl J Med* 299:1392, 1978.
Van Wyk J, Ritzen E: The role of bilateral adrenalectomy in the treatment of congenital adrenal hyperplasia, *J Clin Endocrinol Metab* 88:2993–2998, 2003.
Wedell A: Molecular genetics of congenital adrenal hyperplasia (21-hydroxylase deficiency): implications for diagnosis, prognosis and treatment, *Acta Paediatr* 87:159–164, 1998.
White P, New M, Dupont B: Structure of the human 21-hydroxylase gene, *Proc Natl Acad Sci USA* 83:5111, 1986.
White P, Spieser P: Congenital adrenal hyperplasia due to 21-hydroxylase deficiency, *Endocr Rev* 21(3):245–291, 2000.

THYROID TESTING

Michael T. McDermott

1. What is the single best test to screen for abnormal thyroid gland function?

Serum thyroid-stimulating hormone (TSH) measurement is the best test for assessing thyroid function because the vast majority of cases of thyroid dysfunction are due to primary thyroid disease, to which the pituitary gland responds with predictable changes in TSH secretion. TSH levels are misleading, however, when thyroid dysfunction results from pituitary or hypothalamic disease and in patients with non-thyroidal illnesses. Measurement of serum thyroxine (T_4) and triiodothyronine (T_3) are useful when the TSH level is outside the reference range.

2. How do you interpret the serum TSH level?

When the TSH is elevated, the patient almost always has primary hypothyroidism; when the TSH is low, the patient usually has primary hyperthyroidism. Abnormal serum TSH values reflect mild thyroid dysfunction long before serum T_4 and T_3 levels are outside their reference ranges. Exceptions to these rules occur in patients who have pituitary-hypothalamic disorders or non-thyroidal illnesses. Measurement of serum free T_4 should be performed whenever the TSH level is high; both free T_4 and total T_3 (or free T_3 by equilibrium dialysis) values are often informative when the TSH is low.

3. Explain how the serum TSH is used to manage patients undergoing thyroid hormone therapy.

Thyroid hormone therapy is usually given to patients for one of two purposes, replacement therapy for hypothyroidism or suppression therapy for thyroid cancer. When replacement is the goal, the dosage should be adjusted to maintain the serum TSH level within the reference range. When suppression is the goal, the dosage should be adjusted to keep the serum TSH level low normal or slightly low for most patients and to keep it "undetectable" for those with aggressive or metastatic thyroid cancer.

4. Discuss the advantages of free thyroid hormone assays.

Free T_4 and T_3 assays determine the amounts of unbound, bioactive thyroid hormones in the circulation. Free thyroid hormone measurements fall into two main categories: equilibrium dialysis and analog assays. Equilibrium dialysis methods are more accurate because they are not affected by serum thyroid hormone–binding protein abnormalities. Analog methods, which are used by most commercial laboratories, are variably affected by protein binding. Currently, free T_4 assays are considered reasonably good, but the accuracy of commercially available free T_3 assays remains questionable. This is why many experts still prefer total T_3 over free T_3 measurements.

5. What do total T_4 and T_3 assays measure?

These assays measure the total T_4 and T_3 concentrations in the circulation. More than 99% of circulating T_4 and approximately 98% of T_3 are bound to proteins, such as thyroxine-binding globulin (TBG), thyroxine-binding prealbumin (TBPA or transthyretin), and albumin. Serum total T_4 and T_3 levels can therefore be altered by protein-binding disorders.

6. Name the major disorders of thyroid hormone-binding proteins.

Pregnancy, estrogen use, congenital TBG excess, and familial dysalbuminemic hyperthyroxinemia (FDH) are the most common. FDH is an inherited disorder in which albumin has enhanced affinity

TABLE 32-1. DIAGNOSIS OF DISORDERS OF THYROID HORMONE–BINDING PROTEINS

	TOTAL T_4	TOTAL T_3	T_3 RESIN UPTAKE
Hyperthyroidism	↑	↑	↑
Increased protein-binding state	↑	↑	↓
Hypothyroidism	↓	↓	↓
Decreased protein-binding state	↓	↓	↑

T_4, thyroxine; T_3, triiodothyronine.

for T_4, resulting in increased levels of total T_4 but not T_3. Protein binding of T_4 and T_3 is reduced by androgens and congenital TBG deficiency.

A T_3 resin uptake (T_3RU) measurement helps distinguish protein-binding disorders from true thyroid diseases. The T_3RU is inversely proportional to the protein-binding capacity; accordingly, T_3RU is low when T_4 protein binding is increased and high when T_4 protein binding is reduced. Table 32-1 indicates how these tests are used to make the correct diagnosis.

7. What antithyroid antibody tests are clinically useful?

Anti–thyroid peroxidase (TPO) and antithyroglobulin antibodies are present in the sera of most patients with Hashimoto's thyroiditis. Either test can establish a diagnosis of Hashimoto's disease, but the TPO antibodies are more sensitive. TSH receptor antibodies (TRAbs) and thyroid-stimulating immunoglobulins (TSIs) are detectable in the sera of most patients with Graves' disease; their measurement is not necessary when the diagnosis of Graves' disease is obvious but may be helpful when the diagnosis is in question.

8. How useful are thyroglobulin measurements?

Thyroglobulin (TG) is the major iodoprotein constituent of thyroid follicles. Serum TG levels are mildly increased in many thyroid diseases, but marked elevations are seen mainly with active thyroid cancer and in destructive thyroiditis (subacute, postpartum, or silent thyroiditis). TG measurements are useful for monitoring patients with thyroid cancer. When a patient has been treated and is cancer-free, the serum TG value should be undetectable. Normal or elevated serum TG values in such patients suggest the presence of residual or metastatic thyroid cancer. Most TG assays are not reliable in patients who have anti-TG antibodies because these antibodies interfere with the method of TG measurement.

9. When should a serum calcitonin level be measured?

Calcitonin is made by thyroid parafollicular C cells rather than by follicular cells. Serum calcitonin is elevated in medullary carcinoma of the thyroid (MCT) and in its familial precursor lesion, C-cell hyperplasia. Because MCT is an uncommon thyroid neoplasm, serum calcitonin measurement should not be used in the routine evaluation of most thyroid nodules. It is indicated, however, in a patient who exhibits a feature characteristic of MCT, such as familial occurrence or associated diarrhea.

10. Discuss the utility and interpretation of the radioactive iodine uptake (RAIU) test.

Thyroid follicular cells have iodine symporters or pumps that bring iodine into the cells for thyroid hormone synthesis. The activity of these iodine pumps can be assessed by measuring the radioactive iodine uptake (RAIU). The normal 24-hour RAIU is approximately 10% to 25% in the United States, but this value varies according to location because of geographic differences in dietary iodine intake. The RAIU is most useful in the differential diagnosis of thyrotoxicosis by separating disorders into two distinct categories: high-RAIU thyrotoxicoses and low-RAIU thyrotoxicoses (Table 32-2).

TABLE 32-2. CLASSIFICATION OF THYROTOXICOSIS AS HIGH OR LOW RADIOACTIVE IODINE UPTAKE (RAIU)

High-RAIU thyrotoxicosis	Graves' disease
	Toxic multinodular goiter
	Solitary toxic adenoma
	Thyroid-stimulating hormone (TSH)–secreting tumor
	Human chorionic gonadotropin (hCG)–induced thyrotoxicosis
Low-RAIU thyrotoxicosis	Factitious thyrotoxicosis
	Iodine-induced thyrotoxicosis
	Subacute thyroiditis
	Postpartum thyroiditis
	Silent thyroiditis
	Amiodarone-induced thyrotoxicosis

11. When and why should a thyroid scan be ordered?

A thyroid scan helps distinguish the three most common types of high-RAIU thyrotoxicosis. Graves' disease is characterized by diffuse tracer uptake; toxic multinodular goiter by multiple discrete areas of increased uptake; and the solitary toxic adenoma by a single area of intense uptake. The scan is not helpful in low-RAIU thyrotoxicosis. A thyroid scan is no longer recommended in the evaluation of thyroid nodules unless the serum TSH level is low, in which case the scan can detect the presence of functioning (hot) nodules.

12. What is recombinant human TSH, and how is it used?

Recombinant human TSH (rhTSH) (Thyrogen) is a synthetic human TSH molecule. Thyrogen can be used to stimulate neoplastic thyroid tissue to absorb radioiodine for an imaging procedure. Thyroid cancer tissue ordinarily traps iodine poorly and can be imaged only if the serum TSH is elevated. This elevation can be accomplished either by stopping levothyroxine treatment for 3 to 6 weeks or by giving Thyrogen injections. After the serum TSH level has been increased by either method, serum TG is measured and radioiodine (^{131}I or ^{123}I) is given for whole-body scanning. A positive scan result or detectable TG level indicates the presence of residual or metastatic thyroid cancer. A Thyrogen-stimulated scan with TG measurement has the same accuracy as a levothyroxine withdrawal scan and has the advantage of not causing symptoms of hypothyroidism.

13. How can heterophile antimouse antibodies interfere with assessment of thyroid function?

Heterophile antimouse antibodies (HAMAs) sometimes develop in people who are regularly exposed to rodents, such as laboratory workers, farm workers, and other people who spend a lot of time outdoors, including homeless people. HAMAs can interfere with the measurement of several hormones, including TSH and thyroglobulin. When TSH or thyroglobulin values are not consistent with the clinical picture, interference by HAMAs should be suspected, and the patient questioned about possible exposure to rodents. When a laboratory is alerted to the possibility of HAMA interference, assay conditions can be altered to minimize or eliminate the misleading results.

KEY POINTS 1: THYROID TESTING

1. Serum thyroid-stimulating hormone (TSH) measurement is the best overall test to screen and evaluate patients for thyroid disease and to monitor thyroid hormone replacement therapy.
2. Serum free thyroxine (T_4) should be measured in all patients whose TSH is elevated, and serum free T_4 and total triiodothyronine (T_3) or free T_3 should be measured in patients whose TSH is suppressed.

Continued

KEY POINTS 1: THYROID TESTING—cont'd

3. Anti-thyroid peroxidase (TPO) antibodies are the most accurate test to establish a diagnosis of chronic lymphocytic thyroiditis (Hashimoto's disease).
4. Serum thyroglobulin (TG) is useful for monitoring for recurrence of differentiated thyroid cancer and for assisting in the diagnosis of destructive thyroiditis.
5. Radioactive iodine uptake (RAIU) is used primarily to determine whether patients with thyrotoxicosis have a high-RAIU or low-RAIU disorder.
6. A thyroid scan is used mainly to distinguish among the three most common types of high-RAIU thyrotoxicosis: Graves' disease, toxic multinodular goiter, and a solitary toxic adenoma.

BIBLIOGRAPHY

Andersen S, Pedersen KM, Bruun NH, et al: Narrow individual variations in serum T4 and T3 in normal subjects: a clue to the understanding of subclinical thyroid disease, *J Clin Endocrinol Metab* 87:1068–1072, 2002.

Cavaleri R: Thyroid radioiodine uptake: indications and interpretation, *Endocrinologist* 2:341, 1992.

Demers LM, Spencer CA: Laboratory medicine practice guidelines: laboratory support for the diagnosis and monitoring of thyroid disease, *Thyroid* 13(1):2–126, 2003.

Haugen BR, Pacini F, Reiners C, et al: A comparison of recombinant human thyrotropin and thyroid hormone withdrawal for the detection of thyroid remnant or cancer, *J Clin Endocrinol Metab* 84:3877–3885, 1999.

Nelson JC, Wang R, Asher DT, et al: The nature of analogue-based free thyroxine estimates, *Thyroid* 14:1030–1036, 2004.

Nicoloff JT, Spencer CA: The use and misuse of the sensitive thyrotropin assays, *J Clin Endocrinol Metab* 71:553–558, 1990.

Preissner CM, Dodge LA, O'Kane DJ, et al: Prevalence of heterophilic antibody interference in eight automated tumor marker immunoassays, *Clin Chem* 51:208–210, 2005.

Preissner CM, O'Kane DJ, Singh RJ, et al: Phantoms in the assay tube: heterophile antibody interference with serum thyroglobulin assays, *J Clin Endocrinol Metab* 88:3069–3074, 2003.

Smith SA: Commonly asked questions about thyroid function, *Mayo Clin Proc* 70:573–577, 1995.

Wang R, Nelson JC, Weiss RM, et al: Accuracy of free thyroxine measurements across natural ranges of thyroxine binding to serum proteins, *Thyroid* 10:31–39, 2000.

HYPERTHYROIDISM*

Thanh D. Hoang and Henry B. Burch

1. What is the difference between thyrotoxicosis and hyperthyroidism?

Thyrotoxicosis is the general term for the presence of increased levels of thyroxine (T_4), triiodothyronine (T_3), or both, from any cause. It does not imply that a patient is markedly symptomatic or "toxic." *Hyperthyroidism* refers to causes of thyrotoxicosis in which the thyroid is actively overproducing thyroid hormone.

2. Define the term *autonomy* as it applies to thyroid hyperfunction.

Thyroid autonomy refers to the spontaneous production and secretion of thyroid hormone, independent of thyroid-stimulating hormone (TSH).

3. What is subclinical thyrotoxicosis?

Subclinical thyrotoxicosis is defined as a low serum TSH level with normal free T_4 and T_3. The low TSH concentration can result from either excessive ingestion of thyroid hormone or excessive release of endogenous thyroid hormone. The free T_4 or T_3 level is frequently in the high normal range in affected patients. Clinical symptoms and signs are generally absent or nonspecific.

4. What are the long-term consequences of subclinical thyrotoxicosis?

Some studies have linked subclinical thyrotoxicosis to (1) progression to clinical thyrotoxicosis, (2) skeletal effects, including decreased bone mineral density, accelerated bone loss, and increased fracture risk, particularly in postmenopausal women, and (3) cardiac effects, such as a twofold to threefold higher risk of atrial fibrillation, impaired left ventricular diastolic filling, and impaired ventricular ejection fraction response to exercise. An extensive meta-analysis by Collet and colleagues (see Bibliography) found an increased rate of both cardiovascular and all-cause mortality in patients with subclinical hyperthyroidism. A TSH value below 0.1 mU/L is more likely to be associated with adverse consequences than a TSH value in the range 0.1 to 0.5 mU/L.

5. Does subclinical hyperthyroidism require treatment?

The 2011 American Thyroid Association (ATA)/American Association of Clinical Endocrinologists (AACE) hyperthyroidism management guidelines suggest that patients with TSH levels below 0.1 mU/L who are older than 65 years or who are younger but with symptomatic disease or comorbidities that may be aggravated by mild hyperthyroidism, such as coronary heart disease, should be actively treated. In patients with TSH values between 0.1 and 0.5 mU/L, therapy should at least be *considered* if they are older than 65 years or younger but with comorbidities as previously listed.

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6. List the three most common causes of hyperthyroidism.

- Graves' disease
- Toxic multinodular goiter (TMNG)
- Toxic adenomas or autonomously functioning thyroid nodules (AFTNs)

7. Define Graves' disease

Graves' disease is an autoimmune disorder in which activating autoantibodies directed against the TSH receptor result in continuous stimulation of thyroid hormone production and secretion as well as thyroid growth (goiter). Extrathyroidal manifestations of Graves' disease include ophthalmopathy (proptosis, periorbital edema, extraocular muscle dysfunction, and optic neuropathy), dermopathy (pretibial myxedema), and thyroid acropachy (digital clubbing and edema).

8. Explain toxic multinodular goiter.

TMNG generally arises in the setting of a long-standing multinodular goiter in which certain individual nodules have developed autonomous function and secrete thyroid hormone independent of stimulation by TSH.

9. What are autonomously functioning thyroid nodules?

AFTNs, or toxic adenomas, are benign tumors that have either constitutive activation of the TSH receptor or its signal-transduction apparatus. These tumors frequently produce subclinical thyrotoxicosis and have a predilection for spontaneous hemorrhage. AFTNs generally must be more than 3 cm in diameter before attaining sufficient secretory capacity to produce overt thyrotoxicosis. Often, inefficient iodine processing leads to an excess of T_3 relative to T_4 in AFTNs.

10. What is the Jod-Basedow phenomenon?

The Jod-Basedow phenomenon is iodine-induced thyrotoxicosis following exposure to large quantities of iodine (typically in iodinated radiographic contrast agents for computed tomography [CT] or angiography, but also with the antiarrhythmic drug amiodarone). It was first described following iodine supplementation in people living in regions of endemic iodine deficiency.

11. What are some rarer causes of hyperthyroidism?

Rarer causes of hyperthyroidism include TSH-secreting pituitary adenomas; stimulation of TSH receptors by high levels of human chorionic gonadotropin (hCG), most often in choriocarcinomas in women or germ cell tumors in men; struma ovarii (ectopic thyroid hormone production in thyroid tissue–containing ovarian teratomas); and functional metastatic follicular or papillary thyroid carcinoma. Thyroiditis (postpartum, subacute, painless, radiation- or palpation-induced) and ingestion of excessive exogenous thyroid hormone (iatrogenic, inadvertent, or surreptitious) are causes of thyrotoxicosis but not hyperthyroidism (see question 1).

12. How do thyrotoxic patients present clinically?

Common symptoms of thyrotoxicosis include palpitations, anxiety, agitation, restlessness, insomnia, impaired concentration/memory, irritability or emotional lability, weight loss, heat intolerance, exertional dyspnea, fatigue, hyperdefecation, amenorrhea, oligomenorrhea, hypomenorrhea, anovulation, and hair thinning. Occasionally patients may experience weight gain rather than loss during thyrotoxicosis, presumably owing to polyphagia.

13. What is apathetic hyperthyroidism?

Older patients with hyperthyroidism may lack typical symptoms and signs of sympathetic activation and may present instead with apathy or depression, weight loss, atrial fibrillation, worsening angina pectoris, or congestive heart failure.

14. Describe the physical signs of thyrotoxicosis.

Tremors, tachycardia, flow murmurs, systolic hypertension, warm and moist skin, hyperreflexia with rapid relaxation phases, lid lag/lid retraction, ophthalmopathy, pretibial myxedema, thyroid acropachy,

and a goiter (with a bruit in patients with Graves' disease) may be found in hyperthyroid patients. Eye findings in thyrotoxicosis are discussed in question 15.

15. How does hyperthyroidism cause eye disease?

Lid retraction and stare can be seen with any cause of thyrotoxicosis and are due to sympathetic/adrenergic overactivity. True ophthalmopathy or orbitopathy is unique to Graves' disease and is thought to be caused by thyroid autoantibodies that cross-react with antigens in fibroblasts, preadipocytes, and adipocytes of the retroorbital tissues. Common manifestations of ophthalmopathy include proptosis (exophthalmos), diplopia, and inflammatory changes such as conjunctival injection and periorbital edema.

16. What laboratory testing should be performed to confirm thyrotoxicosis?

Measurement of serum TSH with a third-generation assay (with detection limits of 0.01 mU/L) is the most sensitive means of detecting thyrotoxicosis. Serum free T_4 and T_3 levels should be measured to determine the degree of biochemical thyrotoxicosis. Other associated laboratory findings include mild leukopenia, normochromic normocytic anemia, hepatic transaminitis, elevations of serum alkaline phosphatase and osteocalcin (increased bone turnover), mild hypercalcemia, hyperphosphatemia, and low serum levels of albumin and total cholesterol.

17. When is thyroid antibody testing needed in patients with hyperthyroidism?

The cause of hyperthyroidism can usually be determined with history, physical examination, and radionuclide studies. Testing for TSH receptor antibodies can be used to diagnose Graves' disease during pregnancy, when radionuclide imaging is contraindicated. Such testing is also useful in (1) pregnant women with current or previously treated Graves' disease to determine the risk of fetal and neonatal thyroid dysfunction due to transplacental passage of stimulating or blocking antibodies, (2) biochemically euthyroid patients with ophthalmopathy, (3) patients with alternating periods of hyperthyroidism and hypothyroidism as a result of fluctuations in blocking and stimulating TSH receptor antibodies, and (4) atypical cases in which differentiation of Graves' disease from toxic multinodular goiter is challenging and therapeutically essential.

18. What is the difference between a thyroid scan and an uptake test?

A radioactive iodine uptake (RAIU) test uses radioactive iodine, either ^{131}I or ^{123}I, to quantitatively assess the functional status of the thyroid gland. A small dose of radioisotope is given orally followed by measurement of radioactivity in the area of the thyroid in 4 to 24 hours. Often two measurements are taken, at 4 to 6 hours and at 24 hours. High radioiodine uptake confirms hyperthyroidism whereas *low* (nearly absent) uptake indicates either inflammation and destruction of thyroid tissue with release of preformed hormone into the circulation or an extrathyroidal source of thyroid hormone (Table 33-1). A thyroid scan provides a two-dimensional image showing the distribution of isotope trapping within the thyroid gland. Uniform distribution in a hyperthyroid patient suggests Graves' disease, patchy distribution suggests TMNG, and unifocal activity corresponding to a nodule, with suppression of the rest of the thyroid, suggests a toxic adenoma.

TABLE 33-1. RADIOACTIVE IODINE UPTAKE (RAIU) DIFFERENTIATION OF HYPERTHYROIDISM

	HIGH-RAIU DISORDERS	LOW-RAIU DISORDERS
Common	Graves' disease Toxic multinodular goiter Toxic solitary adenoma	Postpartum thyroiditis Subacute thyroiditis
Rare	Thyroid-stimulating hormone–producing pituitary adenoma Human chorionic gonadotropin–producing choriocarcinoma	Silent thyroiditis Surreptitious or accidental ingestion of levothyroxine (LT_4) or liothyronine (LT_3) Struma ovarii

19. How should hyperthyroidism be treated?

The three main treatment options are antithyroid drugs (ATDs), radioiodine (^{131}I) ablation, and surgery. ATDs available in the United States include methimazole and propylthiouracil. Methimazole is almost always the preferred agent. Owing to concerns about severe hepatotoxicity, propylthiouracil is recommended only in (1) the first trimester of pregnancy (methimazole has been linked to embryopathy when used during the first trimester), (2) thyroid storm therapy because of the ability of propylthiouracil to block T_4-to-T_3 conversion, and (3) patients with minor reactions to methimazole who refuse ^{131}I ablation or surgery. Unless contraindicated, most patients should receive beta-blockers for heart rate control and symptomatic relief. Most thyroidologists in the United States prefer ^{131}I ablation over surgery or prolonged courses of ATDs. Patients scheduled to undergo ^{131}I ablation should be advised to avoid pregnancy for 4 to 6 months and should be cautioned that oral contraceptives may not be fully protective in the hyperthyroid state because of increased levels of sex hormone-binding globulin and higher clearance of the contraceptive.

20. When is surgery indicated for hyperthyroidism?

Surgery is generally not the treatment of choice for hyperthyroidism. It is most often used in the following patients: (1) those with symptomatic compression or large goiters ($>$ 80 g), which is less likely to respond to ATDs or ^{131}I ablation, (2) those with relatively low RAIU values, (3) those in whom thyroid cancer is documented or suspected, (4) those with large nonfunctioning, photopenic, or hypofunctioning nodules, (5) pregnant patients who are allergic to or intolerant of ATDs (^{131}I is contraindicated in pregnancy), (6) those with coexisting hyperparathyroidism requiring surgery, (7) women who plan a pregnancy in less than 4 to 6 months, especially if thyroid-stimulating immunoglobulin (TSH receptor [TSI]) antibody levels are high, and (8) patients who wish to avoid ^{131}I exposure and the potential side effects of ATDs. Surgery may also be preferred when there is moderate to severe active Graves' ophthalmopathy, because use of ^{131}I has been linked to worsening eye disease in this situation. Patients should be euthyroid before surgery in order to decrease the risk of both arrhythmias during anesthesia induction and postoperative thyroid storm.

21. What is the role of iodine in the treatment of hyperthyroidism? What is the Wolff-Chaikoff effect?

Inorganic iodine rapidly decreases the synthesis and release of T_4 and T_3. The transient inhibition of thyroid hormone synthesis by excess iodine is known as the Wolff-Chaikoff effect. However, because this effect generally lasts for about 10 to 14 days, iodine is usually used only after ATDs have been started, to prepare a patient rapidly for surgery, or as an adjunctive measure in patients with thyroid storm. Iodine is also used in some centers to decrease the vascularity of the thyroid prior to thyroidectomy for Graves' disease. Typical doses are Lugol's solution (6.5 mg iodide/drop) 10 drops three times daily or saturated solution of potassium iodide (SSKI, 50 mg iodide/drop) 1 to 2 drops three times daily mixed in water or juice for 10 days prior to surgery.

22. Are other treatments available to lower thyroid hormone levels?

Yes. Two iodine-containing oral cholecystographic agents, ipodate and iopanoic acid, cause dramatic reductions in serum T_3 and T_4 through inhibition of T_4 5′-monodeiodinase. Neither of these agents is currently available in the United States. Other agents occasionally used to treat hyperthyroidism include lithium, which decreases thyroid hormone release, and potassium perchlorate, which inhibits thyroid uptake of iodine. Additionally, cholestyramine 4 g four times daily given with methimazole lowers serum T_4 and T_3 more rapidly than methimazole alone.

23. Which medications block peripheral conversion of T_4 to T_3?

Propylthiouracil, propranolol, glucocorticoids, iopanoic acid, and amiodarone inhibit the peripheral conversion of T_4 to T_3.

24. How effective are ATDs?

Ninety percent of patients taking ATDs become euthyroid without significant side effects. Approximately half of patients attain a remission from Graves' disease after a treatment course of 12 to 18 months.

However, only 30% maintain long-term remission; the remainder experience recurrence of Graves' disease within 1 to 2 years after the drugs are withdrawn. TMNG and AFTNs are not autoimmune diseases; therefore, they do not go into remission. The role of ATDs in these two disorders is only to render a patient euthyroid before surgery or when pretreatment is necessary before ^{131}I therapy (see question 27). The usual starting doses for moderate thyrotoxicosis are methimazole, 10 to 20 mg/day, or propylthiouracil, 50 to 150 mg 3 times/day. Methimazole is recommended for all patients who select ATD therapy for Graves' disease, except in the clinical circumstances listed in question 19.

25. What side effects are associated with ATDs?

- Agranulocytosis is a rare but life-threatening complication of ATD therapy, occurring in approximately 1 in every 200 to 500 patients treated with ATDs. Patients should be instructed to promptly report fever, sore throat, or minor infections that do not resolve quickly. Agranulocytosis appears to be dose-related with methimazole but not with propylthiouracil. Patients experiencing agranulocytosis when taking one ATD should not be exposed to another.
- Hepatotoxicity with occasional progression to fulminant hepatic necrosis can occur with propylthiouracil; cholestatic jaundice has been reported with methimazole. Patients should report right upper quadrant pain, anorexia, nausea, and new pruritus.
- Rashes occur in approximately 2% of patients and can range from limited erythema to an exfoliative dermatitis. Dermatologic reactions to one ATD do not preclude the use of another, although cross-sensitivity occurs in approximately 50% of cases.
- Arthropathy and a lupus-like syndrome can rarely be seen with either propylthiouracil or methimazole.
- Antineutrophil cytoplasmic antibody (ANCA)–positive vasculitis has been associated with propylthiouracil use.
- Potential teratogenicity (so-called methimazole embryopathy) can be associated with methimazole; this includes rare fetal scalp defects (aplasia cutis), choanal atresia, and tracheoesophageal fistulas.

26. What laboratory tests should be monitored in patients taking ATDs?

Serum free T_4 and T_3 levels should be remeasured about 4 weeks after initiation of an ATD, and the dose adjusted accordingly. Because TSH may remain suppressed for several months, free T_4 and T_3 levels are more reliable for assessing thyroid hormone status during this time. Thyroid parameters should be monitored every 4 to 8 weeks until euthyroidism is achieved, with a goal of using the lowest effective ATD dose. Routine monitoring of the white blood cell (WBC) count and liver function, though commonly done in clinical practice, has not been shown to prevent agranulocytosis or hepatotoxicity. A WBC count with differential should be assessed during any febrile illness and at the onset of sore throat/pharyngitis in all patients taking ATDs. Liver function tests should be ordered in patients who experience a pruritic rash, jaundice, light-colored stools or dark urine, arthralgias, abdominal pain or bloating, anorexia, nausea, or fatigue. The ATD should be discontinued if transaminase levels are elevated to two to three times the upper normal limit and fail to improve within 1 week. Liver function values should be monitored every week until resolution of transaminitis after discontinuation of the ATD.

27. How does radioactive iodine work?

Thyroid cells trap and concentrate iodine and use it to make thyroid hormone. ^{131}I is utilized in the same manner as inorganic iodine. Because ^{131}I emits locally destructive beta particles, extensive local thyrocyte damage and ablation of thyroid function occurs over a period of approximately 6 to 18 weeks after treatment. Dosages of ^{131}I should be high enough to cause permanent hypothyroidism and are usually based on the size of the thyroid gland and the pretreatment RAIU value. A typical dose for Graves' disease is 10 to 15 millicuries (mCi); for TMNG, higher doses, 25 to 30 mCi, are given. These doses are effective in 90% to 95% of patients.

28. When is pretreatment with ATDs indicated before ^{131}I ablation?

The use of ATDs before and after radioactive iodine therapy may be considered in (1) patients who are extremely symptomatic or in whom free T_4 levels are three to four times the upper normal limit,

(2) the elderly, and (3) those with substantial comorbidities, such as atrial fibrillation, heart failure, pulmonary hypertension, renal failure, infection, trauma, poorly controlled diabetes mellitus, and cerebrovascular or pulmonary disease. These patients should also be medically stable and treated with beta-adrenergic blocking drugs prior to ^{131}I therapy.

Pretreatment with ATDs helps deplete the thyroid of preformed hormones and thereby to theoretically reduce the risk of radioactive iodine–induced thyroid storm. When pretreatment with ATDs is used, the drugs are generally discontinued 3 to 5 days before ^{131}I is given. However, pretreatment with ATDs is associated with a rapid increase in thyroid hormone levels upon ATD discontinuation. Patients who are not pretreated usually experience a rapid decrease in thyroid hormone levels after ^{131}I therapy. Therefore most patients do not require or benefit from ATD pretreatment.

29. How long after ^{131}I treatment should women wait before becoming pregnant or resuming breast-feeding?

Pregnancy should be deferred for at least 4 to 6 months after ^{131}I ablation to ensure successfully cured hyperthyroidism and corrected hypothyroidism prior to conception. In addition, patients should be taking a stable dose of thyroid hormone replacement and be free of active ophthalmopathy. Breast milk radioactivity, measured in one study after an 8.3-mCi therapeutic dose of ^{131}I, remained unacceptably high for 45 days, prohibiting resumption of breast-feeding after ^{131}I therapy. If technetium ^{99m}Tc or ^{123}I is used for diagnostic studies, breast-feeding may be resumed in 2 to 3 days, with pumping and disposal of breast milk in the interim.

30. Does ^{131}I cause or worsen ophthalmopathy in Graves' disease?

The natural history of Graves' disease is such that up to 25% of patients experience clinically apparent ophthalmopathy. The majority of cases arise in the period from 18 months before to 18 months after the onset of thyrotoxicosis. Thus a fair number of new cases can be expected to coincide with the timing of ^{131}I ablation. However, three randomized clinical trials have shown that ^{131}I therapy is more likely to be associated with new or worsened ophthalmopathy than either ATDs or thyroidectomy. ^{131}I therapy results in a sustained increase in TSH receptor (TSI) antibodies that may be important in exacerbating ophthalmopathy. Patients with preexisting eye disease, those who smoke cigarettes, and those with higher levels of thyroid hormone and high titers of TSH receptor antibodies are more likely to experience worsening. It is therefore prudent to avoid use of ^{131}I in patients with active moderate to severe Graves' ophthalmopathy. In patients with initially mild eye involvement, oral glucocorticoids can be used concurrently to prevent an exacerbation during ^{131}I therapy, particularly in the presence of risk factors for worsening ophthalmopathy.

31. How is thyrotoxicosis managed in pregnancy?

Caution must be used in interpreting thyroid laboratory results during pregnancy, because low TSH values are not uncommon in the first trimester, and total T_4 and T_3 values are elevated by increased thyroxine-binding globulin (TBG) levels. Free T_4 levels, measured with the use of equilibrium dialysis or an assay with trimester-specific reference ranges, are the best indicator of thyroid function during pregnancy. Symptomatic women with marked elevation in trimester-specific free T_4 values or those with total T_4 and/or total T_3 above 1.5 times the upper normal limit should be considered for treatment. Pregnant women with subclinical hyperthyroidism (low TSH, normal free T_4) and asymptomatic or mild hyperthyroidism may be monitored without treatment by measurement of TSH and free T_4 every 4 to 6 weeks. Beta-blockers can be used cautiously and should be slowly tapered off once hyperthyroidism is controlled by ATDs, because of the risks of fetal growth restriction, hypoglycemia, respiratory depression, and bradycardia. Nuclear medicine testing with RAIU or thyroid scanning is contraindicated in pregnancy because of the risk of fetal exposure to isotopes. Because ^{131}I therapy is also contraindicated during pregnancy, treatment options are limited to ATDs and surgery. The American Thyroid Association and the U.S. Food and Drug Administration (FDA) recommend that use of propylthiouracil be limited to the first trimester only, owing to the potentially serious teratogenic effects of methimazole during organogenesis of the first trimester (aplasia cutis, choanal atresia, esophogeal atresia, and tracheoesophageal fistulas). Treatment should be switched to

methimazole at the beginning of the second trimester. A 300-mg daily dose of propylthiouracil is roughly equivalent to a 10- or 15-mg daily dose of methimazole. Thyroid function tests should be obtained 4 weeks after the switch to methimazole to ensure maintenance of euthyroidism. Pregnant patients with Graves' disease require close follow-up to ensure adequate control and to prevent hypothyroidism, because Graves' disease frequently remits during the course of pregnancy. TSH receptor antibodies, which are able to cross the placenta after 26 weeks, should be measured in the third trimester to assess the risk of neonatal thyroid dysfunction. Antepartum testing should include monitoring for fetal tachycardia in mothers with persistent elevations in TSH receptor antibodies, and fetal ultrasound to assess for evidence of fetal goiter or growth restriction.

32. What are the treatments for Graves' ophthalmopathy?

Patients with Graves' orbitopathy should be treated according to the severity of their eye disease. Those with only mild eye involvement may generally be treated with local measures alone, such as tinted lenses for photosensitivity, artificial tears, and raising the head of the bed to prevent worsening retro-ocular edema in the recumbent position overnight. Moderate eye involvement with lid erythema and edema and conjunctival erythema and edema (chemosis) generally requires glucocorticoid therapy. Severe ophthalmopathy, including advanced proptosis or extraocular muscle dysfunction, often requires initial immunomodulatory medication followed by surgical rehabilitative surgery. *Sight-threatening ophthalmopathy* is a medical emergency, occurring either as a result of optic nerve compression by enlarged extraocular muscles at the apex of the orbit or because of corneal ulceration. In the former case, pulse intravenous glucocorticoids should be given immediately and patients should be admitted to the hospital for possible urgent orbital decompression surgery.

KEY POINTS 1: HYPERTHYROIDISM

1. The three most common causes of hyperthyroidism are Graves' disease, toxic multinodular goiter, and toxic adenoma.
2. Thyroiditis can cause severe thyrotoxicosis but generally resolves without intervention and may be followed by a hypothyroid phase.
3. Routine diagnostic testing for hyperthyroidism includes measurements of serum thyroid-stimulating hormone (TSH), free T_4, T_3, radioactive iodine uptake testing, and thyroid scanning with ^{123}I or technetium ^{99m}Tc.
4. The major treatment choices for hyperthyroidism are radioiodine, antithyroid drugs (generally methimazole), and thyroidectomy. Beta-blockers can significantly improve adrenergic symptoms of thyrotoxicosis and do not interfere with testing or later treatment.
5. Treatment is generally indicated in all patients in whom TSH is less than 0.1 mU/L.

BIBLIOGRAPHY

Bahn RS, Burch HB, Cooper DS, et al: The role of propylthiouracil in the management of Graves' disease in adults: report of a meeting jointly sponsored by the American Thyroid Association and the Food and Drug Administration. *Thyroid* 19:673–674, 2009.

Bahn RS: Graves' ophthalmopathy, *New Engl J Med* 362:726–38, 2010.

Bahn RS, Burch HB, Cooper DS, et al: Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists, *Thyroid* 21:593–645, 2011.

Biondi B, Cooper DS: The clinical significance of subclinical thyroid dysfunction, *Endocrin Rev* 29:76–131, 2008.

Boelaert K, Torlinska B, Holder RL, et al: Older subjects with hyperthyroidism present with a paucity of symptoms and signs: a large cross-sectional study, *J Clin Endocrinol Metab* 95:2715–26, 2010.

Burch HB, Shakir F, Fitzsimmons TR, et al: Diagnosis and management of the autonomously functioning thyroid nodule: the Walter Reed Army Medical Center experience, 1975–*1996, Thyroid* 8:871–880, 1998.

Burch HB, Solomon BL, Cooper DS, et al: The effect of antithyroid drug pretreatment on acute changes in thyroid hormone levels after 131I ablation for Graves' disease, *J Clin Endocrinol Metab* 86:3016–3021, 2001.
Collet TH, Gussekloo J, Bauer DC, et al: Subclinical hyperthyroidism and the risk of coronary heart disease and mortality, *Arch Intern Med* 172:799–809, 2012.
Cooper DS: Antithyroid drugs, *N Engl J Med* 352:905–917, 2005.
Luton D, Le Gac I, Vuillard E, et al: Management of Graves' disease during pregnancy: the key role of fetal thyroid gland monitoring, *J Clin Endocrinol Metab* 90:6093–6098, 2005.
Mai VQ, Burch HB: A stepwise approach to the evaluation and management of subclinical hyperthyroidism, *Endocrine Practice* 185:772–780, 2012.
McDermott MT, Ridgway EC: Central hyperthyroidism, *Endocrinol Metab Clin North Am* 27:187–203, 1998.
Stagnaro-Green A, Abalovich M, Alexander E, et al: Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum, *Thyroid* 21:1–45, 2011.
Surks MI, Ortiz E, Daniels GH, et al: Subclinical thyroid disease: scientific review and guidelines for diagnosis and management, *JAMA* 291:228–239, 2004.

HYPOTHYROIDISM

Katherine Weber and Bryan R. Haugen

1. What is hypothyroidism?

Hypothyroidism is a condition that results from inadequate production or action of thyroid hormone, most commonly due to primary hypothyroidism, or failure of the thyroid gland itself. Hypothyroidism can be overt, with a frank decrease in serum thyroxine (T_4) levels and a compensatory increase in thyroid-stimulating hormone (TSH) levels. More commonly seen is subclinical hypothyroidism (also called mild thyroid failure), in which the TSH is mildly elevated but T_4 levels are normal. Subclinical hypothyroidism often manifests with few or no symptoms, but hypercholesterolemia and subtle cardiac abnormalities can be seen.

2. How common is hypothyroidism?

Hypothyroidism is a common condition. The prevalence of overt hypothyroidism in the United States is estimated at 0.3% to 0.4%, whereas that of subclinical hypothyroidism is much higher (4%-8%). The mean age at diagnosis is the mid-50s. Hypothyroidism is much more common in women, with a female-to-male ratio of 3:1. Postpartum hypothyroidism, a transient hypothyroid phase after pregnancy, occurs in 5% to 10% of women.

3. What are the two most common causes of hypothyroidism?

Although many disorders can cause hypothyroidism, the two most common causes are chronic lymphocytic thyroiditis (Hashimoto's disease), an autoimmune form of thyroid destruction, and radioiodine-induced hypothyroidism after treatment of Graves' disease (autoimmune hyperthyroidism).

4. List the less common causes of hypothyroidism.

- Thyroidectomy
- Subacute thyroiditis
- External irradiation to the neck
- Medications (antithyroid drugs, amiodarone, lithium, bexarotene, tyrosine kinase inhibitors, and interferon)
- Infiltrative diseases
- Central (pituitary/hypothalamic) hypothyroidism (Fig. 34-1)
- Congenital defects
- Endemic (iodine-deficient) goiter, which is fairly common outside the United States

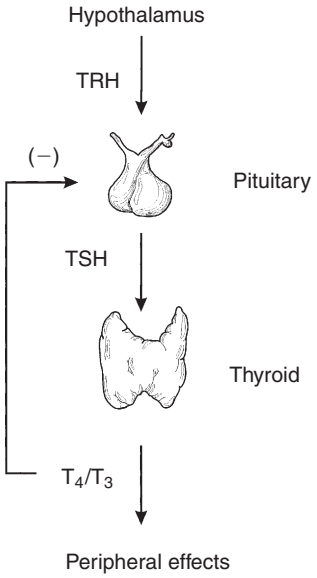

Figure 34-1. Hypothalamic-pituitary-thyroid axis. T_3, triiodothyronine; T_4, thyroxine; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.

5. List the symptoms commonly experienced in hypothyroidism.

Hypothyroidism commonly manifests with nonspecific symptoms, such as fatigue, cold intolerance, depression, weight gain, weakness, joint aches, constipation, dry skin, hair loss, and menstrual irregularities.

6. What findings on physical examination are consistent with hypothyroidism?

Physical findings may be normal with mild thyroid failure and should not deter further workup if clinical suspicions are high. Common signs of moderate to severe hypothyroidism include:

- Hypertension (diastolic hypertension is a clue)
- Bradycardia
- Coarse hair
- Periorbital swelling
- Yellow skin (due to elevations of beta-carotene)
- Carpal tunnel syndrome
- Delayed relaxation of the deep tendon reflexes

7. What does palpation of the thyroid reveal?

The thyroid may be enlarged, normal, or small in hypothyroidism, but thyroid consistency is usually firm.

8. Summarize unusual presentations of hypothyroidism.

Unusual presentations of hypothyroidism include megacolon, cardiomegaly, pericardial effusion, and congestive heart failure (CHF). Severe CHF in one reported patient scheduled for cardiac transplant resolved with thyroid hormone replacement alone.

9. Describe the laboratory values that may be abnormal during hypothyroidism.

Laboratory clues to hypothyroidism include normochromic, normocytic anemia (menstruating women may also have iron deficiency anemia due to excessive bleeding from irregular menses), hyponatremia, hypercholesterolemia, and elevations of creatine phosphokinase.

10. What tests best confirm the diagnosis of hypothyroidism in the outpatient setting?

Many thyroid function tests are available to the clinician, including assessments of TSH, T_4, triiodothyronine (T_3), resin uptake, free T_4, free T_3, and reverse T_3. In the outpatient setting only one test is usually necessary: assessment of TSH. TSH, which is synthesized and secreted from the anterior pituitary gland, is the most sensitive indicator of thyroid function in the nonstressed state. Basically, if the TSH level is normal (range: 0.5-5 mU/L), the patient is euthyroid; if the TSH is elevated ($>$ 5 mU/L), the patient has primary gland failure. In the unusual case in which central hypothyroidism is suspected, a free T_4 measurement is the best screening test.

11. How should total T_4 levels be interpreted?

Care must be taken in interpreting total T_4 levels (occasionally performed on health-screening panels). Many conditions unrelated to thyroid disease cause low or elevated values of total T_4 because more than 99% of T_4 is protein-bound, and total T_4 levels depend on the amount of thyroid hormone–binding proteins, which may vary greatly. The total T_4 level must always be compared with the patient's T_3 resin uptake (T_3RU) value, which reflects the amount of thyroid hormone–binding protein.

12. Explain why thyroid function test results are more difficult to interpret in acutely ill inpatients.

Interpretation of thyroid function test results in acutely ill inpatients is more difficult when hypothyroidism is suspected. Acute nonthyroidal illness may cause suppression of the total T_4, free T_4,

KEY POINTS 1: HYPOTHYROIDISM

1. Thyroid-stimulating hormone (TSH) measurement is the best screening test for primary hypothyroidism in the outpatient setting.
2. Levothyroxine (LT_4) is the preferred initial treatment for hypothyroidism and in healthy young patients can be started at a dose of 1.6 mcg/kg/day.
3. The goal TSH for treatment of primary hypothyroidism is between 0.5 and 2.0 mU/L.
4. Subclinical hypothyroidism (elevated TSH but normal thyroxine/triiodothyronine [T_4/T_3]) is common, and treatment can alleviate symptoms as well as cardiac and lipid abnormalities.

total T_3, free T_3, and TSH levels, and TSH may then be elevated in the recovery phase (see Chapter 39). Medications, such as dopamine and glucocorticoids, may also suppress the TSH value.

13. How do you diagnose hypothyroidism in acutely ill inpatients?

When hypothyroidism is suspected in the stressed, hospitalized patient, a combination of clinical signs (inappropriate bradycardia, puffy facies, dry skin, and delayed relaxation of deep tendon reflexes) and laboratory values (TSH and free T_4 levels) is necessary to exclude or confirm the diagnosis of hypothyroidism. If these values are equivocal, measurement of a reverse T_3 level, which is normal or elevated in nonthyroidal illness and low in hypothyroidism, may prove helpful. Inpatient TSH testing also may be confounded by normal diurnal variations in TSH. TSH levels in euthyroid people may exceed the normal range at night, when patients are frequently admitted. A morning test may help clarify the significance of a mildly elevated TSH.

14. Who should be treated for hypothyroidism?

All patients with overt hypothyroidism should be treated. Treatment is also generally recommended for subclinical hypothyroidism, especially for patients with a persistent TSH value greater than 10 mU/L, because when patients are treated with levothyroxine, they may have an improved sense of well-being and improvements in their cardiac and lipid abnormalities. Thyroid antibodies, an indicator of autoimmune thyroid disease, may help predict which patients with subclinical hypothyroidism will progress to overt hypothyroidism; testing is recommended for patients with minimally elevated TSH values.

15. Which thyroid hormone preparation should you use?

Since 1891, when sheep thyroid extract was first used to treat myxedema, many preparations have been developed and are still available. Currently the best replacement regimen is levothyroxine (LT_4).

16. What other thyroid hormone preparations are available?

Other thyroid hormone preparations include liothyronine (LT_3), which is reserved for special cases because of its potency and short half-life, and desiccated thyroid and thyroglobulin, which give unpredictable serum thyroid hormone concentrations because of variable content and bioavailability.

17. What is the recommended dose of LT_4 for replacement therapy in a hypothyroid patient?

Otherwise healthy, young patients may be started on full replacement doses of LT_4 (1.6 μg/kg/day). Elderly patients and patients with known or suspected cardiac disease should be started on low

doses of LT_4 (25-50 μg/day), which are increased by 25 μg/day every for 4 to 6 weeks or until the TSH value is normal. In patients with subclinical hypothyroidism, consider starting with 50% to 75% of the predicted full replacement dose.

18. What is the appropriate goal for TSH in the treatment of primary hypothyroidism?

Traditionally, the target TSH in treated hypothyroid patients has been between 0.5 and 2.0 mU/L, which represents the lower end of the normal range reported by most laboratories. This target was based on the fact that when the usual reference ranges for TSH were developed, they included subjects with antithyroid antibodies suggestive of occult autoimmune thyroid disease. The "normal" ranges are therefore thought to be skewed toward higher TSH values. When normal subjects with no antithyroid antibodies are evaluated, most have TSH values below 2.5 mU/L. However, two studies have failed to provide evidence that a low-normal TSH value is clinically superior to a value in the high-normal reference range.

19. Discuss the evidence supporting combination T_4/T_3 therapy.

The medical and lay literature has taken a renewed interest in combination therapy. Studies in thyroidectomized animals have shown that T_4 therapy alone does not restore tissue levels of T_4 and T_3 to euthyroid values, even when the TSH value is normalized. Small studies in humans have suggested that patients taking combination therapy have improved cognitive function, mood scores, and cholesterol values as well as decreased weight than when they take LT_4 alone. One study suggested that the response to T_4/T_3 therapy might vary depending on deiodinase gene variations. Although these studies are provocative and intriguing, a large metaanalysis showed no demonstrable difference in symptoms or weight between LT_4 monotherapy and combination therapy, and most experts agree that more information is needed before we can recommend combination T_4/T_3 therapy in most patients. Our current approach is to discuss this information openly with inquiring patients.

20. When should you consider combination T_4/T_3 therapy?

We suggest a trial of LT_4 alone to normalize TSH to within the low-normal range (0.5-2.0 mU/L) for a period of 2 to 4 months. Many patients do extremely well with this approach. Patients who have low-normal TSH while taking LT_4 and still feel "hypothyroid" require further evaluation before LT_3 therapy is considered. We generally exclude anemia and vitamin B_{12} deficiency (associated with Hashimoto's thyroiditis) and inquire about sleep apnea. If results of this assessment are negative, we decrease the LT_4 dosage by 12 to 25 μg, which is taken at night, and add 5 μg of liothyronine (LT_3), to be taken in the morning. The goal is to see whether the patient's symptoms improve without persistent suppression of the serum TSH (measured in the morning before medication is taken). No data clearly support or refute this position; we believe it is a position of "good" medical practice.

21. How should the clinician approach surgery in the hypothyroid patient?

There are two broad categories to consider: emergency/cardiac surgery and elective surgery. Hypothyroidism is associated with minor postoperative complications—gastrointestinal (prolonged constipation, ileus) as well as neuropsychiatric (confusion, psychosis); in addition, the incidence of fever in response to infections is lower. Patients scheduled for elective surgery should wait until TSH values are normalized because of the potential postoperative complications associated with hypothyroidism. However, rates of mortality and major complications (blood loss, arrhythmias, and impaired wound healing) in hypothyroid patients are similar to those in euthyroid patients.

22. Summarize the current recommendations for emergency surgery.

Current recommendations are to proceed with emergency surgery in the hypothyroid patient and to monitor for potential postoperative complications while giving replacement therapy with LT_4. Patients

with ischemic coronary artery disease requiring surgery should proceed without LT_4 replacement because T_4 increases myocardial oxygen demands and may precipitate worsening cardiac symptoms if given before surgery. Postoperatively, the patient should receive replacement therapy with LT_4 at a slow rate and should be monitored for CHF (rate increased in hypothyroid patients undergoing cardiac surgery).

23. How does myxedema differ from hypothyroidism?

Myxedema is a severe, uncompensated form of prolonged hypothyroidism. Complications include hypoventilation, cardiac failure, fluid and electrolyte abnormalities, and coma (see Chapter 38). Myxedema coma is frequently precipitated by an intercurrent systemic illness, surgery, or narcotic/hypnotic drugs. Patients with myxedema coma should receive replacement therapy with 300 to 500 μg of intravenous LT_4 followed by 50 to 100 μg each day. Because conversion of T_4 to T_3 (active hormone) is decreased with severe illness, patients with profound cardiac failure that requires pressors or patients whose TSH level is unresponsive to 1 to 2 days of LT_4 therapy should be given LT_3 at 12.5 μg intravenously every 6 hours.

WEBSITE

National Academy of Clinical Biochemistry: http://www.nacb.org.

BIBLIOGRAPHY

Almandoz J, Gharib H: Hypothyroidism: etiology, diagnosis, and management, *Med Clin N Am* 96:203–221, 2012.

Arem R, Patsch W: Lipoprotein and apolipoprotein levels in subclinical hypothyroidism, *Arch Intern Med* 150:2097–2100, 1990.

Boeving A, Paz-Filho G, Radominski R, et al: Low-normal or high-normal thyrotropin target levels during treatment of hypothyroidism: a prospective, comparative study, *Thyroid* 21:355–360, 2011.

Bunevicius R, Kazanavicius G, Zalinkevicius R, et al: Effects of thyroxine as compared with thyroxine plus triiodothyronine in patients with hypothyroidism, *N Engl J Med* 340:424–429, 1998.

Canaris GJ, Manowitz NR, Mayor G, et al: The Colorado thyroid disease prevalence study, *Arch Intern Med* 104:526–534, 2000.

Celi F, Zemskova M, Linderman J, et al: Metabolic effects of liothyronine therapy in hypothyroidism: a randomized, double-blind, crossover trial of liothyronine versus levothyroxine, *J Clin Endocrinol Metab* 96:3466–74, 2011.

Cooper DS, Halpern R, Wood LC, et al: L-thyroxine therapy in subclinical hypothyroidism, *Ann Intern Med* 101:18–24, 1984.

Demers LM, Spencer CA: Laboratory medicine practice guidelines: laboratory support for the diagnosis and monitoring of thyroid disease, *Thyroid* 13:45–56, 2003.

Elder J, McLelland A, O'Reilly SJ, et al: The relationship between serum cholesterol and serum thyrotropin, thyroxine, and tri-iodothyronine concentrations in suspected hypothyroidism, *Ann Clin Biochem* 27:110–113, 1990.

Grozinsky-Glasberg S, Fraser A, Nahshoni E, et al: Thyroxine-triiodothyronine combination therapy versus thyroxine monotherapy for clinical hypothyroidism: meta-analysis of randomized controlled trials, *J Clin Endocrinol Metab* 91:2592–2599, 2006.

Hay ID, Duick DS, Vliestra RE, et al: Thyroxine therapy in hypothyroid patients undergoing coronary revascularization: a retrospective analysis, *Ann Intern Med* 95:456–457, 1981.

Hollowell JG, Staehling NW, Flanders WD, et al: Serum TSH, T4, and thyroid antibodies in the United States population (1988 to 1994). National Health and Nutrition Examination Survey (NHANES III), *J Clin Endocrinol Metab* 87:489–499, 2002.

Ladenson PW: Recognition and management of cardiovascular disease related to thyroid dysfunction, *Am J Med* 88:638–641, 1990.

Ladenson PW, Levin AA, Ridgway EC, et al: Complications of surgery in hypothyroid patients, *Am J Med* 77:262–266, 1984.

Mandel SJ, Brent GA, Larsen PR: Levothyroxine therapy in patients with thyroid disease, *Ann Intern Med* 119:492–502, 1993.

Panicker V, Saravanan P, Vaidya B, et al: Common variation in the DIO2 gene predicts baseline psychological well-being and response to combination thyroxine plus triiodothyronine therapy in hypothyroid patients, *J Clin Endocrinol Metab* 94:1623–1629, 2009.

Patel R, Hughes RW: An unusual case of myxedema megacolon with features of ischemic and pseudomembranous colitis, *Mayo Clin Proc* 67:369–372, 1992.

Rosenthal MJ, Hunt WC, Garry PJ, et al: Thyroid failure in the elderly: microsomal antibodies as discriminant for therapy, *JAMA* 258:209–213, 1987.

Roti E, Minelli R, Gardini E, et al: The use and misuse of thyroid hormone, *Endocr Rev* 14:401–423, 1993.

Walsh J, Ward L, Burke V, et al: Small changes in thyroxine dosage do not produce measurable changes in hypothyroid symptoms, well-being, or quality of life: results of a double-blind, randomized clinical trial, *J Clin Endocrinol Metab* 91 2624–30, 2006.

THYROIDITIS

Ana-Maria Chindris and Robert C. Smallridge

1. Give the differential diagnosis for thyroiditis.

- Infectious: acute (suppurative), subacute (granulomatous, de Quervain's)
- Autoimmune: chronic lymphocytic (Hashimoto's disease), atrophic (primary myxedema), juvenile, postpartum
- Painless (non-postpartum)
- Drug-induced (certain medications, iodinated contrast material)
- Riedel's struma
- Radiation-induced
- Traumatic
- Tumor embolization

2. What causes acute thyroiditis?

This rare disease has an infectious etiology, most reported pathogens being *Staphylococcus, Streptococcus, Pneumocystis carinii,* and *Mycobacterium* species. Fungal, parasitic, or syphilitic infections have been reported, and immunocompromised patients may be at increased risk. Patients may demonstrate hypothyroid or hyperthyroid symptoms or may remain euthyroid. Rarely, metastatic disease to the thyroid gland can manifest as acute thyroiditis.

3. How is acute thyroiditis managed?

Treatment involves incision and drainage of the abscess or surgical excision and antimicrobials. Children often have a pyriform sinus fistula, which should be surgically repaired.

4. Describe the four stages of subacute thyroiditis.

- *Stage I:* Patients have a painful (unilateral or bilateral) tender thyroid and may have systemic symptoms (fatigue, malaise, fever). Inflammatory destruction of thyroid follicles permits release of thyroxine (T_4) and triiodothyronine (T_3) into the blood, and thyrotoxicosis may ensue.
- *Stage II:* A transitory period (several weeks) of euthyroidism occurs after the T_4 is cleared from the body.
- *Stage III:* With severe disease, patients may become hypothyroid until the thyroid gland repairs itself.
- *Stage IV:* Euthyroid state returns.

5. Summarize the natural history of subacute thyroiditis.

Subacute thyroiditis is probably viral in origin. Histologically, the inflammation is granulomatous. Although patients almost always recover clinically, serum thyroglobulin (Tgb) levels remain elevated, and intrathyroidal iodine content is low for many months (Fig. 35-1). Such findings suggest persistent subclinical abnormalities after an episode of subacute thyroiditis. Nonsteroidal antiinflammatory agents are first-line treatment in mild to moderate cases, whereas steroids may be needed when the condition is more severe. Patients requiring steroids are more likely to become hypothyroid at a later time. Up to 4% of patients have a second episode many years later.

6. What is the most common cause of thyroiditis?

Autoimmune thyroid disease, which is recognized by the presence of thyroid peroxidase (TPO) antibody and, less frequently, thyroglobulin antibody in serum.

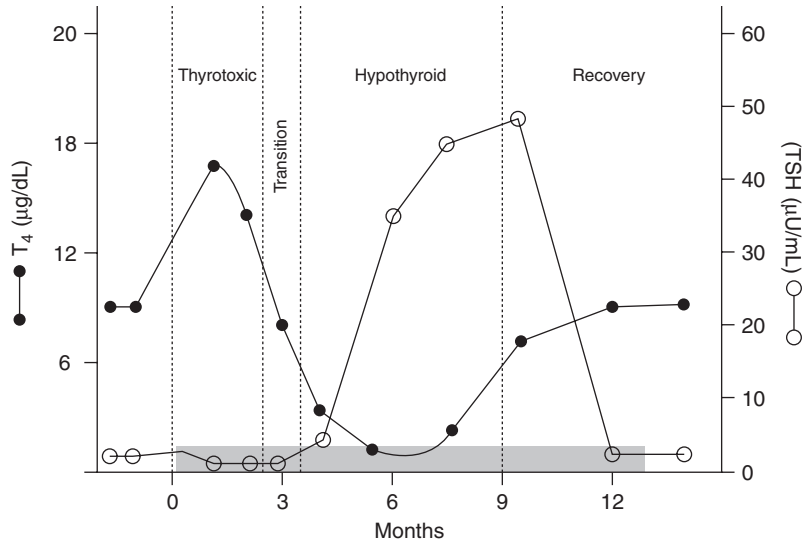

Figure 35-1. Thyroid function during subacute thyroiditis. T4, thyroxine; TSH, thyroid-stimulating hormone.

7. Describe the clinical characteristics of autoimmune thyroid disease.

Chronic lymphocytic thyroiditis (Hashimoto's disease) usually manifests as a euthyroid goiter that progresses to hypothyroidism in middle-aged and older persons, especially women. Atrophic thyroiditis is characterized by a very small thyroid gland in a hypothyroid patient. Some evidence suggests that thyroid growth–inhibitory antibodies may account for the lack of a goiter. Two thirds of adolescents with goiter have autoimmune (juvenile) thyroiditis.

8. Does postpartum thyroiditis follow a different clinical course from that of other types of autoimmune thyroiditis?

Yes. Postpartum disease develops in women between the third and ninth months after delivery, sometimes even 1 year postpartum. It typically follows the stages seen in patients with subacute thyroiditis, although histologically, patients with postpartum disease have lymphocytic infiltration.

9. How common is postpartum thyroiditis?

After delivery, 5% to 10% of women show biochemical evidence of thyroid dysfunction. Approximately one third of affected women have symptoms (either hyperthyroidism, hypothyroidism, or both) and benefit from 6 to 12 months of therapy with levothyroxine (LT_4) if they are hypothyroid. Up to 70% of patients experience recurrence with subsequent pregnancies. The frequency of each clinical presentation is depicted in Figure 35-2.

10. Which patients with postpartum thyroiditis should be treated?

Postpartum thyroiditis is a destructive process; therefore an antithyroidal drug (methimazole) is not effective. If hyperthyroid symptoms are present, beta-blockers can be used. Hypothyroid patients with severe symptoms and those who desire conception should receive treatment with LT_4. In these cases, however, tapering off the medication should be tried 6 to 12 months after initiation, in the attempt to eventually discontinue therapy.

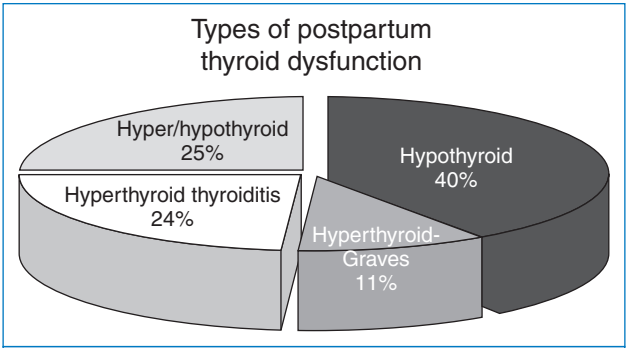

Figure 35-2. Frequency of clinical presentations of postpartum thyroiditis.

TABLE 35-1. SUBACUTE VERSUS POSTPARTUM THYROIDITIS

	SUBACUTE THYROIDITIS	POSTPARTUM THYROIDITIS
Thyroid pain	Yes	No
Erythrocyte sedimentation rate	Increased	Normal
Thyroid peroxidase antibody	Transient increase only	Positive
HLA status	B-35	DR3, DR5
Histology	Giant cells, granulomas	Lymphocytes

11. Summarize the differences between subacute and postpartum thyroiditis.
See Table 35-1.

12. Why does postpartum thyroiditis develop in some women?
Women in whom postpartum thyroiditis develops have underlying, usually asymptomatic, autoimmune thyroiditis. During pregnancy, the maternal immune system is partially suppressed, with a dramatic rebound rise in thyroid antibodies after delivery. Although TPO or thyroglobulin antibodies are not believed to be cytotoxic, they are currently the most reliable markers of susceptibility to postpartum disease.

13. Does thyroid function in patients with postpartum thyroiditis return to normal, as it does in subacute thyroiditis?
Not always. Approximately 20% of women become permanently hypothyroid, and a similar number have persistent mild abnormalities. An annual thyroid-stimulating hormone (TSH) measurement is therefore recommended.

14. Do any factors identify women at increased risk for the development of postpartum thyroiditis?
Women with a higher TPO antibody titer are more likely to have thyroiditis. Thyroiditis develops after delivery in approximately 25% of women with type 1 diabetes mellitus. For high-risk patients, screening for thyroid antibodies and careful monitoring of thyroid function at 3 to 6 months postpartum are indicated.

15. What is painless thyroiditis?
Both men and non-postpartum women may present with transient thyrotoxic symptoms. Like patients with subacute thyroiditis, they often experience subsequent hypothyroidism. Unlike subacute disease,

this disorder is painless. It has been given a variety of names, including hyperthyroiditis, silent thyroiditis, transient painless thyroiditis with hyperthyroidism, and lymphocytic thyroiditis with spontaneously resolving hyperthyroidism. This disease was first described in the 1970s and reached its peak incidence in the early 1980s. It seems to occur less often now.

16. What causes painless thyroiditis?

Some investigators believe that it is a variant of subacute thyroiditis because a small percentage of patients with biopsy-proven subacute disease have had no pain (they may have fever and weight loss and may be mistaken for having systemic disease or malignancy). Others believe that it is a variant of Hashimoto's disease because of similar histologic features. Hashimoto's thyroiditis can occasionally manifest as thyroid pain; rarely, surgery is necessary to relieve symptoms.

KEY POINTS 1: THYROIDITIS

1. In early subacute thyroiditis, radioactive iodine uptake (RAIU) is suppressed and the erythrocyte sedimentation rate is markedly elevated.
2. Thirty to 50% of pregnant women who test positive for TPO antibodies at the end of the first trimester of pregnancy develop postpartum thyroiditis.
3. Amiodarone-induced thyroid disease (AITD) may be due to iodine-induced hyperthyroidism (type 1 AITD) or destruction-induced thyroiditis (type 2 AITD).
4. Subacute thyroiditis may require analgesics (or steroids) and beta-blockers early and levothyroxine (LT_4) during recovery but usually resolves.
5. Acute infectious thyroiditis requires prompt incision and drainage and antimicrobial therapy.

17. What is destruction-induced thyroiditis?

Destruction-induced thyroiditis refers to disorders (subacute, postpartum, drug-induced, and painless thyroiditis) in which an inflammatory infiltrate destroys thyroid follicles and excessive amounts of T_4 and T_3 are released into the circulation.

18. When a patient presents with hyperthyroid symptoms, an elevated T_4 value, and a suppressed TSH value, what test should be ordered next?

A 24-hour radioactive iodine uptake (RAIU) test should be performed. When the thyroid is overactive (as in Graves' disease or toxic nodular disease), the RAIU value is elevated. In destruction-induced thyroiditis, the RAIU value is low, as a result of both suppression of TSH by the acutely increased level of serum T_4 and the diminished ability of damaged thyroid follicles to trap and organify iodine.

19. What is the appropriate therapy for patients with any type of destructive thyroiditis?

In the thyrotoxic stage, beta-blockers relieve adrenergic symptoms. All forms of antithyroid therapy (drugs, radioactive iodine ablation, and surgery) are absolutely contraindicated. Analgesics (salicylates or prednisone) provide prompt relief of thyroid pain. Thyroid hormone relieves hypothyroid symptoms and should be continued for 6 to 12 months, depending on the severity of disease. Some patients require no therapy.

20. Which drugs can induce thyroiditis?

Amiodarone, an iodine-containing antiarrhythmic drug, may cause thyroid damage and thyrotoxicosis. Lithium therapy has been associated with granulomatous thyroiditis as well as with destructive thyroiditis without lymphocytic infiltration. Interferon-alpha (less commonly, interferon-beta) and interleukin-2 (e.g., denileukin diftitox, an antineoplastic agent that combines interleukin-2 with diphtheria toxin) can

TABLE 35–2. TYPE 1 VERSUS TYPE 2 AMIODARONE INDUCED THYROIDITIS

	TYPE 1	TYPE 2
Thyroid size	Goiter; nodules	Normal
Radioactive iodine uptake	↓, normal, ↑	↓↓
Thyroid antibodies	↑, negative	Negative
Interleukin-6	Normal, ↑	↑↑
Doppler flow ultrasonography	↑	↓
Therapy	Antithyroid drugs, potassium perchlorate; thyroidectomy	Antithyroid drugs (?), steroids

↓, decreased; ↑, increased.

cause thyroiditis, and both hyperthyroidism and hypothyroidism have occurred during therapy with these agents. Tyrosine kinase inhibitors (e.g., sunitinib, sorafenib) have been noted to cause hypothyroidism, potentially by causing destructive thyroiditis. Nonionic contrast materials (e.g., HEXABRIX) have been reported to cause destructive thyroiditis.

21. Does amiodarone induce only thyroiditis?

No. Because of the large amount of iodine in this drug, it can cause either iodine-induced hypothyroidism or hyperthyroidism. Distinguishing hyperthyroidism due to iodine excess (type 1 disease) from amiodarone-induced destructive thyroiditis (type 2 disease) can be difficult. Some differentiating features are listed in Table 35-2. Absence of blood flow on Doppler flow ultrasonography is particularly helpful in confirming type 2 disease.

22. What is Riedel's struma?

Riedel's struma is a rare disorder in which the thyroid becomes densely fibrotic and hard. Local fibrosis of adjacent tissues may produce obstructive symptoms that require surgery. In some cases, fibrosis of other tissues (fibrosing retroperitonitis, orbital fibrosis, or sclerosing cholangitis) may occur.

23. How is Riedel's thyroiditis treated?

Surgical removal of the thyroid isthmus may relieve constrictive symptoms. Glucocorticoids have been helpful, as has tamoxifen (by stimulating transforming growth factor-beta, which inhibits fibroblast growth). Use of a combination of mycophenolate mofetil and prednisone has been reported.

24. Are there any other causes of thyroiditis?

Yes. External beam radiotherapy can cause painless thyrotoxic thyroiditis. Various forms of neck trauma (neck surgery, cyst aspiration, seat-belt injury) and tumor emboli have also been reported.

WEBSITE

Thyroid Disease Manager: http://www.thyroidmanager.org. Accessed August 30, 2012.

BIBLIOGRAPHY

Aizawa T, Watanabe T, Suzuki N, et al: Radiation-induced painless thyrotoxic thyroiditis followed by hypothyroidism: a case report and literature review, *Thyroid* 8:273–275, 1998.

Bogazzi F, Bartalena L, Martino E: Approach to the patient with amiodarone-induced thyrotoxicosis, *J Clin Endocrinol Metab* 95(6):2529–2535, 2010.

Carella C, Mazziotti G, Amato G, et al: Clinical review 169: interferon-α-related thyroid disease: pathophysiological, epidemiological, and clinical aspects, *J Clin Endocrinol Metab* 89:3656–3661, 2004.
Feldt S, Schussel K, Quinzler R, et al: Incidence of thyroid hormone therapy in patients treated with sunitinib or sorafenib: a cohort study, *Eur J Cancer* 48:974–981, 2012.
Hennessey J: Riedel's thyroiditis: a clinical review, *J Clin Endocrinol Metab* 96(10):3031–3041, 2011.
Jimenez-Heffernan J, Perez F, Hornedo J, et al: Massive thyroid tumoral embolism from a breast carcinoma presenting as acute thyroiditis, *Arch Pathol Lab Med* 128:804–806, 2004.
Kon YC, DeGroot LJ: Painful Hashimoto's thyroiditis as an indication for thyroidectomy: clinical characteristics and outcome in seven patients, *J Clin Endocrinol Metab* 88:2667–2672, 2003.
Lazarus J: Lithium and thyroid, *Best Pract & Res Clin Endocr & Metab* 23:723–733, 2009.
Meek SE, Smallridge RC: Thyroiditis and other more unusual forms of hyperthyroidism. In Cooper DS, editor: *Medical management of thyroid disease*. New York, 2008, Informa Healthcare, pp 101–144.
Nicholson W, Robinson K, Smallridge R, et al: Prevalence of postpartum thyroid dysfunction: a quantitative review, *Thyroid* 16:573–582, 2006.
Rotenberg Z, Weinberger I, Fuchs J, et al: Euthyroid atypical subacute thyroiditis simulating systemic or malignant disease, *Arch Intern Med* 146:105–107, 1986.
Samuels MH: Subacute, silent and postpartum thyroiditis, *Med Clin N Am* 96:223–233, 2012.
Smallridge RC: Hypothyroidism and pregnancy, *Endocrinologist* 12:454–464, 2002.
Smallridge RC: Postpartum thyroid disease: a model of immunologic dysfunction, *Clin Appl Immunol Rev* 1:89–103, 2000.
Smallridge RC, De Keyser FM, Van Herle AJ, et al: Thyroid iodine content and serum thyroglobulin: cues to the natural history of destruction-induced thyroiditis, *J Clin Endocrinol Metab* 62:1213–1219, 1986.
Stagnaro-Green A, Abalovich M, Alexander E, et al: Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum, *Thyroid,* 21:1081–1125, 2011.
Yu EH, Ko W, Chuang Y, et al: Suppurative *Acinetobacter baumannii* thyroiditis with bacteremic pneumonia: case report and review, *Clin Infect Dis* 27:1286–1290, 1998.

THYROID NODULES AND GOITER

William J. Georgitis

1. What is a goiter?

A goiter is a visible swelling in the anterior neck from an enlarged thyroid gland. Derivation of the term can be traced to the French *goitre,* the Middle French *goitron*, a vulgate Latin term *guttrion,* and the Latin terms *guttrio* and *guttur*. Most of the terms designate the throat.

2. What causes goiter?

The pathogenesis for euthyroid goiter remains an enigma. Proposed mechanisms include:

- Thyroid-stimulating hormone (TSH)–dependent thyroid enlargement to compensate for diminished thyroid hormone production due to environmental goitrogens
- Iodine deficiency
- Inherited biosynthetic defects

Regression of goiter after iodine supplementation and with thyroxine suppression of TSH supports these mechanisms. However, TSH values are not elevated in endemic goiter. Inherited biosynthetic genetic defects for thyroglobulin, thyroperoxidase, intracellular signaling pathways affecting cell life cycles, and the sodium/iodide (Na^+/I^-) symporter have been described.

3. Describe the natural history of diffuse nontoxic goiter.

Simple goiter tends to become multinodular over time. The nodules are heterogeneous in both morphology and function. Autonomous function, defined as TSH-independent production and secretion of thyroid hormone, can evolve. Supplementation programs in iodine-deficient populations clearly decrease the incidence of cretinism and goiter but have also increased the incidence of iodine-associated hyperthyroidism. This Jod-Basedow hyperthyroidism is more likely to occur in older people with autonomous adenomatous goiters. In the United States, this form of hyperthyroidism usually results from iodine excess due to radiographic contrast agents or medications rich in iodine. The thyroid hormone excess may be transient and may not require treatment. When it is severe, antithyroid medications and thyroidectomy can be used. Iodine excess usually precludes radioiodine as a treatment option.

4. How does lithium affect thyroid function?

Lithium has diverse effects on thyroid function. It inhibits iodine uptake, dampens iodotyrosine coupling, alters thyroglobulin structure, blocks thyroid hormone secretion, and has mitogenic effects. Both goiter and hypothyroidism can appear during prolonged exposure to lithium (Fig. 36-1).

5. Describe the mechanism by which lithium produces goiter and hypothyroidism.

The inhibitory effect of lithium on thyroid hormone release provokes an increase in TSH secretion even in patients free of thyroid disease. Compensatory thyroid enlargement then occurs without the development of hypothyroidism. However, patients who have an underlying decrease in thyroid functional reserve, even if baseline thyroid hormone levels are normal, may demonstrate hypothyroidism after lithium initiation. This most commonly occurs in patients with chronic lymphocytic thyroiditis, a past history of subacute thyroiditis, or partial thyroidectomy. Because hypothyroid signs and symptoms may be difficult to decipher in the presence of depression or bipolar disorder, TSH testing before and during lithium treatment is recommended.

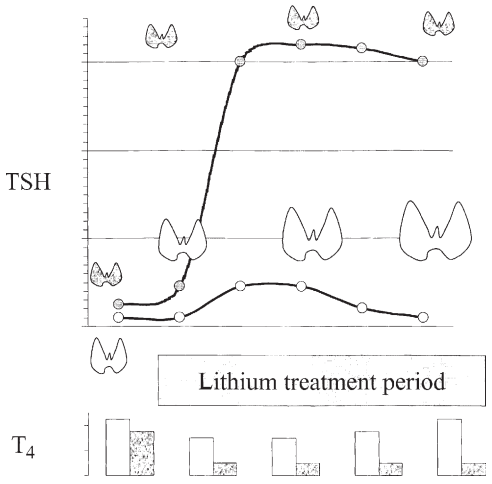

Figure 36-1. Effects of prolonged lithium treatment on thyroid size, T_4 - thyroxine, and TSH - thyroid stimulating hormone. A goitrous case is depicted by open symbols and a non-goitrous hypothyroid case by shaded symbols.

6. How common are thyroid nodules?

Thyroid nodules are common. Prevalence increases linearly with age. The cumulative lifetime chance of a palpable thyroid nodule approaches 6%. The prevalence at autopsy in 90-year-old subjects is about 60%. The vast majority of thyroid nodules are benign. The yield of thyroid cancer in surgical series before the widespread use of fine-needle aspiration (FNA) biopsy averaged about 10%.

7. List the differential diagnosis for a thyroid nodule.

- Adenoma
- Thyroiditis
- Metastatic cancer
- Carcinoma
- Thyroid hemiagenesis
- Lymphoma/sarcoma
- Thyroid cyst
- Parathyroid cyst

8. Can the nature of a thyroid nodule be determined from family history?

Family history is usually not helpful. An exception is medullary thyroid cancers associated with the multiple endocrine neoplasia syndromes. Inheritance of these tumors is autosomal dominant with almost complete penetrance for the abnormal *ret* oncogene.

9. Do personal history and physical examination help define the nature of a thyroid nodule?

In general, no. Most patients with thyroid nodules have no symptoms and normal thyroid function. Thyroid cancer grows without causing pain. Hoarseness, dysphagia, dyspnea, and hemoptysis are rare features that suggest malignancy but also occur in benign thyroid disorders. Report of any of these symptoms by a patient with a visible goiter suggests either rapid growth or involvement of the recurrent laryngeal nerve. An aggressive form of thyroid malignancy, such as lymphoma or anaplastic thyroid cancer, is a consideration. However, both thyroid lymphoma and anaplastic thyroid cancer are rare. Other traits of nodules that suggest malignancy include size greater than 3 cm, fixation to adjacent structures, and palpable cervical lymph nodes.

10. How are most thyroid cancers discovered?

Most thyroid cancers are now discovered by chance. Neck ultrasonography, magnetic resonance imaging (MRI), and computed tomography (CT) studies for myriad indications may first detect a thyroid nodule. Because they are recognized incidentally to the purpose of the procedure, these nodules are termed *thyroid incidentalomas.* In comparison with the past, when medical imaging was less frequent, it is now unusual for thyroid nodules to be found first by the patient or during routine physical examination.

11. What diagnosis should be suspected when a thyroid nodule is first discovered after sudden onset of neck pain?

Hemorrhagic degeneration of a previously unknown benign adenoma is not infrequent. The thyroid capsule is innervated by sensory pain fibers, whereas only autonomic sympathetic and parasympathetic nerves innervate the substance of the thyroid gland. Sudden expansion of a nodule stretches the thyroid capsule, resulting in deep, aching pain that may radiate to the jaw or ear. This clinical presentation may be mistaken for dental abscess, otitis media, or otitis externa. Aspiration of hemorrhagic fluid often relieves the discomfort and confirms the diagnosis. Other thyroid disorders with palpable enlargement and thyroid tenderness to palpation to consider include thyroid neoplasms and de Quervain's subacute thyroiditis.

12. If a nodule is cancer, what kind is it likely to be?

A papillary thyroid cancer or variant of papillary carcinoma is the most common by far (Table 36-1).

13. Does the character of cyst fluid define the etiology of the cyst?

Simple thyroid cysts have yellow, burgundy, or chocolate-colored fluid and are generally benign. Complex thyroid nodules with both cystic and solid components contain brown or hemorrhagic fluid. Complex cysts have a higher risk of malignancy than simple cysts. Cytology of cyst fluid is almost always nonspecific, and often only histiocytes and crenated erythrocytes are seen without thyroid epithelial cells. If the fluid is crystal-clear, like tap water, the lesion is a parathyroid cyst. Serum calcium should be measured to exclude hyperparathyroidism.

14. What should be done if a thyroid cyst recurs after being drained?

One third of thyroid cysts reappear days to weeks after aspiration. If the volume on sequential aspirations does not decrease or the aspirated fluid is grossly bloody, surgical removal of the cyst should be considered.

15. Is the risk of cancer less in multinodular goiter or Hashimoto's disease than in solitary thyroid nodules?

Although autopsy series indicate that up to 75% of thyroid nodules are multiple and that malignancy is rare, any thyroid nodule can be cancerous. Contrary to old axioms, a palpable nodule in the presence of multinodular goiter or lymphocytic thyroiditis seems to have the same risk of cancer as a solitary palpable nodule. There is evidence that TSH levels are a bit higher in patients found to have thyroid cancer than in those with benign nodules. There are even some reports now that thyroid hormone therapy may be a factor associated with a nodule's being malignant rather than benign. Size does matter. Palpable nodules are generally at least 1 cm in greatest dimension. Nodules smaller than 1 cm are often not palpable and have a lower risk of malignancy than larger nodules. The decision to

TABLE 36-1. FREQUENCY OF THYROID CANCER TYPES

Papillary	50%-70%
Follicular	10%-15%
Medullary	1%-2%
Anaplastic	Rare
Primary thyroid lymphoma	Rare
Metastatic to thyroid	Rarely diagnosed

monitor nonpalpable thyroid nodules or perform fine-needle aspiration (FNA) should incorporate ultrasound features including size and other features more often seen with malignant than benign nodules.

16. Summarize the role of FNA in the evaluation of thyroid nodules

FNA is a safe, outpatient procedure with an accuracy of 90% to 95% in adequate specimens interpreted by experienced cytopathologists. FNA should be performed on all readily palpable solitary thyroid nodules, on dominant nodules in a multinodular goiter, and for sub-centimeter nodules with ultrasonographic characteristics suspicious for thyroid cancer. Suspicious ultrasonographic features include hypoechogenicity, ragged borders, stippled calcifications, internal vascularity, and "taller than wide" (meaning the anterior-posterior dimension of the nodule is greater than its tranverse dimension). Malignancy in multinodular goiter may be missed, and sampling multiple nodules or those nodules shown to be suspicious on ultrasound or to be photopenic on thyroid scintigraphy is a consideration. After a serum TSH level is shown to be normal, an FNA is the next evaluation for a thyroid nodule. Most FNAs return benign diagnoses, including adenomatous hyperplasia (benign multinodular goiter), colloid adenoma, and autoimmune thyroiditis. A reading of papillary thyroid cancer, seen in 3% to 5% of FNAs, helps guide planning for thyroid resection.

When the FNA is nondiagnostic, an ultrasound-guided FNA should be done. For indeterminate cytology categories, the revised American Thyroid Association guideline recommends the use of molecular markers to guide management. Currently, this recommendation is based on expert opinion grade evidence. The use of molecular markers is the most exciting addition to the evaluation and management of thyroid nodules in years. Its role is evolving and being defined but shows promise as a cost-effective test by reducing unnecessary thyroidectomies with their attendant cost and morbidity for patients in whom lesions suspicious for cancer prove to be benign and for guiding surgical and medical management decisions for patients with thyroid cancer.

17. Is FNA helpful in diagnosing follicular neoplasms?

Follicular neoplasms are more vexing. FNA cannot reliably differentiate adenoma from carcinoma because features of capsular or vascular invasion that define follicular carcinoma can be determined only on surgical pathology. Aspirates are inadequate for interpretation in about 15% of cases. This rate can be reduced by using ultrasound guidance, especially for the lesion with a cystic component.

18. Should an FNA be performed for a palpable nodule if the TSH is low?

No. A low TSH indicates hyperthyroidism.

19. If the TSH is found to be low, what is the next step?

A thyroid scan, to rule in solitary toxic nodule or toxic multinodular goiter, should be the next test. Although the scan is ordered with the anticipation of finding lesions with autonomous function, a photopenic (cold) nodule may sometimes be encountered.

20. Explain the distinction between cold and hot nodules.

A cold nodule has lower uptake of the radioactive agent than surrounding normal thyroid tissue. Most cold nodules are benign, but virtually all thyroid cancers are cold on scan. The solitary toxic or hot nodule avidly absorbs tracer, whereas uptake in the remainder of the thyroid is suppressed. Solitary toxic nodules are usually more than 3 cm in diameter; most occur in patients older than 40 years. Most solitary toxic thyroid nodules have gain-of-function mutations in the thyrotropin receptor gene. Toxic adenomas are never cancerous.

21. What is the significance of a warm nodule?

In contrast, a warm nodule may be malignant. Some hyperfunctional or isofunctional nodules are really cold nodules that appear to concentrate tracer because they are invested by normal thyroid tissue. Other autonomous nodules fail to secrete sufficient thyroid hormone to suppress TSH to dampen tracer uptake by surrounding normal thyroid tissue. Thyroid scanning after the patient takes a TSH-suppressive dose of thyroid hormone can define the autonomous nature of such a nodule. Autonomous nodules may be monitored by observation alone, whereas all others deserve FNA to exclude thyroid cancer.

22. Who invented the incision used for thyroidectomy?

Theodor Kocher (1841-1917), a Swedish surgeon, devised the incision. He was an innovator, so the physician should be cautious when asking for a "Kocher" in the operating room. Kocher's name is also associated with a surgical forceps, a wrist operation, and a right subcostal incision for cholecystectomy.

23. Which treatment was used first for diffuse toxic goiter (Graves' disease), radioactive iodine or antithyroid medications?

Both methods were developed in the early 1940s. Thiourea, the first goitrogenic substance to be used, had undesirable toxicities and was soon replaced by methimazole and propylthiouracil. Of the fission products developed during World War II, radioactive iodine (radioiodine) ^{130}I was used before ^{131}I. Radioiodine became widely available in about 1946.

24. What goitrous thyroid conditions are treated with radioactive iodine?

Radioiodine treatment is effective for diffuse toxic goiter, toxic nodular goiter, and solitary toxic nodules. Compressive symptoms from benign multinodular goiters in patients judged to be poor surgical risks can also be relieved by radioactive iodine. Although the goiter shrinks only about 30% or less, relief of symptoms is common.

25. What is the role of suppression therapy with thyroxine?

Although thyroxine suppression therapy was widely used in the past on the basis of the belief that it reduced the size of thyroid nodules, randomized controlled studies, including some with objective measurements by ultrasound, indicate that suppression therapy is ineffective. This finding suggests that the apparent reduction in the size of solitary nodules when judged only by palpation probably represented regression of surrounding thyroid rather than of the nodule itself. For euthyroid patients, thyroid hormone is ineffective except in iodine deficiency and for prevention of new nodules after lobectomy in radiation-exposed patients. These exceptions are almost never seen anymore. Routine treatment with TSH-suppressive doses of thyroid hormone for thyroid nodules or goiter probably has more iatrogenic side effects than benefits and is now discouraged.

KEY POINTS 1: THYROID NODULES AND GOITER

1. The cumulative lifetime chance of having a palpable thyroid nodule is about 6%.
2. A thyroid nodule is present in about 60% of 90-year-old persons.
3. The vast majority of thyroid nodules are benign.
4. Nodules in multinodular goiter are heterogeneous in both morphology and function.
5. Fine-needle aspiration of the thyroid is a safe outpatient procedure with an accuracy of 90% to 95% in determining malignancy.

TOP SECRETS

1. When clear watery fluid is aspirated from a thyroid region nodule, the nodule is a parathyroid cyst.
2. If a goiter and hypothyroidism appear during lithium therapy, suspect underlying chronic lymphocytic thyroiditis.
3. Sudden onset of neck pain radiating to the jaw with appearance of a tender thyroid lump is most likely from hemorrhagic degeneration of a benign, not a malignant, thyroid nodule.

WEBSITE

Thyroid disease manager: www.thyroidmanager.org/. Accessed August 30, 2012.

BIBLIOGRAPHY

Chudova D, Wilde JI, Wang ET, et al: Molecular classification of thyroid nodules using high-dimensionality genomic data, *J Clin Endocrinol Metab* 12:5301–5309, 2010.

Cooper DS, Doherty GM, Haugen BR, et al: Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer, *Thyroid* 19:1167–1214, 2009.

Dremier S, Coppee F, Delange F, et al: Thyroid autonomy: mechanism and clinical effects, *J Clin Endocrinol Metab* 81:4187–4193, 1996.

Lazarus JH: The effects of lithium therapy on thyroid and thyrotropin-releasing hormone, *Thyroid* 8:909–913, 1998.

Li H, Robinson KA, Anton B, et al: Cost-effectiveness of a novel molecular test for cytologically indeterminate thyroid nodules, *J Clin Endocrinol Metab* 11:E1719–E1726, 2011.

Mortensen JD, Woolner LB, Bennett WA: Gross and microscopic findings in clinically normal thyroid glands, *J Clin Endocrinol Metab* 15:1270–1280, 1955.

Nikiforov YE, Ohori NP, Hodak SP, et al: Impact of mutational testing on the diagnosis and management of patients with cytologically indeterminate thyroid nodules: a prospective analysis of 1056 FNA samples, *J Clin Endocrinol Metab* 96:3390–3397, 2011.

Oertel YC, Miyahara-Felipe L, Mendoza MG, et al: Value of repeated fine needle aspirations of the thyroid: an analysis of over ten thousand FNAs, *Thyroid* 17:1061–1066, 2007.

THYROID CANCER

Joshua Klopper

1. What are the different types of thyroid cancers?

Thyroid cancer can be divided into three broad subtypes: (1) differentiated thyroid cancer (DTC), which includes papillary thyroid cancer (PTC) and its variants, follicular thyroid cancer (FTC) and Hürthle cell carcinoma; (2) medullary thyroid cancer (MTC); and (3) anaplastic thyroid cancer (ATC), which is a form of undifferentiated thyroid cancer. Other miscellaneous types of thyroid cancers include thyroid lymphoma, mucoepidermoid carcinoma, and metastases to the thyroid gland.

2. Describe the epidemiology of thyroid cancer.

Thyroid cancer is one of the few cancers that have increased in both absolute incidence and mortality over the past several decades; an estimated 56,400 new cases were diagnosed and 1780 deaths occurred in 2012. However, the relative survival is actually improved compared with the 1970s, with an average 5-year survival in 97% of patients. Many new thyroid cancer diagnoses have resulted from increased imaging. The detection of tumors smaller than 1.0 cm has accounted for 50% of the increase since the late 1990s. However, up to 20% of the increase in diagnoses is for tumors larger than 2.0 cm, a finding suggesting that enhanced detection of incidental cancers is not the sole cause of the increased incidence. Thyroid cancer is the fifth most common cancer in women, and it affects women three times as often as it does men. However, the mortality rate in men and women is similar, indicating that thyroid cancer tends to be more aggressive in men.

3. What are the risk factors for thyroid cancer?

In the absence of an inheritable genetic syndrome such as multiple endocrine neoplasia type 2 (MEN2), the main risk factors include a family history and exposure to ionizing radiation, especially at a young age ($<$ 15 years old). This latter factor was demonstrated in the aftermath of the Chernobyl nuclear accident, studies of which suggested a dose-related radiation exposure risk of thyroid cancer that was 5- to 20-fold greater than in unexposed children. Relative iodine deficiency may also have been a predisposing factor.

DIFFERENTIATED THYROID CANCER

4. What are the different forms of DTC?

PTC, the most common form of DTC, encompasses about 80% of all thyroid cancer cases. Included under PTC are the follicular variant of PTC (FVPTC) and rarer aggressive subtypes, such as tall cell variant, sclerosing variant, and other poorly differentiated forms of PTC. FTC, the next most common type of DTC, accounts for about 10% to 15% of thyroid cancer cases overall but perhaps fewer in iodine-replete areas of the world. Finally, pure Hürthle cell carcinomas are composed of invasive follicular cells that have a distinctive oxyphilic change and that may be relatively radioiodine resistant compared with other forms of DTC.

5. Which is easier to diagnose based on thyroid fine-needle aspiration (FNA), PTC or FTC?

PTC has distinctive nuclear features such as enlarged, overlapping nuclei with nuclear grooves and intranuclear pseudoinclusions that allow for a cytopathology diagnosis with a positive predictive value

(PPV) greater than 95%. In contrast, FTC is functionally defined as the invasion of largely normal-appearing follicular cells through a tumor capsule. Because this cannot be ascertained on a cytology aspirate, pure FTC is difficult to diagnose based on thyroid FNA.

6. How do molecular markers play a role in the diagnosis or prognosis of thyroid cancer?

The discovery and utilization of molecular markers that can be assessed in thyroid biopsy aspirates have enhanced the ability of practitioners to predict malignancy in thyroid nodules that have indeterminate FNA cytology (average malignancy risk ~25%). Two commercial tests that use different analyses to predict malignancy risk are available. The Afirma test by Veracyte, Inc., uses a microarray analysis on a gene set that has a high negative predictive value (NPV) of 93% and a 40%-50% PPV for suspicious nodules. This test is very useful in predicting benign lesions and for avoiding unnecessary diagnostic surgery. The miRInform test by Asuragen, Inc., evaluates thyroid nodule aspirates for specific DNA mutation markers (KRAS, HRAS, NRAS, and BRAF mutations) and RNA fusion transcripts (RET/PTC1, RET/PTC3, and PAX8/PPARγ) that are specific for thyroid cancer. RAS mutations carry about an 85% PPV for thyroid cancer, but they can also be present in benign follicular adenomas. The other markers of this panel are functionally 100% predictive of malignancy. Their sensitivity is relatively poor, however, because thyroid cancers may harbor genetic alterations not found in this test. BRAF is present in approximately 30% to 60% of PTCs and predicts greater local invasion, lymph node metastases, radioiodine resistance, and an overall worse prognosis than do other mutations found in DTC.

7. Describe the staging of DTC.

The American Thyroid Association (ATA) recommends the American Joint Commission on Cancer (AJCC) staging system. Thyroid cancer is the only cancer that has age as a component of stage (Table 37-1).

TABLE 37-1. STAGING SYSTEM FOR DIFFERENTIATED THYROID CANCER

	Tumor Size	
T1	≤ 2 cm	
T2	> 2-4 cm	
T3	> 4 cm or minimal invasion	
T4a	Gross invasion	
T4b	Gross invasion into prevertebral area or vessels	
	Lymph Node Status	
N0	No node involved	
N1a	Central nodes (level VI)	
N1b	Other nodes (level I-V, or VII)	
	Metastases	
M0	No distant metastases	
M1	Distant metastases	
	Age < 45	**Age > 45**
Stage I	M0	T1N0M0
Stage II	M1	T2N0M0
Stage III		T1-2, N1aM0
		T3, N0-1a, M0
Stage IVA		T1-3, N1b, M0
		T4a, N0-1b, M0
Stage IVB		T4b, any N, M0
Stage IVC		Any T, any N, M1

From American Joint Committee on Cancer (AJCC): *Cancer staging manual,* ed 6, New York, 2002, Springer.

According to the AJCC system, if a patient is less than 45 years old, stage II disease is the highest stage possible, and then only if distant metastases are present outside the neck. Conversely, in patients who are 45 years old or older, intrathyroidal tumors up to 2 cm are stage I and tumors 2 to 4 cm are stage II. Any locoregional metastases raise the stage to so-called high-risk disease at stage III. Stage IV tumors either have gross invasion into extrathyroidal neck structures or distant metastases.

8. How do PTC and FTC generally metastasize?

PTC typically spreads to locoregional lymph nodes. Outside the neck, the most common site of distant metastases is the lungs, with basilar miliary spread. FTC classically has hematogenous spread and a relatively high rate of bone metastases. Aggressive thyroid cancer of any type can have direct extension or invasion into extrathyroidal soft tissue, fascia, and muscle.

9. How often do metastases occur?

In adults, locoregional lymph node metastases occur as often as 30% to 60% of the time, whereas distant metastases are much rarer, occurring in only 2% to 4% of patients. In pediatric thyroid cancer, the presentation is more aggressive. Regional lymph metastases occur in 60% to 80% of these patients, and distant metastases occur in 10% to 20%.

10. What is the primary treatment for thyroid cancer?

Surgical resection is the primary treatment. The greatest predictor of a successful operation (cancer removal and avoidance of complications) is the surgeon's experience. High-volume thyroidectomy practices consistently have excellent outcomes with minimal complication rates.

11. What determines the extent of the initial surgical procedure?

Ideally, the first thyroid cancer operation is the last. Preoperative neck ultrasound (US) is an invaluable tool for identifying the extent of lymph node metastases in the anterior lateral cervical lymph node chains. US is superior to computed tomography (CT) and magnetic resonance imaging (MRI) because it identifies malignant features of lymph nodes beyond size alone. For known thyroid cancer larger than 1 cm, or when lymph node metastases are detected preoperatively, a near-total thyroidectomy with lymph node resection is the procedure of choice. If the primary tumor is smaller than 1 cm, a hemithyroidectomy may be adequate. The need for prophylactic central neck lymph node dissection (prophylactic because central neck lymph nodes cannot be visualized with an intact thyroid in place) is controversial because of the lack of studies demonstrating improved survival with prophylactic central neck dissection.

12. What is the role of radioactive iodine in thyroid cancer therapy?

Radioiodine can be used for ablating any remnant thyroid tissue after thyroidectomy and can be considered adjuvant therapy after surgery for any locoregional lymph node or distant metastases.

13. Should all patients with thyroid cancer receive radioiodine?

No. Radioiodine therapy is indicated for patients with distant metastases, tumors with gross extrathyroidal extension, and tumors larger than 4.0 cm. Radioiodine therapy is not indicated for unifocal tumors smaller than 1.0 cm because there is no known survival advantage or decrease of recurrence. For thyroid cancers of medium size, patient-specific selection is indicated for determining whether to use radioiodine therapy.

14. How are patients prepared for radioactive iodine therapy?

Thyroid-stimulating hormone (TSH) stimulates iodine uptake into thyroid cells; therefore, TSH should be elevated to enhance uptake into functional thyroid tissue (remnant or DTC tissue). TSH can be elevated by withdrawing thyroid hormone therapy and thereby rendering the patient hypothyroid (usually a 3-week withdrawal from levothyroxine [LT_4] alone without a triiodothyronine [T_3] bridge is adequate) or by using recombinant human TSH (rhTSH [Thyrogen]), which is approved for remnant ablation and has efficacy similar to that of withdrawal preparation. Additionally, a low-iodine diet is recommended

to decrease competition of dietary or "cold iodine" with radioiodine for uptake into thyroid follicular cells. In the absence of other forms of contamination (contrast agents or iodine-containing medications such as amiodarone), 1 week of a strict low-iodine diet is usually adequate to deplete the body of competing nonradioactive iodine.

15. What is the proper dose of radioactive iodine?

No large-scale randomized trial has been conducted to answer this question. For remnant ablation, recent prospective data demonstrates that a dose of 30 mCi has efficacy similar to 100 mCi. For locally invasive and distant metastatic tumors, larger doses may be indicated. The ATA guidelines recommend the following: "The minimum activity (30-100 mCi) necessary to achieve successful remnant ablation should be utilized, particularly for low-risk patients."

16. Is radioactive iodine therapeutic or diagnostic?

Both. The treatment is designed to eradicate residual thyroid cancer after surgery, but patients should have a scan approximately 3 to 10 days after treatment to visualize radioiodine uptake and rule out or detect metastatic disease.

17. What are the complications of radioiodine therapy?

The main acute complications are dry mouth, transient taste alteration, and sialadenitis. Excess tearing from tear duct blockage can also occur. Up to 40% of patients will experience at least one side effect, but these effects generally resolve more than 90% of the time. There is a statistically significant, dose-dependent increased risk of secondary malignancy with radioiodine, but the absolute risk is very small (~10 cases/10,000 patient-years).

18. What is the role of TSH in thyroid cancer therapy?

TSH is trophic to thyroid follicular cells; therefore, TSH suppression therapy is indicated to minimize its growth signal. Excess thyroid hormone is prescribed to target TSH goals, which are generally lower than 0.1 mU/L for high-risk disease and 0.1 to 0.5 mU/L for low-risk disease. TSH suppression therapy provides an overall survival benefit for patients with active thyroid cancer, but this benefit must be balanced with the potential toxicity of thyroid hormone excess, mainly increased bone turnover or osteoporosis and the risk of atrial fibrillation. In the absence of detectable thyroid cancer, the TSH target is the low normal range (e.g., 0.5-2.5 mU/L).

19. What is thyroglobulin (Tg), and how is it assessed?

Tg is a precursor protein for thyroid hormone that is released into the blood by the thyroid gland and by most differentiated thyroid cancer cells. Thus, in the absence of a thyroid gland, Tg is an excellent thyroid cancer tumor marker. It correlates roughly with the mass of thyroid cancer present and can be followed for evidence of tumor growth or stability. Tg antibodies (TgAbs) are reflexively measured with Tg because up to 20% of patients with DTC have detectable TgAbs that interfere with most commercial Tg assays, thus causing false lowering of the reported Tg level. Therefore, in the presence of TgAbs, assessment of disease presence based on Tg measurements should be made with caution. Tg can also be measured from lymph node aspirates after washing the needle with saline solution and running the wash in the Tg assay. Even in the absence of cytologically detectable thyroid cancer in a lymph node aspirate, a positive Tg wash indicates thyroid cancer metastasis to that lymph node.

20. What is a diagnostic radioiodine whole-body scan (WBS)?

Approximately 12 months after initial therapy (surgery and radioiodine therapy), selected patients can receive a low dose of iodine-123 (^{123}I) (~1-5 mCi) under TSH stimulation (ideally with rhTSH preparation), and the next day a scan can assess radiotracer uptake sites. This procedure should always be performed with a Tg measurement under TSH stimulation to correlate the tumor marker with imaging. Visualized WBS uptake is likely to be falsely positive if the Tg level is undetectable. If the WBS is negative, it reduces the likelihood that a future dose

of radioiodine will result in a clinically acceptable response (decrease in tumor mass and/or Tg level).

21. What is the most sensitive combination of tests for detecting residual thyroid cancer?

Persistent thyroid cancer is usually present in the neck; therefore, a sensitive neck US examination, in combination with a stimulated Tg measurement, is more sensitive than a diagnostic WBS. Up to 20% of patients with suppressed TSH will have undetectable Tg that becomes positive under TSH stimulation, a finding indicating the presence of occult disease.

22. What is the relevance of fluorodeoxyglucose (FDG) avidity in thyroid cancer metastases?

FDG uptake on a positron emission tomography (PET) scan indicates increased thyroid cancer aggressiveness and a decreased likelihood of radioiodine uptake in those lesions. In metastatic disease, this is a poor prognostic sign that suggests a need for aggressive therapy, especially when lesions are growing on cross-sectional imaging. A few PET-positive lesions are stable, so clinical criteria should always be assessed before initiating treatment, even with FDG-avid lesions.

23. What are the indications for external beam radiation therapy (EBRT)?

Treatment of gross, unresectable residual disease in the neck, painful bone metastases, or other metastases that threaten critical structures (e.g., vertebral metastases) are indications to consider EBRT.

24. Is there an indication for chemotherapy in thyroid cancer management?

Doxorubicin (Adriamycin) is the only Food and Drug Administration (FDA)–approved chemotherapy for thyroid cancer management, but it is rarely indicated. This drug has relatively high toxicity and low efficacy, and in the era of targeted therapies, such as tyrosine kinase inhibitors, it is rarely prescribed. Indications would include rapidly growing lesions not amenable to surgery, radioiodine, or EBRT. Most clinical trials today use multikinase inhibitors that target the mitogen-activated protein (MAP) kinase pathway and vascular endothelial growth factor (VEGF) receptors, among others. Examples of agents studied include sorafenib, pazopanib, and levatinib, although at the time of this writing, none is FDA approved for DTC.

MEDULLARY THYROID CANCER

25. What is MTC?

MTC is a carcinoma of the calcitonin-secreting parafollicular cells (also known as C-cells), whose primary function is calcitonin secretion. It really is more of a neuroendocrine tumor that arises within the thyroid.

26. What is the epidemiology of MTC?

MTC accounts for 2% to 5% of thyroid cancer cases. There is a slight female predominance, and the mean age at diagnosis is approximately 50 years. Approximately 75% to 80% of cases are sporadic, and the others are heritable.

27. Describe the staging of MTC.

Unlike in DTC, staging of MTC does not use age as a criterion. MTC has a more standard TNM staging scheme in the AJCC classification in which stages I and II are small and larger tumors ($<$ 4 cm) confined to the thyroid gland, and stages III and IV involve extrathyroidal extension of the primary tumor, lateral lymph node metastases, and distant metastases.

28. How does MTC clinically manifest?

Typically, MTC manifests as a painless thyroid nodule or cervical lymphadenopathy that is detected either on examination or incidentally in the setting of imaging for another indication.

29. Is calcitonin a useful marker for the diagnosis of MTC?

Yes. It is extremely specific for the parafollicular cells that give rise to MTC. As neuroendocrine tumors, MTCs also express carcinoembryonic antigen (CEA), thus making this another useful marker. Other neuroendocrine markers, such as chromogranin A, have been used clinically, but to a lesser extent than calcitonin and CEA.

30. What are the hereditary forms of MTC?

Among MTC cases, 20% to 25% are hereditary, occurring in autosomal dominant forms in the setting of MEN2A, MEN2B, and familial MTC (FMTC, which does not have other MEN clinical sequelae). Also see Chapter 51.

31. Do RET proto-oncogene mutations predict disease severity?

Yes. The ATA MTC guidelines rank MTC risk based on genotype-phenotype correlations. For some mutations, such as M918T, thyroidectomy is recommended as soon as possible or prophylactically within the first year of life if there are known MEN2B-affected family members (MTC in MEN2B tends to be very aggressive).

32. What is the primary treatment of MTC?

Surgery is the primary treatment for MTC, thus highlighting the importance of preoperative diagnosis and planning before the initial operation. The use of calcitonin as a preoperative diagnostic test in nodular goiters is controversial; the ATA currently cannot recommend or advise against its routine use preoperatively. A preoperative full neck US scan should be evaluated in all patients with suspected MTC, to optimize the initial surgical procedure.

33. What is the role of radioiodine and TSH suppression for MTC therapy?

None. Parafollicular cells do not contain the sodium-iodine symporter (NIS) protein or TSH receptors and therefore do not respond to either therapy. Radioiodine should not be given. The TSH goal after thyroidectomy is generally in the low normal range.

34. Describe the monitoring for MTC.

Biochemically, the best serum markers for MTC are calcitonin and CEA. These should not be monitored more often than every 3 months because fluctuations in these levels can cause false reassurance or panic if they are checked too often. Based on marker levels, other imaging may be recommended. Generally, if the calcitonin is detectable but lower than 150 pg/mL, a neck US scan is sufficient. If calcitonin levels are higher than 150 pg/mL, a neck US scan and cross-sectional imaging that may include neck and chest CT with contrast, three-phase contrast-enhanced liver CT, or bone MRI of the spine and pelvis can be considered (the liver and bone are common sites of distant MTC metastases).

35. How do the calcitonin and CEA doubling times predict MTC outcomes?

A doubling of the value of these markers in less than or more than 24 months generally predicts progressive disease or general stability of lesions, respectively. A doubling time of less than 6 months indicates a very poor prognosis, with increased mortality and 10-year survival of less than 10%. A doubling time of more than 24 months predicts no or rare deaths in up to 10 years of follow-up. Doubling times between 6 and 24 months have intermediate mortality risks (~25% to 35%).

36. What are the treatment options for metastatic MTC?

Currently, vandetanib and cabozantinib are FDA-approved oral medications for metastatic, progressive MTC. They are multi-targeted tyrosine kinase inhibitors that are generally well tolerated and result in stasis of previously progressive lesions in the majority of patients. Common side effects are skin reactions, hypertension and rare, severe reactions including QT prolongation and sudden death for vandetanib and GI perforatons for cabozantinib; prospective patients should therefore be screened and monitored with an electrocardiogram before and during treatment with vandetanib. Standard chemotherapies tend to be relatively toxic with limited efficacy but are reasonable treatment options if vandetanib is ineffective.

ANAPLASTIC THYROID CARCINOMA

37. What is ATC?

ATC is a completely dedifferentiated form of thyroid cancer. It is not responsive to radioiodine or TSH suppression therapies and by definition always is considered stage IV thyroid cancer.

38. Does ATC arise de novo or from well-differentiated thyroid cancer?

The balance of evidence favors that ATC devolves from DTC. This is based on the discovery of ATC mixed with PTC in numerous cases, as well as cases in patients who developed ATC after initial therapy for PTC. Presumably, the ATC arose from persistent, poorly differentiated PTC that was not successfully treated by the initial therapy.

39. What is the epidemiology of ATC?

Fortunately, ATC is a very rare tumor, accounting for only 1.3% of all thyroid cancer cases. Most diagnoses occur in the sixth and seventh decades of life.

40. What is the prognosis for ATC?

The prognosis is as poor as the worst of all forms of cancer. Most patients die within 6 months of diagnosis despite aggressive treatment. One-year survival rates range from 10% to 20%, although there are some long-term survivors.

41. How does ATC clinically manifest?

The classic presentation is a rapidly expanding neck mass, usually associated with pathologically enlarged lymph nodes, and often with hoarseness, dysphagia, and possibly hemoptysis. Cross-sectional imaging is appropriate for evaluation of distant metastases because these are often evident at initial presentation.

42. What are the treatment strategies for ATC?

A careful staging assessment is critical for patients with newly diagnosed ATC because a palliative approach may be the most appropriate and humane option. In patients who are candidates, complete surgical resection of the primary tumor results in prolonged survival. EBRT has also been shown to improve survival time. In general, multimodality therapy is optimal with complete surgical resection, EBRT, and chemotherapy (taxane-based therapies show the most promise). Clinical trials are focusing on the use of multitargeted kinase inhibitors after or in combination with EBRT and chemotherapy.

BIBLIOGRAPHY

Alexander EK, et al: Preoperative diagnosis of benign thyroid nodules with indeterminate cytology, *N Engl J Med* 367: 705–715, 2012.

Aschebrook-Kilfoy B, et al: Thyroid cancer incidence patterns in the United States by histologic type, 1992-2006, *Thyroid* 21:125–134, 2011.

Ball DW: Medullary thyroid cancer: monitoring and therapy, *Endocrinol Metab Clin North Am* 36:823–837, viii, 2007.

Baloch ZW, et al: The National Cancer Institute Thyroid fine needle aspiration state of the science conference: a summation, *Cytojournal* 5:6, 2008.

Biondi B, Cooper DS: Benefits of thyrotropin suppression versus the risks of adverse effects in differentiated thyroid cancer, *Thyroid* 20:135–146, 2010.

Brown AP, et al: The risk of second primary malignancies up to three decades after the treatment of differentiated thyroid cancer, *J Clin Endocrinol Metab* 93:504–515, 2008.

Cardis E, Hatch M: The Chernobyl accident: an epidemiological perspective. *Clin Oncol (R Coll Radiol)* 23:251–260, 2011.

Cooper DS, et al: Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer, *Thyroid* 19:1167–1214, 2009.

Elisei R, et al: Follow-up of low-risk differentiated thyroid cancer patients who underwent radioiodine ablation of postsurgical thyroid remnants after either recombinant human thyrotropin or thyroid hormone withdrawal, *J Clin Endocrinol Metab* 94:4171–4179, 2009.

Enewold L, et al: Rising thyroid cancer incidence in the United States by demographic and tumor characteristics, 1980-2005, *Cancer Epidemiol Biomarkers Prev* 18:784–791, 2009.
Foote RL, et al: Enhanced survival in locoregionally confined anaplastic thyroid carcinoma: a single-institution experience using aggressive multimodal therapy, *Thyroid* 21:25–30, 2011.
Frasoldati A, et al: Role of thyroglobulin measurement in fine-needle aspiration biopsies of cervical lymph nodes in patients with differentiated thyroid cancer, *Thyroid* 9:105-111, 1999.
Grewal RK, et al: Salivary gland side effects commonly develop several weeks after initial radioactive iodine ablation, *J Nucl Med* 50:1605–1610, 2009.
Haas V, et al: Unusual manifestation of anaplastic thyroid cancer, *Acta Medica (Hradec Kralove)* 51:233–236, 2008.
Kim HK, et al: Daily urine iodine excretion while consuming a low-iodine diet in preparation for radioactive iodine therapy in a high iodine intake area, *Clin Endocrinol (Oxf)* 75:851–856, 2011.
Kloos RT, et al: Medullary thyroid cancer: management guidelines of the American Thyroid Association, *Thyroid* 19: 565–612, 2009.
Klopper J, Haugen B: Can calcitonin and carcinoembryonic antigen doubling times predict progression of thyroid carcinoma? *Nat Clin Pract Endocrinol Metab* 4:428–429, 2008.
Kurzrock R, Sherman SI, Ball DW, et al. Activity of XL184 (Cabozantinib), an oral thyrosine kinase inhibitor, in patients with medullary thyroid cancer. *J Clin Oncol.* 2011 Jul 1;29(19):2660-6.
La Quaglia MP, et al: Differentiated thyroid cancer: clinical characteristics, treatment, and outcome in patients under 21 years of age who present with distant metastases. A report from the Surgical Discipline Committee of the Children's Cancer Group, *J Pediatr Surg* 35:955–959, 2000.
Mallick U, et al: Ablation with low-dose radioiodine and thyrotropin alfa in thyroid cancer. *N Engl J Med* 366:1674–1685, 2012.
McIver B, et al: Anaplastic thyroid carcinoma: a 50-year experience at a single institution, *Surgery* 130:1028–1034, 2001.
Nikiforov YE, et al: Molecular testing for mutations in improving the fine-needle aspiration diagnosis of thyroid nodules, *J Clin Endocrinol Metab* 94:2092–2098, 2009.
Schlumberger M, et al: Strategies of radioiodine ablation in patients with low-risk thyroid cancer, *N Engl J Med* 366:1663–1673, 2012.
Serhal DI, et al: Rapid rise in serum thyrotropin concentrations after thyroidectomy or withdrawal of suppressive thyroxine therapy in preparation for radioactive iodine administration to patients with differentiated thyroid cancer, *J Clin Endocrinol Metab* 89:3285–3289, 2004.
Siegel R, et al: Cancer statistics, 2012. *CA Cancer J Clin* 62:10–29, 2012.
Spencer CA, Lopresti JS: Measuring thyroglobulin and thyroglobulin autoantibody in patients with differentiated thyroid cancer, *Nat Clin Pract Endocrinol Metab* 4:223–233, 2008.
Stavrakis AI, et al: Surgeon volume as a predictor of outcomes in inpatient and outpatient endocrine surgery, *Surgery* 142:887–899, 2007.
Stulak JM, et al: Value of preoperative ultrasonography in the surgical management of initial and reoperative papillary thyroid cancer, *Arch Surg* 141:489–494, 2006.
Thornton K, et al: Vandetanib for the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease: U.S. Food and Drug Administration drug approval summary, *Clin Cancer Res* 18:3722–3730, 2012.
Xing M, et al: BRAF mutation predicts a poorer clinical prognosis for papillary thyroid cancer, *J Clin Endocrinol Metab* 90:6373–6379, 2005.
Zhang L, et al: Risk factors for neck nodal metastasis in papillary thyroid microcarcinoma: a study of 1066 patients, *J Clin Endocrinol Metab* 97:1250–1257, 2012.

THYROID EMERGENCIES

Michael T. McDermott

1. What is thyroid storm?

Thyroid storm or crisis is a life-threatening condition characterized by an exaggeration of the manifestations of thyrotoxicosis. When thyroid storm was first described, the acute mortality rate was nearly 100%. Today, the prognosis is significantly improved if appropriate therapy is initiated early; however, the mortality rate continues to be approximately 20%.

2. How do patients develop thyroid storm?

Thyroid storm usually occurs in patients who have unrecognized or inadequately treated thyrotoxicosis and a superimposed precipitating event, such as thyroid surgery, nonthyroid surgery, infection, or trauma.

3. What are the clinical manifestations of thyroid storm?

Fever (> 102° F) is the cardinal manifestation. Tachycardia is usually present, and tachypnea is common, but the blood pressure is variable. Cardiac arrhythmias, congestive heart failure, and ischemic heart symptoms may develop. Nausea, vomiting, diarrhea, and abdominal pain are frequent features (Fig. 38-1). Central nervous system manifestations include hyperkinesis, psychosis, and coma. A goiter is a helpful finding but is not always present.

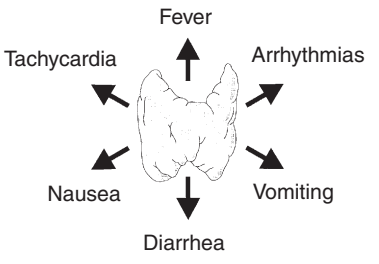

Figure 38-1. Symptoms of thyroid storm.

4. What laboratory abnormalities are seen in thyroid storm?

Serum thyroxine (total T_4 and free T_4) and triiodothyronine (total T_3 and free T_3) are usually significantly elevated, and serum thyroid-stimulating hormone (TSH) is undetectable. These hormone levels, however, cannot reliably distinguish patients with thyroid storm from those who have uncomplicated thyrotoxicosis. Other common findings include anemia, leukocytosis, hyperglycemia, azotemia, hypercalcemia, and elevated liver enzymes.

5. How is the diagnosis of thyroid storm made?

The diagnosis must be made on the basis of suspicious but nonspecific clinical findings. If the diagnosis is strongly suspected, waiting for the results of tests may cause a critical delay in the initiation of effective lifesaving therapy. Clinical features are therefore the key. Table 38-1 provides a useful scoring system to aid in diagnosis.

TABLE 38-1. THYROID STORM SCORING SYSTEM (Ref: Burch HD, 1993)

FEATURE	SCORE
Fever	
99-99.9	5
100-100.9	10
101-101.9	15
102-102.9	20
103-103.9	25
≥ 104	30
Central Nervous System	
Absent	0
Mild agitation	10
Moderate	20
Severe	30
Cardiac: Pulse	
99-109	5
110-119	10
120-129	15
130-139	20
≥ 140	25
Atrial fibrillation	10
Cardiac: Congestive Heart Failure	
Absent	0
Mild (edema)	5
Moderate (rales)	10
Severe (pulmonary edema)	15
Gastrointestinal	
Absent	0
Nausea, vomiting, diarrhea, or pain	10
Jaundice	20
Precipitant History	
Absent	0
Present	10
Score	**Thyroid Storm**
< 25	Unlikely
25-44	Suggestive
≥ 45	Likely

6. What other conditions may mimic thyroid storm?

Similar presentations may be seen with sepsis, pheochromocytoma, and malignant hyperthermia.

7. How should patients with thyroid storm be treated?

The immediate goals are to decrease thyroid hormone synthesis, to inhibit thyroid hormone release, to reduce the heart rate, to support the circulation, and to treat the precipitating condition. Because $beta_1$-adrenergic receptors are significantly increased in patients with this condition, $beta_1$-selective blockers are the preferred agents for heart rate control.

8. What drugs are used to decrease thyroid hormone synthesis?

- Propylthiouracil, 600 to 1200 mg daily (oral, rectal, or nasogastric [NG] tube)
- Methimazole, 60 to 120 mg daily (oral, rectal, NG tube, or intravenous [IV])

9. List drugs used to inhibit thyroid hormone release

- Sodium iodide (NaI), 1 g over 24 hours (IV)
- Potassium iodide (SSKI), 5 drops every 6 to 8 hours (oral)
- Lugol solution, 10 drops every 6 to 8 hours (oral)

10. What drugs are used to reduce the heart rate?

- Esmolol, 500 mg over 1 minute, followed by 50 to 300 mg/kg/minute infusion (IV)
- Metoprolol, 5 to 10 mg every 2 to 4 hours (IV)
- Diltiazem, 60 to 90 mg every 6 to 8 hours orally, or 0.25 mg/kg over 2 minutes, followed by infusion of 10 mg/minute (IV)

11. What other interventions are critical for resolution of thyroid storm?

- Intravenous fluids
- Stress glucocorticoid doses (hydrocortisone, methylprednisolone, dexamethasone)
- Identification and treatment of the underlying cause of thyroid storm

12. When traditional therapy fails, what additional options should be considered?

Plasma exchange and plasmapheresis can be lifesaving measures in patients with thyroid storm who have not adequately responded to the foregoing standard measures.

13. Define myxedema coma.

Myxedema coma is a life-threatening condition characterized by an exaggeration of the manifestations of hypothyroidism. Myxedema coma originally had a mortality rate of 100%. Today, the outlook is much improved for appropriately treated patients; the mortality rate in more recent studies has varied from 0% to 45%.

14. How do patients develop myxedema coma?

Myxedema coma usually occurs in older patients who have inadequately treated or untreated hypothyroidism and a superimposed precipitating event. Important events include prolonged cold exposure, infection, trauma, surgery, myocardial infarction, congestive heart failure, pulmonary embolism, stroke, respiratory failure, gastrointestinal bleeding, and administration of various drugs, particularly those with a depressive effect on the central nervous system.

15. What are the clinical manifestations of myxedema coma?

Hypothermia, bradycardia, and hypoventilation are common. Blood pressure, although generally reduced, is more variable. Pericardial, pleural, and peritoneal effusions are often found. Ileus is frequently present, and acute urinary retention may be seen. Central nervous system manifestations include seizures, stupor, and coma (Fig. 38-2). Deep tendon reflexes are absent or exhibit a delayed relaxation phase. Typical hypothyroid skin and hair changes are often apparent. A goiter, although frequently absent, is a helpful finding. A thyroidectomy scar may also be an important clue.

16. What laboratory abnormalities are seen in myxedema coma?

Serum T_4 (total and free T_4) and T_3 (total and free T_3) levels are usually low, and TSH is significantly elevated. Other frequent abnormalities include anemia, hyponatremia, hypoglycemia, and elevated serum levels of cholesterol and creatine kinase (CK). Arterial blood gases often reveal carbon dioxide retention and hypoxemia. The electrocardiogram often shows sinus bradycardia, various types and degrees of heart block, low voltage, and T-wave flattening.

17. How is the diagnosis of myxedema coma made?

The diagnosis must be made on clinical grounds on the basis of the findings described earlier. Serum levels of thyroid hormones are reduced and the TSH level is elevated, but the delay involved in waiting for test results may unnecessarily postpone the initiation of effective therapy.

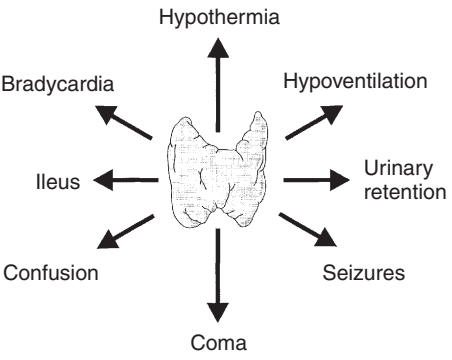

Figure 38-2. Symptoms of myxedema coma.

18. How should patients with myxedema coma be treated?

The goals are to replace the depleted thyroid hormone pool rapidly, to replace glucocorticoids, to support vital functions, and to treat any precipitating conditions. The normal total body pool of T_4 is about 1000 μg (500 μg in the thyroid, 500 μg in the rest of the body).

19. How are circulating thyroid hormones rapidly replaced?

Levothyroxine (LT_4), liothyronine (LT_3), or both may be used. The best regimen remains undetermined, but the combination of LT_4 plus LT_3 is recommended. Regimens for LT_4 alone, LT_3 followed by LT_4, and LT_4 plus LT_3 are as follows:

- LT_4 alone: LT_4, 200 to 300 μg over 5 minutes (IV), followed by 50 to 100 μg/day (oral or IV)
- LT_3 followed by LT_4: LT_3, 50 to 100 μg over 5 minutes (IV), followed by LT_4, 50 to 100 μg/day (oral or IV)
- LT_4 plus LT_3: LT_4, 200 to 300 μg over 5 minutes plus LT_3, 20 to 50 μg over 5 minutes (IV), followed by LT_4, 50 to 100 μg/day, and LT_3, 20 to 30 μg/day (oral or IV)

20. What other interventions are critical for resolution of myxedema coma?

- Oxygen
- IV fluids
- Mechanical ventilation (if necessary)
- Rewarming (blankets or central rewarming)
- Stress glucocorticoid doses (hydrocortisone, methylprednisolone, dexamethasone)
- Identification and treatment of the underlying cause of myxedema coma

KEY POINTS 1: THYROID EMERGENCIES

1. Thyroid storm is a life-threatening form of severe thyrotoxicosis that usually has a precipitating factor and a high mortality rate if it is not treated promptly and appropriately.
2. When thyroid storm is diagnosed or suspected, treatment with antithyroid drugs, cold iodine, beta-blockers, and stress doses of glucocorticoids, along with management of any precipitating factors, should be promptly initiated.
3. Myxedema coma is a life-threatening form of severe hypothyroidism that often has a precipitating cause and a high mortality rate if it is not promptly and adequately treated.
4. When myxedema coma is diagnosed or suspected, management should include rapid repletion of thyroid hormones, stress glucocorticoid doses, and treatment of any precipitating causes.

BIBLIOGRAPHY

Brooks MH, Waldstein SS: Free thyroxine concentrations in thyroid storm, *Ann Intern Med* 93:694–697, 1980.
Burch HD, Wartofsky L: Life-threatening thyrotoxicosis: thyroid storm, *Endocrinol Metab Clin North Am* 22:263–278, 1993.
Dillmann WH: Thyroid storm, *Curr Ther Endocrinol Metab* 6:81–85, 1997.
Fliers E, Wiersinga WM: Myxedema coma, *Rev Endocr Metab Disord* 4:137–141, 2003.
Jordan RM: Myxedema coma: pathophysiology, therapy, and factors affecting prognosis, *Med Clin North Am* 79:185–194, 1995.
Koball S, Hickstein H, Gloger M, et al: Treatment of thyrotoxic crisis with plasmapheresis and single pass albumin dialysis: a case report, *Artif Organs* 34:E55–E58, 2010.
Kokuho T, Kuji T, Yasuda G, Umemura S: Thyroid storm induced multiple organ failure relieved quickly by plasma exchange therapy, *Ther Apher Dial* 8:347–349, 2004.
Nicoloff JT: Myxedema coma: a form of decompensated hypothyroidism, *Endocrinol Metab Clin North Am* 22:279–290, 1993.
Pittman CS, Zayed AA: Myxedema coma, *Curr Ther Endocrinol Metab* 6:98–101, 1997.
Rodriguez I, Fluiters E, Perez-Mendez LF, et al: Severe mental impairment and poor physiologic status are associated with mortality in myxedema coma, *J Endocrinol* 180:347–350, 2004.
Sarlis NJ, Gourgiotis L: Thyroid emergencies, *Rev Endocr Metab Disord* 4:129–136, 2003.
Tietgens ST, Leinung MC: Thyroid storm, *Med Clin North Am* 79:169–184, 1995.
Tsitouras PD: Myxedema coma, *Clin Geriatr Med* 11:251–258, 1995.
Yamamoto T, Fukuyama J, Fujiyoshi A: Factors associated with mortality of myxedema coma: report of eight cases and literature survey, *Thyroid* 9:1167–1174, 1999.
Yeung S-CJ, Go R, Balasubramanyam A: Rectal administration of iodide and propylthiouracil in the treatment of thyroid storm, *Thyroid* 5:403–405, 1995.

CHAPTER 39

EUTHYROID SICK SYNDROME

Michael T. McDermott

1. What is euthyroid sick syndrome?

Euthyroid sick syndrome refers to changes in serum thyroid-stimulating hormone (TSH), serum thyroid hormone, and tissue thyroid hormone levels that occur in patients with various nonthyroidal illnesses and starvation. It is not a primary thyroid disorder but instead results from changes in thyroid hormone secretion, transport, and metabolism induced by the nonthyroidal illness.

2. What hormone changes occur in patients with mild to moderate nonthyroidal illnesses?

Serum total triiodothyronine (T_3) and free T_3 and tissue T_3 levels decrease as a result of reduced conversion of thyroxine (T_4) to T_3 in peripheral tissues, predominantly the liver, where hepatic deiodinase type I (D1) activity is decreased. Serum free T_4 and TSH levels usually remain within the reference range in the mildest form of this condition.

3. Describe the hormone changes in patients with moderate to severe nonthyroidal illnesses.

Serum total T_3 and free T_3 levels decrease further; total T_4 also decreases, and the T_3 resin uptake (T_3RU) increases. The latter changes result from reduced binding of thyroid hormones to their transport proteins because of both impaired protein synthesis and the presence of circulating inhibitors of protein binding. Serum TSH levels remain normal or become decreased at this stage. Free T_4 may be normal, decreased, or increased.

4. Describe the hormone changes associated with recovery from nonthyroidal illnesses.

Free T_4 decreases, and TSH increases. As hepatic protein synthesis improves and circulating inhibitors of protein binding disappear, serum free T_4 levels drop transiently with a compensatory increase in serum TSH levels before complete normalization occurs. Serum T_3 levels also eventually normalize.

5. How can euthyroid sick syndrome be distinguished from hypothyroidism?

In euthyroid sick syndrome, serum T_3 is decreased proportionately more than T_4, the T_3RU is high, and TSH is normal or mildly decreased and then mildly increased during recovery. In primary hypothyroidism, serum T_4 is reduced proportionately more than T_3, the T_3RU is low, and TSH is increased. Other tests may also be helpful. In euthyroid sick syndrome, free T_4 is usually normal and reverse T_3 (rT_3) is increased; in hypothyroidism, both free T_4 and rT_3 are decreased.

6. What causes euthyroid sick syndrome?

Euthyroid sick syndrome is believed to be caused by increased circulating cytokines and other inflammation mediators resulting from the underlying nonthyroidal illness. These mediators inhibit the thyroid axis at multiple levels, including the pituitary (decreased TSH secretion), the thyroid (decreased T_4 and T_3 responses to TSH), transport proteins (decreased thyroid hormone binding), and peripheral tissues (decreased conversion of T_4 to T_3).

7. What is the function of the deiodinase enzymes?

Deiodinases are selenocysteine enzymes that activate and deactivate thyroid hormones by removing iodine molecules. Deiodinase enzymes have three known subtypes: D1, deiodinase 2 (D2), and deiodinase 3 (D3) (Table 39-1 and Fig. 39-1). D1 converts T_4 to T_3 in the liver and kidneys, thus producing the majority of circulating T_3, and converts reverse T_3 (rT_3) to diiodothyronine (T_2); D1 has a higher affinity for rT_3 than for T_4. D2 converts T_4 to T_3 in the brain and pituitary gland, thus producing the majority of cellular T_3 in these tissues; D2 has a higher affinity for T4 than for rT_3. D3 converts T_4 to rT_3 and T_3 to T_2.

8. What changes in deiodinase function are seen in euthyroid sick syndrome?

D1 activity is significantly reduced and D3 activity is enhanced in euthyroid sick syndrome. These changes are responsible for the low serum T_3 and high serum rT_3 levels that are characteristic of this condition.

TABLE 39–1. DEIODINASE ENZYMES: SELENOCYSTEINE ENZYMES THAT DEIODINATE THYROID HORMONES

	DEIODINASE 1 (D1)	DEIODINASE 2 (D2)	DEIODINASE 3 (D3)
Substrate	$rT_3 >> T_4$	$T_4 >> rT_3$	$T_4 + T_3$
Tissue	Liver Kidney	Brain Pituitary Fat	Placenta Brain
Function	Clear rT_3 ↑ Serum T_3	↑ Cellular T_3 ↑ Serum T_3	Protect fetus ↓ Cellular T_3 Clear $T_4 + T_3$

rT_3, Reverse triiodothyronine; T_3, triiodothyronine; T_4, thyroxine.

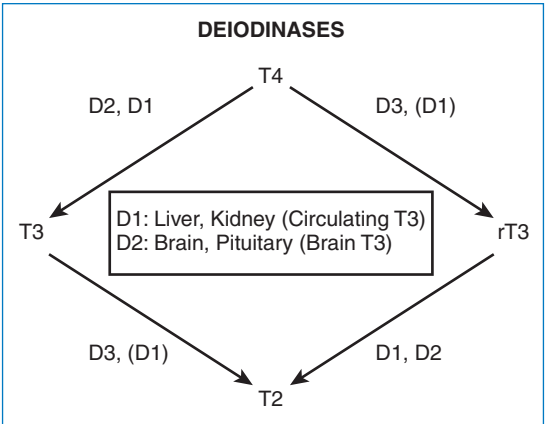

Figure 39-1. Deiodinase function.

KEY POINTS 1: EUTHYROID SICK SYNDROME

1. Euthyroid sick syndrome is not a thyroid disorder but is instead a group of changes in serum thyroid-stimulating hormone (TSH) and thyroid hormones and tissue thyroid hormone levels that result from cytokines and inflammatory mediators produced during nonthyroidal illnesses.
2. Mild euthyroid sick syndrome is characterized by a decrease in serum triiodothyronine (T_3) levels resulting from reduced conversion of thyroxine (T_4) to T_3 in the liver and other tissues.
3. More severe nonthyroidal illnesses cause decreased serum TSH, low total T_4, and increased T_3 resin uptake (T_3RU) secondary to suppressed pituitary TSH secretion and reduced thyroid hormone binding to transport proteins.
4. Transient elevation of serum TSH is often seen as patients recover from a nonthyroidal illness.
5. Euthyroid sick syndrome appears to be an adaptive response to reduce tissue metabolism and preserve energy during systemic illnesses. Therefore, treatment with thyroid hormone is not generally recommended but may be beneficial in patients with chronic heart failure.

9. Is euthyroid sick syndrome an adaptive mechanism, or is it harmful?

Many experts consider euthyroid sick syndrome to be an adaptive mechanism that may reduce peripheral tissue energy expenditure during the nonthyroidal illness. Conversely, other experts argue that the alterations in circulating thyroid hormone levels may be harmful and may accentuate the effects of the nonthyroidal illness. This issue is likely to remain controversial for years to come.

10. Should patients with euthyroid sick syndrome be treated with thyroid hormones?

Management of euthyroid sick syndrome is also controversial. Liothyronine (LT_3) therapy was shown in a randomized controlled trial to improve ventricular performance and the neuroendocrine profile in patients with chronic heart failure. Interventional studies have not yielded other consistent or convincing evidence of benefit from treating euthyroid sick syndrome patients with either LT_3 or levothyroxine (LT_4). Experts agree that large, prospective studies in a variety of settings are needed. Therefore, thyroid hormone therapy cannot, at present, be generally recommended for patients with euthyroid sick syndrome, except possibly those with chronic heart failure.

11. Does euthyroid sick syndrome have any prognostic significance?

Low serum T_3 levels have significant prognostic value. The degree of reduction of serum T_3 has been shown to predict a poor prognosis in patients with ischemic heart disease, heart valve disease, congestive heart failure, meningococcal sepsis, and a variety of illnesses in the intensive care setting. Patients with extremely low serum T_3 levels have a high mortality rate.

12. Are levels of thyroid hormone ever elevated in patients with nonthyroid diseases?

The serum T_4 may be transiently elevated in patients with acute psychiatric illnesses and various acute medical illnesses. The mechanisms underlying such elevations of T_4 are not well understood but may be mediated by alterations in neurotransmitters or cytokines. This condition must be distinguished from true thyrotoxicosis.

BIBLIOGRAPHY

Adler SM, Wartofsky L: The nonthyroidal illness syndrome, *Endocrinol Metab Clin North Am* 36:657–672, 2007.
Debaveye Y, Ellger B, Mebis L, et al: Regulation of tissue iodothyronine deiodinase activity in a model of prolonged critical illness, *Thyroid* 18:551–560, 2008.

DeGroot LJ: Dangerous dogmas in medicine: the nonthyroidal illness syndrome, *J Clin Endocrinol Metab* 84:151–164, 1999.

den Brinker M, Joosten KF, Visser TJ, et al: Euthyroid sick syndrome in meningococcal sepsis: the impact of peripheral thyroid hormone metabolism and binding proteins, *J Clin Endocrinol Metab* 90:5613–5620, 2005.

Huang SA, Bianco AC: Reawakened interest in type III iodothyronine deiodinase in critical illness and injury, *Nat Clin Pract Endocrinol Metab* 4:148–154, 2008.

Iervasi G, Pingitore A, Landi P, et al: Low serum free triiodothyronine values predict mortality in patients with cardiac disease, *Circulation* 107:708–711, 2003.

Kimura T, Kanda T, Kotajima N, et al: Involvement of circulating interleukin-6 and its receptor in the development of euthyroid sick syndrome in patients with acute myocardial infarction, *Eur J Endocrinol* 143:179–184, 2000.

Nagaya T, Fujieda M, Otsuka G, et al: A potential role of activated NF-kappa B in the pathogenesis of euthyroid sick syndrome, *J Clin Invest* 106:393–402, 2000.

Peeters RP, Kester MH, Wouters PJ, et al: Increased thyroxine sulfate levels in critically ill patients as a result of a decreased hepatic type I deiodinase activity, *J Clin Endocrinol Metab* 90:6460–6465, 2005.

Peeters RP, van der Geyten S, Wouters PJ, et al: Tissue thyroid hormone levels in critical illness, *J Clin Endocrinol Metab* 90:6498–6507, 2005.

Peeters RP, Wouters PJ, Kaptein E, et al: Reduced activation and increased inactivation of thyroid hormone in tissues of critically ill patients, *J Clin Endocrinol Metab* 88:3202–3211, 2003.

Peeters RP, Wouters PJ, van Toor H, et al: Serum 3, 3', 5'-triiodothyronine and 3, 5, 3'-triiodothyronine/rT3 are prognostic markers in critically ill patients and are associated with tissue deiodinase activities, *J Clin Endocrinol Metab* 90: 4559–4565, 2005.

Pingitore A, Galli E, Barison A, et al: Acute effects of triiodothyronine (T_3) replacement therapy in patients with chronic heart failure and low-T_3 syndrome: a randomized, placebo controlled study, *J Clin Endocrinol Metab* 93:1351–1358, 2008.

Pingitore A, Landi P, Taddei MC, et al: Triiodothyronine levels for risk stratification of patients with chronic heart failure, *Am J Med* 118:132–136, 2005.

Plikat K, Langgartner J, Buettner R, et al: Increasing thyroid dysfunction is correlated with degree of illness and mortality in intensive care unit patients, *Metabolism* 56:239–244, 2007.

Spratt DI, Frohnauer M, Cyr-Alves H, et al: Triiodothyronine replacement does not alter the hemodynamic, metabolic, and hormonal responses to coronary artery surgery, *Am J Physiol Endocrinol Metab* 293:E310–E315, 2007.

Vanhorebeek I, Langouche L, Van den Berghe G: Endocrine aspects of acute and prolonged critical illness, *Nat Clin Pract Endocrinol Metab* 2:20–31, 2006.

CHAPTER 40

THYROID DISEASE IN PREGNANCY

Linda Barbour

1. How does normal pregnancy affect maternal thyroid function?

The profound hormonal influences that change the physiology of pregnancy and the increased metabolic demands of the fetus cause significant changes in maternal thyroid function (Table 40-1).

2. Why must thyroid function tests be interpreted cautiously in pregnancy?

The influence of estrogen and human chorionic gonadotropin (hCG) on circulating thyroid hormone levels requires that thyroid function tests in pregnancy be interpreted cautiously. Estrogen increases thyroid-binding globulin (TBG) by two- to threefold beginning a few weeks after conception. The result is an approximately 50% increase in serum total thyroxine (TT_4) and total triiodothyronine (TT_3) levels because circulating thyroid hormones are highly protein bound. Throughout pregnancy, the range for both hormones should be approximately 1.5 times the nonpregnant range. Measurement of the triiodothyronine (T_3) resin uptake (T_3RU), which is inversely related to serum thyroid binding capacity, is correspondingly low, so that the calculated free thyroxine (T_4) index (FT_4I; product of multiplying the total T_4 by the T_3RU) is usually normal. Although the measured free T_4 (FT_4) and free T_3 (FT_3) levels are usually normal in pregnancy, they must be interpreted with caution because the reference ranges provided by manufacturers have been established using pools of nonpregnant sera. These free assays may also be influenced by changes in TBG and albumin unless they are measured by an equilibrium dialysis method or online solid phase extraction–liquid chromatography/tandem mass spectrometry (LC/MS/MS), but these methods are expensive and usually not available. Only 0.03% of serum TT_4 content is unbound to serum proteins and is the FT_4 available for tissue uptake. Further, the very high TBG levels, the low albumin levels, and the high nonesterified fatty acids characteristic of pregnancy may all affect the FT_4 immunoassays. A slightly low FT_4 in the late second or third trimester may be normal or may represent true hypothyroidism and should be interpreted in the context of the thyroid-stimulating hormone (TSH) and TT_4 levels. If TSH is less than 3.0 mU/L and TT_4 is 1.5-fold elevated, it is unlikely that the patient has true hypothyroidism. If possible, pregnancy-specific norms for FT_3 and FT_4 should be established by the laboratory.

TSH values are also affected by the thyrotropic effect of hCG; in one large series, the 95% confidence limits were as low as 0.03 mU/L in the first and second trimesters and 0.13 mU/L in the third trimester, with an upper limit of normal of less than 3.0 mU/L in the first trimester and less than 3.5 mU/L in

TABLE 40-1. THYROID FUNCTION TESTS DURING NORMAL PREGNANCY

	FIRST TRIMESTER	SECOND TRIMESTER	THIRD TRIMESTER
Total T_4	1.5× ↑	1.5× ↑	1.5× ↑
Total T_3	1.5× ↑	1.5× ↑	1.5× ↑
T_3RU	↓	↓	↓
Free T_4 index	Normal	Normal	Normal
TSH	↓ or normal	↓ or normal	Slight ↓ or normal
Free T_4	Usually normal	Usually normal	Usually normal

T_3, Triiodothyronine; T_3RU, T_3 resin uptake; T_4, thyroxine; TSH, thyroid-stimulating hormone; ↑, increased; ↓, decreased.

the second and third trimesters. Ethnicity-related differences are also significant. Black and Asian women have TSH values that are, on average, 0.4 mU/L lower than in white women. Guidelines from both the American Thyroid Association (ATA) and the Endocrine Society recommend that an upper TSH limit of 2.5 mU/L be used in the first trimester and 3.0 mU/L in the second and third trimesters, especially if thyroid peroxidase (TPO) antibodies are positive and individual laboratories do not offer gestation-specific normal ranges. The TSH must also be interpreted in the context of the actual thyroid hormone levels. If the TT_4 and TT_3 are less than 1.5-fold elevated compared with the nonpregnancy range and the FT_4 and FT_3 hormones are not increased, the suppressed TSH may reflect the effect of hCG, but it could also be caused by subclinical hyperthyroidism from Graves' diseases or a hot nodule. None of these conditions warrants treatment.

3. What particular effects may be seen during the first trimester?

During the first trimester, high hCG levels may stimulate thyroid T_4 secretion sufficiently to suppress the serum TSH into the range of 0.03 to 0.5 mU/L in up to 15% of pregnant women. In a study of women with hCG concentrations higher than 200,000 IU/L (which is not uncommon in twin pregnancies), the TSH was less than or equal to 0.2 mU/L in 67% of women. The TSH may be slightly suppressed in the second trimester, but by the third trimester, it is usually within the normal range. The beta subunit of hCG has 85% sequence homology in the first 114 amino acids with TSH and can bind to and stimulate the TSH receptor. Levels of hCG higher than 50,000 IU/L, which may be seen when hCG peaks at the end of the first trimester, can therefore increase the FT_4 level enough to suppress the serum TSH. However, the TSH is usually detectable, the TT_4 is less than 1.5-fold elevated above the nonpregnancy range, and FT_4 is usually within the normal range. A TSH in the high-normal range ($>$ 2.5-3.0) during the first trimester is therefore suggestive of subclinical hypothyroidism.

4. Why must the mother significantly increase thyroid hormone production during pregnancy?

- Maternal plasma volume expands 30% to 40%, requiring a concomitant expansion of the thyroid hormone pool.
- Placental type 3 deiodinase (D3) activity results in increased maternal T_4 metabolism to reverse T_3.
- Transfer of T_4 across the placenta to the fetus occurs.
- High TBG levels decrease the levels of free hormone.
- Gastrointestinal absorption of exogenous thyroid hormone may be impaired by iron in prenatal vitamins.

5. What factors may compromise maternal ability to increase thyroid hormone production?

Women with limited thyroid reserve as a result of thyroiditis, partial ablation, or surgical resection may be unable to increase thyroid hormone production during pregnancy and often develop hypothyroidism. Women with inadequate iodine intake may also develop hypothyroidism and a goiter because iodine requirements increase by approximately 40% to 50% in pregnancy.

6. What is the "goiter of pregnancy"?

The goiter of pregnancy has been well described in iodine-deficient areas of the world, but it does not occur in geographic regions that are iodine replete. In fact, one of the first pregnancy tests to be developed in iodine-deficient areas was a loosely braided choker necklace that broke when a woman developed such a goiter. The thyroid gland increased in size with each subsequent pregnancy.

7. Why do iodine requirements increase in pregnancy?

Iodine requirements increase markedly during pregnancy as a result of increased urinary iodine losses secondary to the 50% to 100% increase in glomerular filtration rate (GFR) during pregnancy, the diversion of iodine to the fetus for thyroid hormone synthesis, and increased maternal thyroid hormone requirements.

8. What is the recommended iodine intake during pregnancy, and how can it be met?

The World Health Organization's recommendations for iodine intake are 250 μg/day during pregnancy and lactation and 150 μg/day in the nonpregnant state. Iodine insufficiency is an increasing problem in the United States as a result of the availability of deiodinated salt and is estimated at 5% to 10%. Because most prenatal vitamins do not contain iodine, women of childbearing age should be instructed to use only iodinated salt or to make sure to ingest a prenatal vitamin containing iodine.

9. What happens if iodine intake is insufficient?

If iodine intake is insufficient, thyroid hormone production drops, resulting in increased secretion of TSH, which then stimulates thyroid gland growth. Thyroid volume commonly increases by 30% or more during pregnancy in iodine-deficient regions and often does not completely regress after delivery. Many European and developing countries with endemic iodine deficiency do not supplement with iodine; therefore, women are at risk of iodine-deficiency goiters during pregnancy. When iodine intake is severely deficient, overt hypothyroidism results both in the mother and the fetus. Endemic cretinism occurs if severe hypothyroidism secondary to iodine deficiency goes unrecognized and untreated at birth.

10. What happens to thyroid gland volume in iodine-replete areas during pregnancy?

In iodine-replete areas, such as the United States, thyroid gland volume may increase by 10% to 15%, primarily as a result of pregnancy-induced vascular swelling of the gland. Although this enlargement can be recognized by ultrasound, it cannot usually be appreciated by palpation. Therefore, any goiter found during pregnancy in an iodine-replete area should be evaluated in the same manner as a goiter occurring outside of pregnancy.

11. Does thyroid hormone cross the placenta?

Thyroid hormone crosses the placenta poorly but significantly, partly because of the high placental activity of the type 3 monodeiodinase (D3) that converts T_4 to reverse T_3 (rT_3) and T_3 to T_2. However, it is now clear that some T_4 does cross the placenta, because fetuses with complete thyroid agenesis have approximately 30% to 40% of the normal amount of thyroid hormone at birth. The amount of maternal thyroid hormone transported across the placenta appears to be protective to the brain, and neurologic development of the newborn usually progresses normally as long as thyroid supplementation is begun immediately after birth. Evidence also suggests that transthyretin, a circulating thyroid hormone binding protein synthesized and secreted by the placenta, may provide a mechanism for delivery of thyroid hormone to the fetus. To date, six thyroid hormone transporters have been identified in placental tissue. However, T_3 crosses the placenta poorly, and T_3 preparations should not be used in pregnancy.

12. Does iodine cross the placenta?

Iodine easily crosses the placenta for use by the fetal thyroid, which, after 12 to 14 weeks of gestation, takes up iodine even more avidly than does the maternal thyroid.

13. What about thyrotropin-releasing hormone (TRH) and TSH?

TRH, but not TSH, also crosses the placenta and has been used in experimental protocols to attempt to accelerate fetal lung maturity.

14. Summarize the ability of thyroid-related antibodies to cross the placenta.

Immunoglobulin G (IgG) TSH receptor-stimulating antibodies (thyroid-stimulating immunoglobulins [TSI] and TSH receptor antibodies [TRAB]) cross the placenta as early as 18 to 20 weeks of gestation and can occasionally cause fetal or neonatal hyperthyroidism in infants of women with Graves' disease when antibody levels are at least 2.5-fold elevated. It is recommended that both TSI and TRAB be measured because if either antibody is 2.5 to 3 times normal, surveillance for fetal Graves' disease is indicated. Although anti-TPO antibodies and antithyroglobulin (TG) antibodies can also cross, they usually

have no clinical significance in affecting fetal thyroid function. In rare cases, they may be associated with thyrotropin receptor-blocking antibodies that can cause transient neonatal hypothyroidism.

15. List common medications that cross the placenta.

- Propylthiouracil (PTU)
- Methimazole (MMI)
- Beta-blockers

16. Describe fetal thyroid function and brain development.

At approximately 12 to 14 weeks of gestation, the fetal thyroid gland develops, and the hypothalamic-pituitary-thyroid axis begins to function. Before 16 weeks, however, the fetus relies solely on transplacental delivery of T_4. Significant amounts of thyroid hormone cross the placenta in the first trimester and early second trimester before the fetal thyroid begins functioning, and they appear necessary for normal brain development. Thyroid hormones and type 2 deiodinase (D2) have been observed in the fetal cerebral cortex by 5 to 7 weeks. These findings emphasize the importance of maternally derived T_4 conversion to T_3 in the brain in influencing neuronal and astrocyte proliferation and migration early in pregnancy. Rat studies indicate that fetal brain T_3 depends on an adequate supply of T_4 and cannot be replenished by T_3 alone. In early pregnancy, when adequate fetal thyroid hormone is crucial for normal neurologic development, fetal brain T_4 levels reflect maternal levels. Further, T_4 is taken up by receptors on fetal brain astrocytes and is deiodinated to produce T_3, thus underscoring the importance of maternal T_4 in pregnancy.

17. Is fetal thyroid hormone production independent of the mother?

After the first and early second trimesters, the fetal hypothalamic-pituitary-thyroid axis is fairly independent of the mother, with the exception of its dependence on adequate maternal iodine stores. Antithyroid drugs or high levels of TSI or TRAB may, however, affect fetal thyroid function or cause goiter development at this stage. Thyroid hormone and TBG levels increase in the fetus and plateau at about 35 to 37 weeks of gestation. High fetal levels of rT_3 and low T_3 levels are maintained throughout the pregnancy as a result of the high placental D3 activity. The fetal pituitary-thyroid axis is relatively immature, however, considering the increased fetal TSH levels relative to the low level of T_4 production at birth. At the time of labor and in the early neonatal period, there are dramatic increases in T_4 levels and the capacity of the liver to convert T_4 to T_3.

18. What is gestational transient thyrotoxicosis or thyrotoxicosis related to hyperemesis gravidarum?

Gestational transient thyrotoxicosis (GTT) refers to maternal hyperthyroidism caused by elevated levels of hCG, which binds to the TSH receptor and can stimulate thyroid hormone release. Levels greater than 75,000 IU/mL, which may be seen in women with hyperemesis gravidarum, twin gestation, and especially molar pregnancies, can often cause hyperthyroidism. Posttranslational modification of the sialylation of hCG can change its affinity for the TSH receptor and half-life in the circulation, thus resulting in elevated thyroid hormone levels in the first half of pregnancy. A woman who presents with hyperthyroidism, vomiting, and a positive pregnancy test should have a fetal ultrasound examination to exclude a molar pregnancy.

Women with hyperemesis gravidarum (persistent nausea and vomiting accompanied by electrolyte derangements and at least a 5% weight loss) commonly have abnormal thyroid function tests. In one of the largest series yet to be published, half of the 57 women with hyperemesis gravidarum had elevated FT_4 levels.

19. What are the most common causes of hyperthyroidism in pregnancy? During what period of gestation is hyperthyroidism most likely to occur?

Hyperthyroidism complicates pregnancy in about 0.2% of women. Graves' disease, the most common cause of hyperthyroidism in pregnancy, accounts for nearly 85% of the cases. Autoimmune thyroid disease is most likely to manifest in the first trimester or the postpartum period because the immune

suppression of pregnancy has been shown to decrease thyroid antibody levels significantly during the second and third trimesters. Other causes include toxic multinodular goiters, solitary toxic adenomas, iodine-induced hyperthyroidism, and subacute thyroiditis. As noted earlier, hCG-induced hyperthyroidism is common in women with hyperemesis gravidarum or hydatidiform moles and also usually manifests in the first trimester.

20. Summarize the diagnostic approach to the pregnant woman with hyperthyroidism.

Normal pregnancy can produce clinical features that mimic hyperthyroidism, such as heat intolerance, mild tachycardia, increase in cardiac output, a systolic flow murmur, peripheral vasodilatation, and a widened pulse pressure. Weight loss may be obscured by the weight gain of pregnancy. As in the nonpregnant state, hyperthyroidism in pregnancy is usually characterized by low serum TSH levels and increased serum levels of FT_4. However, in interpreting thyroid tests in pregnant women, it is important to realize that serum TSH levels are also frequently low in normal pregnant women, especially during the first trimester of pregnancy (see Question 2).

21. How can the various causes of hyperthyroidism be differentiated with certainty?

Radioisotope scans are contraindicated during pregnancy; therefore, the differential diagnosis of hyperthyroidism in pregnant women must be based on the history, physical examination, and laboratory testing. An obstetric ultrasound study may be indicated to exclude a hydatidiform mole or to look for twin pregnancies.

22. What findings help distinguish Graves' disease from GTT?

Although a diffusely enlarged thyroid gland with a bruit in a woman with ophthalmopathy and prepregnancy symptoms strongly suggests Graves' disease, the diagnosis is often less clear because these findings may be absent. If a woman is actively vomiting, the distinction between early Graves' disease and gestational hyperthyroidism accompanied by hyperemesis gravidarum may be particularly difficult. It is unusual, however, for women to develop hCG-induced hyperthyroidism at hCG levels less than 50,000 IU/mL. Clues pointing to Graves' disease rather than hCG-induced hyperthyroidism include the presence of a goiter, ophthalmopathy, onycholysis, or preexisting hyperthyroid symptoms antedating the pregnancy. In addition, TSI or TRAB levels are often positive and T_3 levels are generally higher in Graves' disease because hyperemesis gravidarum results in a compromised nutritional state and decreased conversion of T_4 to T_3 in peripheral tissues.

23. Why is it important to distinguish GTT from Graves' disease?

It may be difficult to differentiate GTT from other causes of hyperthyroidism because autoimmune hyperthyroidism also commonly manifests during the first trimester of pregnancy, and the biochemical profile of the two conditions is similar. However, it is extremely important to determine whether the thyrotoxicosis results from Graves' disease or GTT because the latter usually resolves without antithyroid treatment by approximately 18 weeks when hCG levels decline. It is rarely necessary to treat with beta-blocker therapy or antithyroid drugs given that the hyperthyroid state is usually self-limited. Hyperthyroidism is probably not the cause of the nausea. Instead, it appears that hCG mediates both the hyperthyroidism and the nausea by different mechanisms.

24. Why is the woman's original country of residence significant?

Women who have goiters from areas of endemic iodine deficiency and who move to the United States may develop iodine-induced hyperthyroidism when they suddenly become iodine replete. Hot nodules can also occur and do not improve in later pregnancy with the immune suppression of pregnancy.

25. What are the risks of Graves' disease to the mother?

Inadequately treated hyperthyroidism in the mother can result in preeclampsia, weight loss, tachycardia, proximal muscle weakness, anxiety, and atrial fibrillation. Left ventricular dysfunction can occur

and is usually reversible, but it may persist for several weeks after biochemical hyperthyroidism has been corrected. This cardiac condition may place the pregnant woman at risk for the development of congestive heart failure, especially in the presence of superimposed preeclampsia, infection, anemia, or at the time of delivery. Thyroid storm can rarely occur in these women.

26. What are the risks to the fetus of maternal Graves' disease?

Inadequately treated maternal hyperthyroidism can result in fetal tachycardia, severe growth restriction, premature births, and a ninefold increased incidence of low birth weight in the infants. Congenital malformations are probably not increased in babies born to mothers with either treated or untreated hyperthyroidism. Inadequately treated maternal hyperthyroidism can cause suppression of the hypothalamic-pituitary-thyroid axis, thus resulting in temporary central hypothyroidism in the neonate and the inability of the neonate to mount an appropriate TSH response.

27. Describe the possible effects on the fetus of high levels of TSH receptor-stimulating antibodies and how they manifest in the fetus,

In about 2% to 5% of cases, fetal or neonatal hyperthyroidism can develop as a result of very high levels of maternal TSH receptor-stimulating antibodies (TSI or TRAB). Because transplacental passage of IgG is limited, this condition rarely occurs unless either the TSI (functional assay measuring cyclic adenosine monophosphate [cAMP]) or TRAB (TSH receptor antibodies by radioimmunoassay) are at least 2.5- to 3-fold elevated in the second and third trimesters. Fetal manifestations include goiter, tachycardia, advanced bone age, and growth restriction, or hydrops. All women with Graves' disease or a history of Graves' disease should be tested for TSI and TRAB. Numerous cases of fetal Graves' disease have been reported in mothers previously treated with ablative doses of iodine-131 (^{131}I) and who are taking thyroid replacement. Therefore, any woman with a history of Graves' disease should have TSI and TRAB antibodies checked by 22 weeks of gestation. If either antibody is elevated at least 2- to 3-fold, an ultrasound examination should be performed at the time of the fetal anatomy scan at approximately 20 weeks to evaluate for evidence of fetal Graves' disease and every 4 to 6 weeks or as clinically indicated for the remainder of pregnancy.

28. How are such effects treated?

Hyperthyroidism in the fetus should be confirmed by percutaneous umbilical sampling if the cause of the goiter is in doubt because high doses of maternal PTU can also cause a goiter and render the fetus hypothyroid. Fetal tachycardia is usually present but is not completely specific or sensitive, and growth restriction is usually a late sign of fetal Graves' disease. Increased central vascularity of the gland may be helpful to suggest that the goiter is secondary to fetal Graves' disease. Treatment consists of administering high doses of PTU to the mother so that a sufficient amount of medication is delivered into the fetal circulation. There is minimal experience using MMI for the treatment of fetal Graves' disease, so PTU is usually recommended. Occasionally, mothers are already hypothyroid as a result of previous ablation or surgery or are rendered hypothyroid with these high PTU doses; in these situations, maternal supplementation with T_4, which crosses the placenta less well than the PTU, may be required.

29. Why is neonatal hyperthyroidism more common than fetal hyperthyroidism?

Neonatal hyperthyroidism is more common than fetal hyperthyroidism because of the high activity of placental D3, the relatively low serum T_3 levels in utero, and the effects of maternal antithyroid drugs on the fetus. TSH receptor-stimulating antibodies, passed transplacentally, remain at high levels after birth and stimulate the neonatal thyroid to produce excess thyroid hormone.

30. How does neonatal hyperthyroidism manifest?

Neonatal hyperthyroidism may manifest as irritability, failure to thrive, hyperkinesis, diarrhea, poor feeding, jaundice, tachycardia, poor weight gain, thrombocytopenia, goiter, and, less commonly, exophthalmos, cardiac failure, hepatosplenomegaly, hyperviscosity syndrome, or craniosynostosis. If the mother had been receiving antithyroid drugs during pregnancy, it may take 5 to 10 days for the neonate to manifest symptoms because of the residual effects of the medication.

31. What is the mortality rate of neonatal hyperthyroidism?

The neonatal mortality rate may be as high as 30% if the condition is unrecognized.

32. How should hyperthyroid infants be treated?

They may require antithyroid medications until the antibody levels wane, which usually occurs by 12 weeks.

33. How can pregnant women with Graves' disease be safely treated in pregnancy?

Treatment of overt hyperthyroidism (elevated T_4 levels) is definitely indicated to decrease morbidity in both mother and fetus. Thionamide therapy and the judicious use of beta-blockers until TT_4 or FT_4 levels are in the high-normal range or slightly above the normal range for pregnancy comprise the preferred treatment. Unless the patient has severe T_3 thyrotoxicosis, the TT_3 is usually not routinely monitored because TT_3 normalization has been reported to cause hypothyroidism in the infant at birth. Cold iodine should be avoided and radioactive iodine is absolutely contraindicated because they readily cross the placenta and are concentrated by the fetal thyroid after 10 to 12 weeks of gestation. However, pregnant women with thyroid storm can be safely treated with cold iodine after PTU administration along with dexamethasone and judicious use of beta-blockers, similar to nonpregnant women.

34. Should subclinical hyperthyroidism be treated in pregnancy?

No. TSH remains suppressed normally in some pregnant women. In a series of more than 400 women with subclinical hyperthyroidism, pregnancy outcomes in untreated women were no different from those of women without suppressed TSH. Furthermore, such treatment risks the unnecessary exposure of the fetus to antithyroid drugs. Therefore, no matter the cause (Graves' disease versus hCG mediated versus warm nodule), a suppressed TSH level alone without elevated thyroid hormones should not be treated in pregnancy.

35. Which is preferable in pregnant women, PTU or MMI?

PTU is clearly the preferred drug to treat hyperthyroidism in the first trimester because of the small but real risk of congenital malformations with MMI. MMI has been infrequently associated with a scalp deformity in the infant (aplasia cutis), choanal or esophageal atresia, or omphalocele, with a total malformation rate of 4.1% versus 1.9% in women taking PTU versus 2.1% in controls. Although PTU was thought initially to cross the placenta less well than MMI, this has been challenged; the risk of fetal hypothyroidism is much more directly related to whether the mother's T_4 levels are kept at the upper limit of the pregnancy range than to whether MMI or PTU was used. The Food and Drug Administration (FDA) reported acute fulminant hepatitis in 22 adults who were taking PTU, with 12 adult deaths. The investigators estimated the risk of PTU-related liver injury to be 1:1000 and a 1:10,000 risk for acute liver failure requiring transplant or death. There were 2 reported cases related to pregnancy, and both cases also had evidence of fetal liver injury. Because of this concern, the Endocrine Society and ATA recommendations are that women be switched from PTU to MMI in the second trimester if it can be done effectively and not compromise the optimal titration of antithyroid drugs. The usual conversion of PTU to MMI is about 15:1 (e.g., 150 mg PTU is approximately equal to 10 mg MMI), but maternal FT_4 or TT_4 levels need to be rechecked and carefully followed because women may respond differently to these antithyroid drugs. If a woman predominantly manifests T_3 thyrotoxicosis, PTU may be superior to MMI because PTU also decreases the conversion of T_4 to T_3.

36. How are PTU and MMI dosed during pregnancy?

Because both PTU and MMI cross the placenta, the lowest possible doses should be given, with a goal of maintaining the mother's serum FT_4 in the high-normal range or the TT_4 approximately 1.5 times the nonpregnancy range. The serum TSH level often remains persistently suppressed in women with FT_4 and TT_4 levels in these ranges and should never be used to titrate the dose of antithyroid drugs during pregnancy. Approximately 1% to 3% of newborns exposed to PTU in utero develop transient neonatal hypothyroidism or a small goiter. This is rare when PTU or MMI doses are

titrated to maintain FT_4 in the upper limits or slightly above the normal range for pregnancy, but it is more common if the FT_4 levels fall into the middle or lower-normal range or if attempts are made to normalize the TSH. If PTU is switched to MMI later in pregnancy, the FT_4 or TT_4 levels should be rechecked in 2 to 4 weeks and then every 4 to 6 weeks throughout pregnancy to titrate the antithyroid drugs optimally. Although it is unknown whether monitoring liver function tests is beneficial in preventing severe hepatotoxicity, it is reasonable for women on PTU to have liver functions checked on a monthly or bimonthly basis and be advised to report any new symptoms immediately.

Fortunately, antithyroid drug doses can usually be markedly decreased by the second and especially the third trimester because of the decreasing TSI levels that accompany the natural immunosuppression of pregnancy. In fact, many women require minimal or no drug at term, especially if they have small goiters, but it is important to ensure that they are not hyperthyroid at delivery to reduce the risk of hyperthyroid complications to the cardiovascular system. Most women have a rebound in their hyperthyroidism postpartum, and, therefore, postpartum thionamide therapy must be increased.

37. Discuss the role of beta-blockers during pregnancy.

Beta-blockers are indicated to treat symptomatic hyperadrenergic signs and symptoms until antithyroid drug therapy has rendered the patient euthyroid. However, beta-blockers should be discontinued when the patient becomes euthyroid because long-term treatment with these drugs has been associated with intrauterine growth restriction. No compelling data indicate that one beta-blocker is safer than another; however, metoprolol and propranolol are usually favored over atenolol.

38. Why is radioactive iodine contraindicated in pregnancy?

Radioactive iodine is contraindicated in pregnancy because, after 12 to 14 weeks of gestation, the fetal thyroid gland has avidity for iodine that is 20 to 50 times that of the maternal thyroid. Accordingly, any dose of radioiodine will be more highly concentrated in fetal thyroid tissue and can easily ablate the fetal gland.

39. Can cold iodine be given during pregnancy?

Cold iodine (e.g., Lugol's solution or saturated solution of potassium iodide [SSKI]) should also be avoided in pregnancy except in women with thyroid storm. If it must be given after 10 to 12 weeks, the fetus should be monitored for the development of a goiter, and the duration should be limited, if possible, to 3 days.

40. Does surgery have a role during pregnancy?

Surgery is rarely indicated during pregnancy but may be necessary in women who are unable to take antithyroid drugs (i.e., because of agranulocytosis) or who are refractory to high doses of antithyroid medications. If necessary, it is best to perform surgery in the second trimester before fetal viability. The rationale for this timing is the significant increase in the risk of miscarriage in the first trimester and of preterm labor when surgery is performed after 24 weeks.

41. Should a woman be counseled to terminate a pregnancy if she inadvertently receives a ^{123}I scan or an ablative dose of ^{131}I?

A woman who receives ^{123}I for a thyroid scan early in pregnancy can be reassured for the most part because the fetus has not developed the ability to concentrate iodine before 10 weeks and the radiation exposure from this test is low, with a half-life of only approximately 8 hours. An ablative dose of ^{131}I given early in pregnancy, however, is cause for greater concern because the half-life of ^{131}I is 8 days, and the radiation is more destructive to the thyroid gland. Generally, if the dose is given very early, when the fetal thyroid gland is not yet trapping iodine, the relatively low thyroid and total body irradiation dose is probably not sufficient to justify termination of the pregnancy.

42. How may the risk to the fetus be minimized?

It may be useful in this situation to give PTU to block the recycling of ^{131}I in the fetal thyroid gland if PTU can be given within 1 week of ^{131}I treatment. If the fetus does develop hypothyroidism, it can be

diagnosed in utero by percutaneous umbilical sampling, and T_4 treatment may be given through amniotic fluid injections, although such treatment is still experimental. Certainly, all women of childbearing age, regardless of contraceptive measures, should have a pregnancy test before receiving any dose of ^{123}I or ^{131}I, and efficacious contraception should be ensured.

43. How should women with Graves' disease be counseled about treatment alternatives before becoming pregnant?

Many experts recommend definitive treatment with ^{131}I (after a negative pregnancy test) in a woman of childbearing age who wishes to become pregnant. In a series of nearly 300 women given radioiodine for thyroid cancer therapy, no significant differences in stillbirths, preterm births, low-birth-weight infants, or congenital malformations were reported in subsequent pregnancies. Effective birth control must be established, and then women should optimally wait for at least 6 months after regaining a stable euthyroid status before trying to conceive. Women with Graves' disease who undergo ablation therapy with ^{131}I may continue to have high (more than three times normal) TSI or TRAB antibodies for 1 year, and these increase the risk of fetal Graves' disease. For women with very high TRAB antibodies who wish to become pregnant, surgery is a reasonable option. In women who are stable on low doses of thionamides, these drugs should not be problematic during pregnancy, but it is highly likely that thionamide doses will have be adjusted during pregnancy and the postpartum period. Women requiring high antithyroid drug doses or who have large goiters should be counseled about the benefits of definitive therapy before becoming pregnant.

44. Describe the natural history of Graves' disease in the postpartum period.

Approximately 70% of women have a postpartum relapse of Graves' disease, usually within the first 3 months after delivery, as the natural immunosuppression of pregnancy disappears. Antithyroid therapy must almost always be increased during this time.

45. What treatment options can be recommended for women who wish to breast-feed?

Because PTU is more highly protein bound and may cross less efficiently into breast milk than MMI, it was previously recommended that nursing mothers be treated with PTU rather than MMI. However, MMI doses up to 20 mg have been safely used in nursing mothers without any evidence of neonatal hypothyroidism. Therefore, because of the concerns about PTU-induced hepatotoxicity, women are usually counseled that they can safely nurse as long as these MMI doses are not exceeded. Nursing women requiring antithyroid drugs should tell their pediatrician, and thyroid function tests in the neonates may be indicated, especially if the woman is taking more than 300 mg of PTU or more than 20 mg of MMI per day.

46. Can a nursing mother undergo a diagnostic ^{123}I scan if the cause of the hyperthyroidism is in question?

A diagnostic ^{123}I scan can be performed if the woman is willing to interrupt breast-feeding for 2 to 3 days. Both ^{123}I and technetium-99 (^{99}Tc) pertechnetate are excreted into breast milk with an effective half-life of 5 to 8 and 2 to 8 hours, respectively.

47. Can ablative therapy with ^{131}I be offered to nursing women?

Ablative therapy with ^{131}I cannot be offered unless the women is willing to give up nursing altogether, because even a 5-mCi dose requires discontinuation of breast-feeding for at least 56 days. Further, it is recommended that ^{131}I should not be given to women until at least 4 weeks after breast-feeding has ceased, to avoid high levels in breast tissue.

48. Can beta-blockers be used in nursing women?

Beta-blockers can be used if necessary in breast-feeding mothers. However, atenolol may produce higher breast milk concentrations than other beta-blockers, and there are rare reports of neonatal bradycardia in infants of mothers who nursed while taking this drug. The lowest doses of propranolol or metoprolol are preferred.

49. When should a nursing woman take antithyroid drugs?

It is always best if a mother takes antithyroid drugs immediately after nursing, to avoid exposing the infant to peak concentrations of the drug.

50. Does hypothyroidism pose a risk to the pregnant patient, and should all pregnant women be screened?

Hypothyroidism occurs in approximately 2% to 4% of pregnancies, and overt hypothyroidism occurs in approximately 0.5%. Because of maternal and fetal concerns, a case can be made to screen all pregnant women in the first trimester. It has been shown that targeted screening of only high-risk women fails to detect approximately 25% to 35% of women with elevated TSH values. However, there is a lack of consensus about whether all pregnant women should be screened or whether only women with risk factors should be tested (aggressive case finding). It has not been definitively demonstrated that screening all pregnant women and appropriately treating those with abnormal thyroid function decreases adverse pregnancy outcomes. A randomized controlled trial did not clearly show a benefit of screening and treating all women with a TSH level higher than 2.5 mU/L and elevated TPO antibodies. However, in a secondary analysis, the low-risk women in the screening group had a decrease in adverse outcomes compared with low-risk women in the case finding group, but only if all possible adverse outcomes were included as a composite outcome. Certainly, any pregnant woman with the following should be screened: risk factors for hypothyroidism, including a positive family history, use of amiodarone or lithium, a history of any type of thyroid disease, possible iodine deficiency, presence of a goiter, known thyroid antibodies, symptoms suggestive of thyroid disease; autoimmune disorders including type 1 diabetes mellitus; a history of head or neck irradiation; or a history of preterm delivery. Women more than 30 years old or with a body mass index (BMI) of at least 40 kg/m^2 also have a higher risk than the normal population. Untreated hypothyroidism, especially when overt, can cause maternal anemia, myopathy, and congestive heart failure. It has also been associated with an increased risk of preterm delivery, pregnancy loss, gestational hypertension, placental abruption, low-birth-weight infants, postpartum hemorrhage, and the possibility of neurodevelopmental delay in the infant. The ATA stated that there are insufficient data for or against screening, and the American College of Obstetrics and Gynecology (ACOG) stated that there are insufficient data to recommend screening. The Endocrine Society stated that their committee was divided in its recommendation; approximately half the members recommended screening, and half stated that there was insufficient evidence for or against screening.

51. Should pregnant women with recurrent pregnancy loss be screened for TPO antibodies, and, if they are found, should thyroid hormone be offered despite a normal TSH?

There are both positive and negative studies suggesting that TPO antibodies may be related to pregnancy loss despite a euthyroid state, but, on balance, there appears to be a positive association. It is not clear whether these women have decreased thyroid reserve as a possible cause because women with positive TPO antibodies are more likely to develop subclinical hypothyroidism later in gestation. It is also unknown whether these antibodies could directly cause miscarriage or are simply markers of other autoimmune diseases that could be associated with pregnancy loss. Evidence indicates that these antibodies may affect trophoblast function. A single randomized controlled trial suggested that treating unselected euthyroid women who were TPO antibody positive with low doses of thyroid hormone could decrease first trimester loss but not loss later in pregnancy. However, many of the losses occurred so early that initiating treatment before the loss would not have been possible, and it is difficult to understand on a mechanistic basis how only several days of treatment could prevent pregnancy loss. This study also demonstrated that delivery at less than 37 weeks of gestation was decreased in the treated group, but gestational ages of the groups were not reported. Therefore, until further studies support or refute this study, it is not recommended that women be checked for TPO antibodies unless thyroid disease is suspected. Women who are TPO antibody positive clearly have approximately a 15% risk of developing subclinical hypothyroidism later in pregnancy and a 50% chance of postpartum thyroiditis; they should be monitored closely for these developments.

52. How do thyroid hormone requirements change during pregnancy?

Thyroid hormone requirements in treated hypothyroid patients often increase during pregnancy, with up to 75% of pregnant women requiring an increase in thyroxine dosage of 25% to 50%. One study confirmed that 85% of pregnant women required an increase in levothyroxine of 47% by 16 weeks of gestation, although most of these women were athyreotic. Because requirements increased as early as 5 weeks of gestation, women who are athyreotic may need to increase their thyroid hormone dosage by 20% to 25% as soon as pregnancy is confirmed.

KEY POINTS 1: THYROID DISEASE IN PREGNANCY

1. Approximately 15% of normal pregnant women and the majority of women with twin pregnancies have a suppressed thyroid-stimulating hormone (TSH) level, especially in the first trimester.
2. All women at risk for thyroid disease should be screened in the first trimester.
3. TSH, total thyroxine (TT_4) and total triiodothyronine (TT_3) normal ranges change in pregnancy, and free T_4 assays by analog methods may be inaccurate.
4. Gestational thyrotoxicosis associated with hyperemesis gravidarum can cause overt hyperthyroidism.
5. Graves' disease most often manifests in the first trimester with improvement in later pregnancy, but it commonly exacerbates after delivery.
6. Subclinical hyperthyroidism should not be treated in pregnancy.
7. Thyroid hormone requirements usually increase in pregnancy, beginning in the first trimester, and it is reasonable to increase thyroid hormone doses by 25% in athyreotic women as soon as pregnancy is confirmed.
8. Postpartum thyroiditis occurs in approximately 5% of physiologically normal women and approximately 25% of women with type 1 diabetes.

53. What causes the rapid increase in thyroid hormone requirements in early pregnancy?

The rapid increase in thyroid hormone requirements that occurs in the first trimester may result from the sudden increase in the estrogen-stimulated TBG pool associated with pregnancy. This change can be especially striking in women undergoing assisted reproduction, during which hormonal therapy may stimulate very high estrogen levels.

54. When should the TSH be checked in pregnancy, what doses of thyroid hormone should be prescribed, and at what level of TSH should therapy be directed?

The serum TSH level should be checked as soon as pregnancy is confirmed, and an appropriate increase in levothyroxine dose should be made. One study suggested that athyreotic women requiring full replacement doses should receive a 25% dose increase as soon as pregnancy is confirmed despite a normal TSH. Another trial supported that this can be done by adding 2 tablets of levothyroxine per week to the patient's regimen. As discussed earlier, the TSH may be mildly suppressed in normal women during the first trimester as a result of the thyrotropic influence of hCG. Therefore, unless a woman is symptomatically hyperthyroid or has frankly elevated serum FT_4 levels, the levothyroxine dosage should not be reduced in response to the finding of a low first-trimester TSH level.

Both the Endocrine Society and the ATA support that pregnant women with subclinical hypothyroidism (TSH $>$ 2.5 or 3.0 mU/L but $<$ 10 mU/L; FT_4 within the normal range) should be treated if they have positive TPO antibodies. The Endocrine Society also supports treatment in such women without TPO antibodies if the TSH is repeated and found to be greater than 2.5 mU/L in the first trimester or

greater than 3.0 mU/L in the second or third trimesters. These women can usually be adequately treated with 50 μg of levothyroxine. The ACOG does not clearly recommend that subclinical hypothyroidism be routinely treated in pregnancy.

Pregnant women with overt hypothyroidism (elevated TSH; FT_4 below the normal range) should be given full levothyroxine replacement doses immediately; this can be estimated at 2 μg/kg in pregnancy. The TSH should be checked 4 weeks after a dose change and every 4 weeks throughout midgestation to maintain TSH levels up to 2.5 mU/L while the fetus is dependent on maternal thyroid hormone. TSH can then be followed every 4 to 8 weeks for the remainder of pregnancy to maintain serum TSH levels up to 3.0 mU/L in the second and third trimesters. In women who have had a thyroidectomy for thyroid cancer, the goal of maintaining a suppressed but detectable serum TSH without rendering them thyrotoxic should be adhered to during pregnancy. The thyroid hormone dose should be reduced almost immediately after delivery to avoid hyperthyroidism postpartum, and the TSH should be checked at 6 weeks postpartum. Pre-pregnancy doses may be instituted as soon as the woman has lost the majority of her pregnancy weight gain.

55. When should a pregnant woman take her thyroid hormone?

It is extremely important to advise the pregnant woman to take her thyroid hormone and her prenatal vitamins or iron supplements at different times, because ferrous sulfate can bind to thyroxine and decrease its bioavailability. High doses of calcium and soy can also interfere with thyroid hormone absorption.

56. What is the risk of abnormal fetal and neonatal intellectual development in infants born to mothers who are hypothyroid during the first trimester of pregnancy?

All newborns in the United States are screened for hypothyroidism because it is well established that infants who have severe congenital hypothyroidism but who then receive thyroid hormone therapy at birth appear to have fairly normal intellectual growth and development. Overt hypothyroidism is defined as decreased serum FT_4 or TT_4 levels (in the context of pregnancy norms) in association with an increased serum TSH. In pregnancy, a TSH level higher than 10 mU/L is also usually treated as overt hypothyroidism regardless of FT_4 or TT_4 levels. Although overt hypothyroidism is known to have serious effects on the fetus, the fetal effects of maternal subclinical hypothyroidism (TSH $>$ 2.5 mU/L in the first trimester or $>$ 3.0 mU/L in the second and third trimesters, but FT_4 within the normal range) is a subject of ongoing debate. Several publications suggested that psychomotor and intellectual development may be impaired in infants born to mothers who were subclinically hypothyroid during the first trimester of pregnancy, although the differences from control subjects in these studies were small and often became insignificant when the infants were tested later in childhood. Some retrospective studies suggested that infants born to mothers with subclinical hypothyroidism have slightly decreased neurodevelopmental testing results. However, in the ongoing CATS (Controlled Antenatal Thyroid Screening) study, the overall outcomes on IQ testing at 3 years of age between universally screened and unscreened pregnancies were not significantly different when treatment was initiated at 12 weeks in the screened group. A multicenter placebo-controlled randomized controlled trial to evaluate the effects of levothyroxine treatment on subclinical hypothyroidism is being conducted by the Maternal Fetal Medicine Unit of the National Institutes of Health (NIH). The primary outcome will be child IQ at 5 years of age, and it is anticipated that the results of this study will be available in 2015.

57. What strategies can reduce the risk to the fetus?

It seems prudent to attempt to identify and appropriately treat hypothyroidism in women of childbearing age who wish to become pregnant (preconception), as well as in pregnant women in the first trimester. However, serum TSH levels in normal women often decline in the first trimester as a result of the influence of hCG. Thus, a TSH level greater than 2.5 mU/L in the first trimester may be inappropriately high, especially when accompanied by TPO antibodies, whereas a TSH level of 0.1 mU/L may be appropriately low because of the thyroid-stimulating activity of high hCG levels.

58. How should a thyroid nodule be evaluated during pregnancy?

The evaluation of a solitary or dominant thyroid nodule in a pregnant woman is similar to that in nonpregnant women. Ultrasound is indicated to evaluate for multiple nodules and for ultrasonographic features suggestive of malignancy (microcalcifications, hypoechoic patterns, irregular margins, nodules that are taller than they are wide, or intranodular vascularity). If the woman has a high or normal serum TSH, fine-needle aspiration (FNA) should be offered for predominantly solid thyroid nodules larger than 1 cm. FNA should also be recommended in women with nodules 5 mm to 1 cm if these women have a high-risk family history (multiple endocrine neoplasia type 2 [MEN 2], familial papillary thyroid carcinoma, familial polyposis, familial medullary carcinoma), a high-risk personal history (rapid onset or growth of nodule, history of head and neck irradiation during childhood, hoarseness, persistent cough), or ultrasound features suggestive of malignancy. Women with complex nodules 1.5 to 2 cm or larger should also receive an ultrasound-guided FNA. Women who have nodules discovered in the last month of pregnancy could reasonably have FNA delayed until after delivery, but it is usually helpful to make the diagnosis of thyroid cancer during pregnancy so that appropriate planning of surgical treatment can be made. Women found to have a thyroid nodule and a suppressed TSH may have a warm or hot nodule. Warm or hot nodules are rarely malignant but are often nondiagnostic on FNA. For that reason, a pregnant woman with a suppressed TSH and a nodule should undergo a radioisotope scan postpartum to determine whether the nodule is warm or cold before obtaining an FNA. FNA specimens should be evaluated with the same criteria as used for nonpregnant patients.

59. What is the likelihood that thyroid nodules discovered during pregnancy are malignant?

Data suggest that thyroid nodules discovered during pregnancy may have a higher risk of being malignant. However, this finding is likely partly the result of selection or sampling bias, because many young women do not have systematic health examinations until they become pregnant. Depending on the patient population, the incidence of biopsied benign nodules is greater than 80%, whereas differentiated thyroid cancer has been found in 5% to 40% of biopsies. Most malignant nodules are papillary thyroid carcinoma. FNA cytology is highly accurate in diagnosing papillary carcinoma, whereas cytology showing follicular or Hürthle cell neoplasms predicts only a 5% to 15% risk of malignancy. When the serum TSH is normal, fewer than 20% of FNA specimens are nondiagnostic.

60. How should a thyroid nodule be managed during pregnancy?

If the cytology suggests or confirms papillary thyroid cancer, the best time to offer a thyroidectomy is in the second trimester, to avoid the risk of miscarriage in the first trimester and preterm labor in the third trimester. The risk of preterm labor or adverse fetal outcomes related to surgery performed in the second trimester is exceedingly rare. If the nodule is less than 2 cm and has not rapidly increased in size, and the patient has no lymphadenopathy, it may be reasonable to postpone thyroidectomy until after pregnancy and administer thyroid suppression therapy in the meantime, with careful attention to avoiding elevated T_4 levels. It is appropriate to administer thyroid hormone to achieve a suppressed but detectable TSH level in pregnant women with a recent history of thyroid cancer, thyroid cancer diagnosed in pregnancy, or a highly suspicious thyroid nodule as long as the FT_4 or TT_4 levels are not increased above the normal range for pregnancy. Disease-specific survival has not been shown to be affected by whether thyroidectomy for a malignant nodule is performed during pregnancy or immediately postpartum as long as the nodule shows well-differentiated thyroid cancer. However, some evidence suggests that recurrence, based on serum TG levels or rising thyroid antibody titers, may be slightly higher in women who wait to have surgery postpartum compared with women who elect to have surgery performed in the second trimester.

61. How common is postpartum thyroiditis? Who is at risk?

Postpartum thyroid dysfunction occurs in approximately 5% to 10% of women, with a much higher incidence in certain populations. In one series, 25% of women with type 1 diabetes mellitus developed postpartum thyroid dysfunction; it is therefore recommended that this population be routinely screened in the postpartum period. In another series of 152 women with TPO antibodies detected at 16 weeks of gestation, postpartum thyroiditis occurred in 50%; of these, 19% had hyperthyroidism

alone, 49% had hypothyroidism alone, and the other 32% had hyperthyroidism followed by hypothyroidism. Women with a family history of thyroid disease are also at increased risk and may be candidates for screening with TPO antibodies during pregnancy or with thyroid function tests in the postpartum period. Women known to be TPO antibody positive should have a TSH test performed at 6 to 12 weeks and at 6 months postpartum or as clinically indicated.

62. Characterize the histopathology of postpartum thyroiditis.

The disorder is highly associated with circulating TPO antibodies, and the histology is identical to that of Hashimoto's thyroiditis with diffuse mononuclear cell infiltration and destruction of thyroid follicles.

63. Summarize the clinical course of postpartum thyroiditis.

Classically, the clinical course consists of three phases, but not all women manifest each phase.

64. Describe phase 1 of postpartum thyroiditis.

At 1 to 3 months after delivery, affected women develop hyperthyroidism secondary to immunologically mediated destruction of thyroid follicles, resulting in the release of stored thyroid hormone into the circulation. Such women may experience anxiety, irritability, palpitations, fatigue, and insomnia, but commonly this phase does not come to clinical attention. Symptomatic patients are best treated with low-dose beta-blockers, which must soon be tapered and discontinued as the thyrotoxic phase spontaneously resolves. Use of PTU or MMI is not indicated because the hyperthyroidism in these patients is caused by destruction of their gland and not by increased thyroid hormone synthesis.

65. How can phase 1 of postpartum thyroiditis be distinguished from Graves' disease?

Occasionally, there is a question about the cause of the hyperthyroidism, because Graves' disease commonly appears or exacerbates in the first several months postpartum. Distinguishing between the two conditions is facilitated by measurement of a serum thyroglobulin level and TPO antibodies (both are high in postpartum thyroiditis) and TSH receptor-stimulating antibodies (often elevated with Graves' disease). However, the most definitive test is a ^{123}I-uptake test (low in postpartum thyroiditis and high in Graves' disease), if the mother is willing to interrupt nursing for 2 to 3 days.

66. Describe phase 2 of postpartum thyroiditis.

More commonly, women present with stage 2 of postpartum thyroiditis, which is characterized by hypothyroidism alone or following transient hyperthyroidism (phase 1), at about 4 to 8 months after delivery. Nonspecific symptoms include fatigue, depression, impaired concentration, poor memory, aches and pains, dry skin, and weight gain, all of which may be overlooked by the clinician. Symptoms may predate the onset of thyroid function abnormalities in women with positive TPO antibodies and may persist for some time after a euthyroid state is achieved.

67. How is phase 2 of postpartum thyroiditis treated?

Women with abnormal thyroid function tests and symptoms consistent with hypothyroidism should be treated with levothyroxine replacement for approximately 6 to 12 months or at least until 1 year after delivery. At that time, discontinuation of levothyroxine therapy can be attempted to identify the 70% to 80% of women who will return to the euthyroid state by 12 months after delivery.

68. Describe the natural history of postpartum thyroiditis.

Most women return to a euthyroid state at 12 to 18 months postpartum. However, thyroid function tests should then be followed at least annually in women who become euthyroid. In a series of 43 patients with postpartum thyroiditis, 23% of the women were hypothyroid at 2 to 4 years, and, in a longer series, approximately 50% of women were hypothyroid 7 to 9 years later. Women with the highest TPO antibody titers and the most severe hypothyroidism appear to be at the highest risk of developing permanent hypothyroidism. If a woman becomes euthyroid within a year postpartum, she has a high likelihood (70%) of developing postpartum thyroiditis after a subsequent pregnancy.

BIBLIOGRAPHY

ACOG Committee Opinion: Subclinical hypothyroidism in pregnancy, *Obstet Gynecol* 110:959–960, 2007.

Alexander EK, Marqusee E, Lawrence E, et al: Timing and magnitude of increases in levothyroxine requirements during pregnancy in women with hypothyroidism, *N Engl J Med* 351:241–249, 2004.

American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, Cooper DS, GM, et al: Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer, *Thyroid* 19:1167–1214, 2009.

American Thyroid Association Taskforce on Thyroid Disease During Pregnancy and Postpartum, Stagnaro-Green A, Abalovich A, et al: Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and Postpartum, *Thyroid* 21:1081–1125, 2011.

Anckaert E, Poppe K, Van Uytfanghe K: FT_4 immunoassays may display a pattern during pregnancy similar to the equilibrium dialysis ID-LC/tandem MS candidate reference measurement procedure in spite of susceptibility towards binding protein alterations, *Clin Chim Acta* 411:1348–1353, 2010.

Azizi F, Khoshniat M, Bahrainian M, Hedayati M: Thyroid function and intellectual development of infants nursed by mothers taking methimazole, *J Clin Endocrinol Metab* 85:3233–3238, 2000.

Casey BM, Dashe JS, Wells CE, et al: Subclinical hyperthyroidism and pregnancy outcomes, *Obstet Gynecol* 107:337–341, 2006.

Cleary-Goldman J, Malone FD, Lambert-Messerlian G, et al. Maternal thyroid hypofunction and pregnancy outcome, *Obstet Gynecol* 112:85–92, 2008.

Cooper DS, Rivkees SA: Putting propylthiouracil in perspective, *J Clin Endocrinol Metab* 94:1881–1882, 2009.

De Groot L, Abalovich M, Alexander E, et al: Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline, *J Clin Endocrinol Metab* 97:2543–2565, 2012.

Garsi JP, Schlumberger M, Rubino C, et al: Therapeutic administration of ^{131}I for differentiated thyroid cancer: radiation dose to ovaries and outcome of pregnancies, *J Nucl Med* 49:845–852, 2008.

Glinoer D, Rihai M, Grun JP: Risk of subclinical hypothyroidism in pregnant women with asymptomatic autoimmune thyroid disorders, *J Clin Endocrinol Metab* 79:197–204, 1994.

Goodwin TM, Hershman JM: Hyperthyroidism due to inappropriate production of human chorionic gonadotropin, *Clin Obstet Gynecol* 40:32–44, 1997.

Haddow JE, Cleary-Goldman J, McClain MR, (FaSTER) Research Consortium: Thyroperoxidase and thyroglobulin antibodies in early pregnancy and preterm delivery, *Obstet Gynecol* 116:58–62, 2010.

Huel C, Guibourdenche J, Vuillard E, et al: Use of ultrasound to distinguish between fetal hyperthyroidism and hypothyroidism on discovery of a goiter, *Ultrasound Obstet Gynecol* 33:412–420, 2009.

Kahric-Janic N, Soldin SJ, Soldin OP, et al: Tandem mass spectrometry improves the accuracy of free thyroxine measurements during pregnancy, *Thyroid* 17:303–311, 2007.

Kempers MJE, Van Tijn DA, Van Trotensburg ASP, et al: Central congenital hypothyroidism due to gestational hyperthyroidism: detection where prevention failed, *Clin Endocrinol Metab* 88:5851–5857, 2003.

Lazarus JH, Bestwick JP, Channon S, et al: Antenatal thyroid screening and childhood cognitive function, *N Engl J Med* 366:493–501, 2012.

Lockwood CM, Grenache DG, Gronowski AM: Serum human chorionic gonadotropin concentrations greater than 400,000 IU/L are invariably associated with suppressed serum thyrotropin concentrations, *Thyroid* 19:863–868, 2009.

Luton D, Le Gac I, Vuillard E, et al: Management of Grave's disease during pregnancy: the key role of fetal thyroid gland monitoring, *J Clin Endocrinol Metab* 90:6093–6098, 2005.

Momotani N, Yamashita R, Makino F, et al: Thyroid function in wholly breast-feeding infants whose mothers take high doses of propylthiouracil, *Clin Endocrinol* 53:177–181, 2000.

Moosa M, Mazzaferri EL: Outcome of differentiated thyroid cancer diagnosed in pregnant women, *J Clin Endocrinol Metab* 82:2862–2866, 1997.

Nachum Z, Rakover Y, Weiner E, et al: Grave's disease in pregnancy: prospective evaluation of a selective invasive treatment protocol, *Am J Obstet Gynecol* 189:159–165, 2003.

Negro R, Formoso G, Mangieri T, et al: Levothyroxine treatment in euthyroid pregnant women with autoimmune thyroid disease: effects on obstetrical complications, *J Clin Endocrinol Metab* 91:2587–2591, 2006.

Negro R, Schwartz A, Gismondi R, et al: Increased pregnancy loss rate in thyroid antibody negative women with TSH levels between 2.5 and 5.0 in the first trimester of pregnancy, *J Clin Endocrinol Metab* 95:E44–E448, 2010.

Negro R, Schwartz A, Gismondi R, et al: Universal screening versus case finding for detection and treatment of thyroid hormonal dysfunction during pregnancy, *J Clin Endocrinol Metab* 95:1699–1707, 2010.

Panesar NS, Li CY, Rogers MS: Reference intervals for thyroid hormones in pregnant Chinese women, *Ann Clin Biochem* 38:329–332, 2001.

Patel J, Landers K, Huika L, et al: Delivery of maternal thyroid hormones to the fetus, *Trends Endocrinol Metab* 22: 164–170, 2011.

Pelag D, Cada S, Peleg A, et al: The relationship between maternal serum thyroid-stimulating immunoglobulin and fetal and neonatal thyrotoxicosis, *Obstet Gynecol* 99:1040–1043, 2002.

Pop V, Brouwers EP, Vader HL, et al: Maternal hypothyroxinaemia during early pregnancy and subsequent child development: a 3-year follow-up study, *Clin Endocrinol (Oxf)* 59:282–288, 2003.

Rushworth FH, Backos M, Rai R, et al: Prospective pregnancy outcome in untreated recurrent miscarriers with thyroid autoantibodies, *Hum Reprod* 15:1637–1639, 2000.

Sam S, Molitch ME: Timing and special concerns regarding endocrine surgery during pregnancy, *Endocrinol Metab Clin North Am* 32:337–354, 2003.

Sapin R, D'Herbomez M, Schlienger JL: Free thyroxine measured with equilibrium dialysis and nine immunoassays decreased in late pregnancy, *Clin Lab* 50:581–584, 2004.

Soldin OP, Tractenberg RE, Hollowell JG, et al: Trimester-specific changes in maternal thyroid hormone, thyrotropin, and thyroglobulin concentrations: trends and associations across trimester in iodine sufficiency, *Thyroid* 14:1084–1090, 2004.

Vaidya B, Anthony S, Bilous M: Detection of thyroid dysfunction in early pregnancy: universal screening or target high-risk case finding? *J Clin Endocrinol Metab* 92:203–207, 2007.

Vannucchi G, Perrino N, Rossi S, et al: Clinical and molecular features of differentiated thyroid cancer diagnosed during pregnancy, *Eur J Endocrinol* 162:145–151, 2010.

Vulsma T, Gons MH, de Vijlder JJ: Maternal-fetal transfer of thyroxine in congenital hypothyroidism due to a total organification defect or thyroid agenesis, *N Engl J Med* 321:13–16, 1989.

Walker JA, Illions EH, Huddleston JF, et al: Racial comparisons of thyroid function and autoimmunity during pregnancy and the postpartum period, *Obstet Gynecol* 106:1365–1371, 2005.

Yassa L, Marqusee E, Fawcett R, et al: Thyroid Hormone Early Adjustment in Pregnancy (the THERAPY) trial, *J Clin Endocrinol Metab* 95:3234–3241, 2010.

Yoshihara A, Noh J, Yamaguchi T, et al: Exposure to methimazole during the first trimester of pregnancy increases the risk of congenital anomalies, *J Clin Endocrinol Metab* (Epub ahead of print), 2012.

CHAPTER 41

PSYCHIATRIC DISORDERS AND THYROID DISEASE

Alexandra L. Migdal and James V. Hennessey

1. How well established is the relationship between thyroid disease and psychiatric symptoms?

Since the publication of the Clinical Society of London's "Report on Myxoedema" in 1888, it has been recognized that thyroid disease may give rise to psychiatric disorders that can be corrected by reestablishment of normal thyroid hormone levels. Later, Asher reemphasized that patients with profound hypothyroidism may present with depressive psychosis. As outlined in Table 41-1, the symptoms of hypothyroidism often mimic those of depression, whereas those of hyperthyroidism include anxiety, dysphoria, emotional lability, and intellectual dysfunction, as well as mania or depression, the latter especially characteristic among elderly patients presenting with apathetic thyrotoxicosis.

2. What abnormalities of thyroid function are found in psychiatric disorders?

Because patients with thyroid disease may manifest frank psychiatric disorders that are reversible with endocrine therapy, the thyroid axis has been extensively studied in patients presenting with a wide variety of behavioral disturbances. Various abnormalities of thyroid function have been identified, particularly in depression. In most depressed subjects, the basal serum thyroid-stimulating hormone (TSH), thyroxine (T_4), and triiodothyronine (T_3) levels are within the normal range, although in one report, a third of such patients were observed to have suppressed TSH levels.

TABLE 41-1. CLINICAL FEATURES COMMON TO BOTH THYROID DISEASES AND MOOD DISORDERS

	HYPOTHYROIDISM	MOOD DISORDERS	HYPERTHYROIDISM
Depression	Yes	Yes	Yes
Diminished interest	Yes	Yes	Yes
Diminished pleasure	Yes	Yes	No
Decreased libido	Yes	Yes	Sometimes
Weight loss	No	Yes	Yes
Weight gain	Yes	Sometimes	Occasionally
Appetite loss	Yes	Yes	Sometimes
Increased appetite	No	Yes	Yes
Insomnia	No	Yes	Yes
Hypersomnia	Yes	Yes	No
Agitation or anxiety	Occasionally	Yes	Yes
Fatigue	Yes	Yes	Yes
Poor memory	Yes	Yes	Occasionally
Cognitive dysfunction	Yes	Yes	Yes
Impaired concentration	Yes	Yes	Yes
Constipation	Yes	Sometimes	No

Adapted from Hennessey JV, Jackson IMD: The interface between thyroid hormones and psychiatry. *Endocrinologist* 6:214–223, 1996.

3. What abnormalities of the thyrotropin-releasing hormone (TRH) stimulation test may be observed in depressed patients?

A "blunted" TSH response to TRH administration (defined as a TSH rise $<$ 5 mU/L) is seen in approximately 25% of depressed subjects. The blunted TSH response is said to be observed more often in unipolar than bipolar depression, but differentiating these disorders with TRH testing has been disappointing. The blunted TSH response is a "state" marker that normalizes on recovery from depression.

4. Describe a mechanism for the blunted TSH response to TRH in affective disorders.

The mechanism for the blunted TSH response in affective disorders is not known; however, glucocorticoids, known to inhibit the hypothalamic-pituitary-thyroid axis, are elevated in depression and could be responsible. This suppressed TSH response is not specific to depression and may be observed in alcohol withdrawal, starvation, normal male aging, renal failure, acromegaly, Cushing's syndrome, and hypopituitarism. The blunting may also result from medications such as T_4, glucocorticoids, growth hormone, somatostatin, dopamine, and phenytoin, all of which have been reported to diminish this response.

5. Can abnormalities in the TSH circadian rhythm be identified in depression?

In normal subjects, TSH begins to rise in the evening before the onset of sleep and reaches a peak between 11:00 PM and 4 AM. In depression, the nocturnal TSH surge is frequently absent, resulting in reduced thyroid hormone secretion. This finding supports the view that functional central hypothyroidism may occur in some depressed subjects. Sleep deprivation, which has an antidepressant effect, returns the TSH circadian rhythm to normal. The mechanism for the impaired nocturnal TSH rise is unknown.

6. Is autoimmune thyroid disease frequently present in the depressed patient?

Although the blunted TSH response is well recognized in depression, it is less clearly appreciated that an enhanced TSH response may occur in up to 15% of depressed subjects with normal baseline thyroid function tests. Most such patients have antithyroid antibodies, a finding suggesting that the TSH hyperresponse may indicate latent hypothyroidism caused by autoimmune thyroiditis. When autoimmunity is tested using the antithyroid peroxidase antibody (anti-TPO) rather than the less specific antimicrosomal antibody, the prevalence of autoimmune thyroid disease is even higher. Not all studies, however, have found an increased prevalence of antithyroid antibodies in depressed subjects when compared with matched control groups.

7. What is the frequency of elevated T_4 values in psychiatric patients?

Approximately 20% of patients admitted to a hospital with acute psychiatric presentations, including schizophrenia and major affective disorders, but rarely dementia or alcoholism, may demonstrate mild elevations in their serum T_4 levels and, less often, T_3 levels. The basal TSH is usually normal but may demonstrate blunted TRH responsiveness in up to 90% of such patients. These findings do not appear to represent thyrotoxicosis, and the abnormalities spontaneously resolve within 2 weeks without specific therapy. Such phenomena may be secondary to central activation of the hypothalamic-pituitary-thyroid axis resulting in enhanced TSH secretion with consequent elevation in circulating T_4 levels.

8. What is the most consistent abnormality of the thyroid axis in hospitalized depressed patients?

In depressed patients, the most consistent abnormality of the thyroid axis may be an increase in serum total or free T_4 levels, although usually within the conventional reference range. This elevation generally regresses following successful treatment of the depression.

9. What is the prevalence of hypothyroid dysfunction in psychiatric populations?

Thyroid function test abnormalities are common in older individuals. In otherwise normal female patients who are more than 60 years old, the prevalence of elevated TSH values and/or positive antithyroid antibodies is 10% or more. Subjecting apparently asymptomatic individuals with slight elevations of

serum TSH but normal T_4 and T_3 levels to a battery of psychological tests has revealed significant differences from control subjects on scales measuring memory, anxiety, somatic complaints, and depression in many but not all studies reported. It is becoming increasingly recognized that depression is much more common in elderly individuals. Whether borderline hypothyroidism plays a role in these behavioral disturbances requires clinical attention. Further investigation should also be directed at studying the outcomes of intervention with levothyroxine.

Among alcoholic patients and those suffering from anorexia nervosa, suppressed T_3 levels with elevations in reverse T_3 and normal TSH values are consistent with the euthyroid sick syndrome. These findings likely result from caloric deprivation.

10. Which medications affect thyroid function and thyroid function tests?

Medications commonly used to treat psychiatric illness have been shown to affect thyroid function tests (Table 41-2).

11. How does lithium affect the pituitary-thyroidal axis?

Lithium carbonate, used to treat bipolar disorders, interferes with both the release and organification of thyroid hormone. Therapeutic lithium levels diminish both T_3 and T_4 release from the thyroid gland, whereas at higher (probably toxic) levels, iodine uptake and organification may also be inhibited. Following a 3-week therapeutic course of lithium carbonate, suppression of serum T_4 and T_3 levels and associated elevations of basal serum TSH values and exaggerated TSH responses to TRH administration may be noted; these abnormalities generally return to normal within 3 to 12 months, even if the medication is continued.

12. What is the most common thyroid disorder in lithium-treated patients?

Goiter is the most common thyroid disorder in lithium-treated patients. Hypothyroidism can also occasionally develop, particularly in patients who have thyroid glands that have been compromised by disorders such as Hashimoto's thyroiditis and Graves' disease previously treated with 131-iodine therapy. However, it is uncommon for hypothyroidism to occur if pretreatment thyroid function was completely normal and patients are thyroid antibody negative. If considered clinically necessary, lithium may be continued and T_4 added to treat patients who develop goiter or hypothyroidism.

TABLE 41-2. IMPACT OF PSYCHOTROPIC MEDICATIONS ON THYROID FUNCTION TESTS

MEDICATION	MECHANISM	TEST FINDINGS
Lithium carbonate	↓ thyroglobulin hydrolysis, ↓ T_4 and T_3 release	TSH ↑ (transiently), hypothyroidism, goiter
Antipsychotics		
Perphenazine	↑ TBG concentration	↑ T_4, nl free T_4
Anticonvulsants		
Phenytoin	↑ hepatic clearance of T_4	↓ T_4, ± ↓ free T_4, nl TSH
Carbamazepine	↓ T_4 binding, ↑ hepatic clearance	↓ T_4, ± ↓ free T_4, nl TSH
Phenobarbital	↑ hepatic clearance	↓ T_4, ± ↓ free T_4, nl TSH
Valproic acid	↓ T_4 binding (?), ↑ hepatic clearance (?)	↓ T_4, ± ↓ free T_4, nl TSH
Narcotics		
Heroin	↑ TBG concentration	↑ T_4, nl free T_4
Methadone	↑ TBG concentration	↑ T_4, nl free T_4
Miscellaneous		
Amphetamines	↑ TSH secretion (?)	↑ T_4, ↑ free T_4

nl, normal; T_3, triiodothyronine; T_3RU, T_3 resin uptake; T_4, thyroxine; TBG, thyroxine-binding globulin; TSH, thyroid-stimulating hormone ; ↑, increased ; ↓, decreased.

Adapted from Hennessy JV, Jackson IMD: The interface between thyroid hormones and psychiatry. *Endocrinologist* 6:214–223, 1996.

13. How does phenytoin affect laboratory tests and the function of the thyroid?

The effects of phenytoin (Dilantin), occasionally used for bipolar disorder, on thyroid function are quite complex. Suppressed values of total T_4 and, occasionally, free T_4 are observed in a significant minority of patients who are treated on a long-term basis with phenytoin alone and in more than 75% of patients in whom the drug is combined with carbamazepine (Tegretol). The lower total T_4 levels are likely secondary to displacement of T_4 from thyroxine-binding globulin (TBG), whereas the reduced free T_4 levels result from enhanced clearance of T_4 through phenytoin-induced hepatic microsomal oxidative enzyme activity. Generally, the suppressed T_4 levels are accompanied by normal T_3 and free T_3 levels and normal TSH concentrations. Normal basal TSH values with diminished TSH responses to TRH have been attributed to potential phenytoin agonism at the T_3 receptor. However, other studies have suggested that this may be an assay artifact because free T_4 values have been found to be normal or mildly elevated in analyses using undiluted serum.

14. Describe the effects of carbamazepine on thyroid function.

Carbamazepine (Tegretol) is used increasingly in bipolar disorder. Long-term use with maintenance of therapeutic serum levels suppresses serum T_4 values in more than 50% of patients. This may be the result of enhanced hepatic metabolism of T_4. TRH stimulation testing before and after initiation of carbamazepine therapy reveals that TSH responsiveness is reduced by the addition of this drug; this finding has led to speculation that carbamazepine may inhibit thyroid function through effects on the pituitary gland. Displacement of T_4 from TBG, similar to that seen with phenytoin, has additionally been cited as a potential effect.

15. How do phenobarbital, valproic acid, and other psychotropic medications affect thyroid function?

Both phenobarbital and valproic acid are reported to lower serum levels of T_4 in patients treated on a long-term basis, the former via enhanced hepatic T_4 clearance and the latter likely from protein binding changes. Heroin, methadone, and perphenazine commonly increase serum TBG levels and therefore may elevate serum total T_4 levels, although TSH and free T_4 values remain normal. Amphetamines induce hyperthyroxinemia through enhanced secretion of TSH, an effect that appears to be centrally mediated.

16. How do antidepressant therapies affect thyroid function?

Antidepressants do not generally cause abnormal peripheral thyroid hormone levels but may affect thyroid hormone metabolism in the central nervous system (CNS). Selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) appear to promote activity of type 2 deiodinase (D2), which increases conversion of T_4 into T_3 in the brain. However, peripheral circulating total T_4 and free T_4 levels, often show a modest decline, though still within the normal range after treatment with various pharmacologic classes of antidepressants, or electroconvulsive therapy (ECT). There are case reports of sertraline-, paroxetine-, and escitalopram-related asymptomatic hypothyroidism, but more recent studies evaluating fluoxetine and sertraline have shown no clinically significant change in thyroid function test results.

17. Are there caveats for antidepressant use in individuals with thyroid disease?

The use of TCAs in thyrotoxic patients should be pursued with caution because cardiac dysrhythmias may be exacerbated or precipitated. Further, the monoamine oxidase (MAO) inhibitors may cause hypertension in thyrotoxic patients, although these drugs generally do not affect thyroid function or serum thyroid hormone levels.

18. Has T_4 been used as sole treatment for depression?

Asher's report on "myxoedematous madness" demonstrated that thyroid hormone deficiency resulted in depression that reversed with thyroid hormone administration. This led to studies of the role of thyroid hormone therapy alone in the treatment of depression and other psychiatric diseases and open studies of high-dose T_4 for refractory bipolar and unipolar depression. Euthyroid individuals with typical hypothyroid symptoms who are considered depressed on psychological testing do not improve when treated with T_4.

In fact, patients presenting with symptoms of hypothyroidism with normal thyroid function test results respond more positively to placebo. Although initial reports of T_3 as single therapy were promising, these studies were methodologically flawed, so the role of thyroid hormone by itself in the treatment of depression in the absence of abnormal thyroid function has not been established.

19. Are neuropsychiatric abnormalities demonstrable among patients with mild thyroid failure?

Studies have shown that symptomatic patients with subclinical hypothyroidism (elevated serum TSH but normal T_4 and T_3 levels) can have significant impairment of memory-related abilities, health status, and mood, as well as anxiety, somatic complaints, and depressive features, when compared with euthyroid controls. Greater than 60% of patients with subclinical hypothyroidism report some degree of depressive symptoms. Effects of treatment with levothyroxine have been mixed. Some studies suggested that normalization of thyroid function with levothyroxine therapy, as determined by the serum TSH, may completely reverse these neuropsychiatric features. Conversely, other studies suggested that hypothyroid patients receiving levothyroxine replacement may continue to experience neuropsychiatric abnormalities despite a normal TSH when compared with controls of similar age and sex. Further, when thyroid hormone is withdrawn from subjects with underlying hypothyroidism, gradually increasing cognitive deficits, sadness, and anxiety symptoms are observed over the ensuing few weeks. These findings indicate that the patient presenting with depression must be assessed for thyroid dysfunction because the presence of even subclinical hypothyroidism may provide an opportunity for resolution of the depression with thyroid hormone treatment.

20. How effective is the combination of levothyroxine and liothyronine in the treatment of neuropsychiatric symptoms of hypothyroidism?

Murray introduced thyroid hormone therapy to the clinical world in 1891. From the beginning, this was a treatment based on a combination of T_4 and T_3 derived from animal thyroid extracts. Variability of the animal extracts in regard to T_4 and T_3 content and ratios from batch to batch and brand to brand led to the replacement of "natural" combination therapy using extracts with pharmaceutically more precise synthetic T_4 and T_3. Eventually, the simplicity of T_4 monotherapy was adopted as usual therapy. The T_4 dosage was titrated based on symptoms until more sensitive TSH assays became available. During the 1980s, sensitive TSH assays allowed titration of thyroid hormone therapy to "normal," and this resulted in significant dose reductions of as much as 100 μg per day. Once euthyroid, however, some patients continued to complain of symptoms consistent with some components of hypothyroidism. Since that time, multiple reports have appeared evaluating the effectiveness of combining T_3 with T_4 to improve neuropsychological outcomes. The 1999 report of Bunevicius et al, for example, seemed to indicate that substituting 12.5 μg of T_3 for 50 μg of the individual's usual T_4 dose resulted in improvement in mood and neuropsychological function. Several double-blind randomized controlled trials designed to correct design flaws of previous trials subsequently failed to reproduce the positive effects reported by Bunevicius et al and did not demonstrate improvement in self-rated mood, well-being, or depression scales with the addition of T_3 to T_4 therapy. Moreover, these studies failed to demonstrate differences in cognitive function, quality of life, or subjective satisfaction with treatment, but they did report that anxiety scores were significantly worse in patients treated with the T_4-T_3 combination. However, a subset of patients may benefit from T_3 supplementation. Preliminary evidence suggests that patients with certain mutations in the D2 gene may have a positive response to T_3 potentiation, but prospective trials have not yet been conducted. At this time, it does not appear justified to use combined T_4 and T_3 treatment in hypothyroid patients who complain of depressive symptoms after biochemical euthyroidism is restored.

21. Can combination antidepressant medication and thyroid hormone enhance the response to depression treatment?

Adjuvant therapy has been said to be logical when depression fails to resolve after 6 weeks of adequate antidepressant medication. Such resistance occurs in about 30% to 45% of cases. The role of adjuvant thyroid hormone with TCAs has been investigated in euthyroid patients with depression for more than

25 years. T_3 doses of 25 to 50 μg daily increase serum T_3 levels and cause suppression of serum TSH and T_4 values. Two separate therapeutic effects of T_3 therapy have been studied: first, its ability to accelerate the onset of the antidepressant response; and second, its ability to augment antidepressant responses among those considered pharmacologically resistant.

22. How effective is thyroid hormone for the acceleration of the antidepressant response?

Given that the antidepressant effect of TCAs is known to be delayed, the role of T_3 in accelerating the therapeutic onset of these drugs has been investigated. Several reports detailing the clinical outcomes of starting T_3 (5-40 μg daily) along with varying doses of TCAs, as well as SSRIs, at the outset of therapy have appeared in the literature. The study populations were inhomogeneous, consisting of patients with various types of depression. Furthermore, the studies had important methodologic limitations, including small sample sizes, inadequate medication doses, lack of serum medication level monitoring, and variable outcome measures. Because two relatively large, prospective, randomized placebo-controlled studies came to opposite conclusions, it still has not been clearly established that T_3 accelerates the antidepressant effect of TCAs. A meta-analysis of double-blind clinical trials comparing SSRI-T_3 treatment with SSRIs alone showed no significant difference in remission rates.

23. Can T_3 therapy augment the clinical antidepressant response?

An additional hypothesis is that adding small doses of T_3 to the antidepressant therapy of patients who have little or no initial response will enhance the clinical effectiveness of the antidepressant. Resistance to antidepressants is defined as inadequate remission after 2 successive trials of monotherapy with different antidepressants in adequate doses, each for 4 to 6 weeks before changing to alternative therapies. However, a course of 8 to 12 weeks of ineffective antidepressant therapy is commonly deemed unacceptable, and strategies designed to augment the response are being sought. Early studies assessing T_3 effectiveness in augmenting the antidepressant response were neither placebo controlled nor focused on patient populations that could be directly compared. The first placebo-controlled, double-blind, randomized study reported results in 16 unipolar depressed outpatients who had experienced no improvement in their clinical outcomes with TCAs alone. The intervention consisted of adding 25 μg of T_3 or placebo daily for 2 weeks before the patients were crossed over to the opposite treatment for an additional 2 weeks. No beneficial effect of T_3 was apparent. The only other placebo-controlled, randomized, double-blind trial investigating this question involved 33 patients with unipolar depression treated with either desipramine or imipramine for 5 weeks before random assignment to placebo or 37.5 μg of T_3 daily. After 2 weeks of observation on T_3, during which TCA levels were monitored, significantly more patients treated with T_3 (10 of 17; 59%) had a positive response than did placebo-treated patients (3 of 16; 19%). A subsequent open clinical trial of imipramine-resistant depression, using a prolonged TCA treatment period preceding the addition of T_3, showed no demonstrable T_3 effect.

24. What evidence is there that the effect of SSRIs and ECT may be enhanced by the addition of T_3?

The SSRI group of substances (including fluoxetine and sertraline) is the preferred antidepressant treatment in the United States today. A large, double-blind, placebo-controlled study to determine the role of T_3 as augmentation therapy did not demonstrate an effect of T_3 in augmenting the response of paroxetine (an SSRI) therapy in patients with major depressive disorder, but a similar study using sertraline and T_3 showed a conflicting positive response. Responders in the Cooper-Kazaz report seemed to have had lower circulating thyroid hormone levels before treatment and to have experienced greater decreases in TSH levels as a result of the intervention. This finding may indicate that patients benefiting from the addition of T_3 may have been subtly hypothyroid, and the addition of T_3 compensated for this deficiency. A metaanalysis of the available data suggests that coadministration of T_3 and SSRIs has no significant clinical effect in depressed patients when compared with SSRIs alone. More research is necessary to determine whether those patients with a functional type 1 deiodinase (D1) gene polymorphism may be more responsive to T_3 cotreatment.

T_3 has been reported to augment the antidepressant effect of ECT. However, there is little to no evidence to guide the duration of treatment with T_3, and there are few studies on the side effects of long-term administration.

25. Are any psychiatric conditions recognized to respond to pharmacologic doses of T_4?

For the 10% to 15% of patients with bipolar disorder with four or more episodes of manic-depressive psychosis yearly (rapid cyclers), the prevalence of autoimmune thyroid disease may reach 50% or higher. Therapeutic intervention with standard therapy such as lithium is frequently disappointing. Open-label studies treating such patients with T_4 in pharmacologic doses sufficient to suppress serum TSH and elevate T_4 levels to approximately 150% of normal showed that treatment may decrease the manic and depressive phases in both amplitude and frequency, and it led to remission in some patients. Given these encouraging results, controlled studies on the efficacy of T_4 or T_3 seem warranted.

26. Are mechanisms of thyroid hormone action on the brain known?

Thyroid hormones play a critical role in the development and function of the CNS. T_3 receptors are widely distributed throughout the brain, and there is much evidence that thyroid hormone regulates brain function through interaction with the catecholaminergic system. Thyroid hormone action in brain tissue is accomplished through the binding of T_3 to its nuclear receptor. The T_3 is derived from T_4 by the action of D2, which is located throughout the CNS.

27. Should T_4 or T_3 be used in treating the depressed patient?

Most studies using thyroid hormone as adjuvant therapy have used T_3 rather than T_4. In those reports assessing the advantages of one over the other, T_3 was considered superior. In a randomized trial combining T_4 or T_3 with antidepressants, only 4 of 21 patients (19%) treated with 150 μg/day of T_4 for 3 weeks responded, whereas 9 of 17 (53%) responded with 37.5 μg/day of T_3. Further studies of open T_4 treatment in antidepressant-resistant patients have appeared, but the lack of controls makes outcome interpretation difficult. One of these studies indicated that responders to T_4 had significantly lower pretreatment serum T_4 and reverse T_3 levels, a finding leading the investigators to believe that the responders may have been subclinically hypothyroid. Adjuvant therapy with T_4 rather than T_3 may be indicated when subclinical hypothyroidism or rapid cycling bipolar disease is present. Because T_4 equilibrates in tissues more slowly than T_3, treatment with T_4 for at least 6 to 8 weeks, and preferably longer, would be necessary to determine its efficacy in this situation.

As personalized medicine evolves, therapies will inevitably become more directed. Research directed at type 1 deiodinase (D1), which is important for serum conversion of T_4 to T_3, suggests that certain polymorphisms of D1 may be associated with a positive response to T_3 potentiation of SSRIs. These patients with certain alleles have inherently lower D1 activity and therefore have naturally lower serum T_3 levels. When compared with placebo, these patients have decreased depression scores at 8 weeks with T_3 supplementation in combination with sertraline.

Conversely, there is evidence that specific subsets of patients may not respond to T_3 potentiation. Genetic researchers have identified an organic anion transporting polypeptide (OATP) that is thought to be key in delivery of T_4 to the brain. Polymorphisms in the *OATP1C1* gene appear to be linked to increased depressive symptoms among patients with hypothyroidism. These patients do not appear to have any decrease in depressive scores with T_3 supplementation when compared with controls. The clinical significance of these findings is yet to be determined, but it may have a meaningful impact on the future of depressive treatment.

28. Describe the proposed mechanisms linking thyroid function and depression.

It has been postulated that D2 activity in the CNS is deficient in depression, thereby giving rise to a state of brain hypothyroidism coexisting with systemic euthyroidism. Alternatively, D2 activity may be depressed by the elevated cortisol levels seen in depression and stress, thus resulting in T_4 instead being converted to reverse T_3 (rT_3) by "inner ring" brain 5 deiodinase (type III deiodinase [5D-III]) activity, with decreased T_3 and increased rT_3 levels. Notably, T_3 treatment is feasible because T_3 is not dependent on transport by transthyretin, which is low in depression, and therefore would ensure adequate T_3 delivery across the blood-brain barrier to the brain.

29. Do antidepressant medications have a mechanistic connection to the action of thyroid hormone in the brain?

It has been shown that desipramine, a TCA, and fluoxetine, an SSRI, both enhance D2 activity in the CNS, thus presumably increasing the availability of T_3 in the brain. This could conceivably account for the clinical efficacy of these classes of drugs.

30. What recommendations can be made for the thyroid evaluation in psychiatric patients?

It seems prudent to check thyroid function test results in those psychiatric patients who are at increased risk for developing thyroid disease. Women more than 45 years of age, patients with known autoimmune diseases, individuals with a family history of thyroid disease, and those receiving lithium or suffering from dementia should be screened for underlying thyroid abnormalities. Patients receiving medications known to influence the interpretation of thyroid function tests should have these considered when interpreting the results of testing.

31. Who should receive thyroid hormone with the intent of relieving psychiatric symptoms?

It is recommended that T_4 therapy be offered to any depressed patient with an elevated serum TSH, especially if it is accompanied by increased antithyroid antibody titers or a low free T_4. Thyroid hormone replacement may alleviate the depression in these individuals. Conversely, antidepressant therapy, if required, may be ineffective before normalization of thyroid axis parameters. One observation suggests that there is a subset of patients with hypothyroidism who are taking T_4 and who experience higher depression and anxiety scores than their euthyroid counterparts. These patients in particular, who may have D2 gene polymorphisms, may benefit from the addition of T_3, but prospective trials have not yet been conducted. In patients with refractory depression but normal systemic thyroid function, adjuvant T_3 therapy may not be worth considering.

KEY POINTS 1

1. The symptoms of hypothyroidism often mimic those of depression, whereas those of hyperthyroidism may be confused with mania or depression.
2. Approximately 20% of patients admitted to the hospital with acute psychiatric presentations, including schizophrenia and major affective disorders, but rarely dementia or alcoholism, may demonstrate mild elevations in their serum thyroxine (T_4) levels, and less often their triiodothyronine (T_3) levels, that usually resolve within 2 weeks without specific thyroid therapy.
3. Normalization of the serum TSH with levothyroxine therapy may completely reverse the neuropsychiatric features of hypothyroidism.
4. Based on the results of prospective controlled studies, it would not appear justified to use combined T_4 and T_3 treatment in hypothyroid patients who complain of depressive symptoms after biochemical euthyroidism is restored. However, research into D2 polymorphisms suggests that a subset of patients may experience some clinical benefit from T_3 supplementation.
5. Although a large double-blind, placebo-controlled study to determine the role of T_3 as augmentation therapy did not demonstrate an effect of T_3 in augmenting the response of paroxetine therapy in patients with major depressive disorder, a more recent metaanalysis of the available data on T_3 augmentation demonstrated very mixed results. Therefore, it is difficult to make strong recommendations for or against augmentation therapy.
6. It is recommended that T_4 therapy be offered to any depressed patient with an elevated serum thyroid-stimulating hormone (TSH) level, especially if it is accompanied by increased antithyroid antibody titers or low free T_4.

BIBLIOGRAPHY

Applehof BC, et al: Triiodothyronine addition to paroxetine in the treatment of major depressive disorder, *J Clin Endocrinol Metab* 89:6271–6276, 2004.

Asher R: Myxoedematous madness, *Br Med J* 22:555–562, 1949.

Bauer M, Whybrow PC: Thyroid hormones and the central nervous system in affective illness: interactions that may have clinical significance, *Integr Psychiatry* 6:75–100, 1988.

Bauer M, et al: Effects of supraphysiological thyroxine administration in healthy controls and patients with depressive disorders, *J Affect Disord* 68:285–294, 2002.

Bell RJ, et al: Well-being, health-related quality of life and cardiovascular disease risk profile in women with subclinical thyroid disease: a community-based study, *Clin Endocrinol* 66:548–556, 2007.

Bocchetta A, Loviselli A: Lithium treatment and thyroid abnormalities, *Clin Pract Epidemiol Ment Health* 2:23, 2006.

Brent GA, Larsen PR: Treatment of hypothyroidism. In Braverman LE, Utiger RD, editors: *Werner and Ingbar's the Thyroid: A Fundamental and Clinical Text*, Philadelphia, 2000, Lippincott Williams & Wilkins, pp 853–860.

Bunevicius R, et al: Effects of thyroxine as compared with thyroxine plus triiodothyronine in patients with hypothyroidism, *N Engl J Med* 340:424–429, 1999.

Chopra IJ, Solomon DH, Huang TS: Serum thyrotropin in hospitalized psychiatric patients: evidence for hyperthyrotropinemia as measured by ultrasensitive thyrotropin assay, *Metabolism* 93:538–543, 1990.

Cooper DS, et al: L-Thyroxine therapy in subclinical hypothyroidism: a double-blind, placebo-controlled trial, *Ann Intern Med* 101:18–24, 1984.

Cooper-Kazaz R, Lerer B: Efficacy and safety of triiodothyronine supplementation in patients with major depressive disorder treated with specific serotonin reuptake inhibitors, *Int J Neuropsychopharmacol* 11:685–699, 2008.

Cooper-Kazaz R, et al: Combined treatment with sertraline and liothyronine in major depression: a randomized, double-blind, placebo-controlled trial, *Arch Gen Psychiatry* 64:679–688, 2007.

Cooper-Kazaz R, et al: Preliminary evidence that a functional polymorphism in type 1 deiodinase is associated with enhanced potentiation of the antidepressant effect of sertraline by triiodothyronine, *J Affect Disord* 116:113–116, 2009.

de Carvalho GA, et al: Effects of selective serotonin reuptake inhibitors on thyroid function in depressed patients with primary hypothyroidism or normal thyroid function, *Thyroid* 19:691–697, 2009.

Demartini B, et al: Prevalence of depression in patients affected by subclinical hypothyroidism, *Panminerva Med* 52: 277–282, 2010.

Eker SS, et al: Reversible escitalopram-induced hypothyroidism, *Gen Hosp Psychiatry* 32:559, e5–7, 2010.

Fava M, et al: Hypothyroidism and hyperthyroidism in major depression revisited, *J Clin Psychiatry* 56:186–192, 1995.

Fliers E, et al: Efficacy of triiodothyronine (T_3) addition to paroxetine in major depressive disorder: a randomized clinical trial. In Annual Meeting of the Endocrine Society: *The Endocrine Society*, Philadelphia, 2003, pp S19–S12.

Gharib H, et al: Consensus statement: subclinical thyroid dysfunction. A joint statement on Management from the American Association of Clinical Endcrinologists, the American Thyroid Association, and the Endocrine Society, *J Clin Endocrinol Metab* 90:581–585, 2005.

Grozinsky-Glasberg S, et al: Thyroxine-triiodothyronine combination therapy versus thyroxine monotherapy for clinical hypothyroidism: meta-analysis of randomized controlled trials, *J Clin Endocrinol Metab* 91:2592–2599, 2006.

Gulseren S, et al: Depression, anxiety, health-related quality of life, and disability in patients with overt and subclinical thyroid dysfunction, *Arch Med Res* 37:133–139, 2006.

Hage MP, Azar ST: The link between thyroid function and depression, *J Thyroid Res* 2012: 590–648, 2012.

Hein MD, Jackson IMD: Thyroid function in psychiatric illness, *Gen Hosp Psychiatry* 12:232–244, 1990.

Hennessey JV, Jackson IMD: The interface between thyroid hormones and psychiatry, *Endocrinologist* 6:214–223, 1996.

Jackson IMD, Whybrow PC: The relationship between psychiatric disorders and thyroid function, *Thyroid Update,* 9:1–7, 1995.

Jackson IMD: The thyroid axis and depression, *Thyroid* 8:951–956, 1998.

Joffe RT: Is the thyroid still important in major depression? *J Psychiatry Neurosci* 31:367–368, 2006.

Jorde R, et al: Neuropsychological function and symptoms in subjects with subclinical hypothyroidism and the effect of thyroxine treatment, *J Clin Endocrinol Metab* 91:145–153, 2006.

Monzani F, et al: Subclinical hypothyroidism: neuro-behavioral features and beneficial effect of L-thyroxine treatment, *Clin Invest* 71:367–371, 1993.

Murray GR: Note on the treatment of myxoedema by hypodermic injections of an extract of the thyroid gland of a sheep, *Br Med J* 2:796–797, 1891.

Nelson JC: Augmentation stategies in depression, *J Clin Psychiatry* 61(Suppl 1):13–19, 2000.

Panicker V, et al: A paradoxical difference in relationship between anxiety, depression and thyroid function in subjects on and not on T_4: findings from the HUNT study, *Clin Endocrinol (Oxf),* 71:574–580, 2009.

Panicker V, et al: Common variation in the DIO2 gene predicts baseline psychological well-being and response to combination thyroxine plus triiodothyronine therapy in hypothyroid patients, *J Clin Endocrinol Metab* 94:1623–1629, 2009.

Papakostas GI, et al: Simultaneous initiation (coinitiation) of pharmacotherapy with triiodothyronine and a selective serotonin reuptake inhibitor for major depressive disorder: a quantitative synthesis of double-blind studies, *Int Clin Psychopharmacol,* 24:19–25, 2009.

Pardridge WM: Carrier medicated transport of thyroid hormones through the rat blood-brain barrier: primary role of albumin bound hormone, *Endocrinology* 105:605–612, 1979.

Parle J, et al: A randomized controlled trial of the effect of thyroxine replacement on cognitive function in community-living elderly subjects with subclinical hypothyroidism: the Birmingham Elderly Thyroid study, *J Clin Endocrinol Metab* 95:3623–3632, 2010.

Pollock M.A, et al: Thyroxine treatment in patients with symptoms of hypothyroidism but thyroid function tests within the reference range: randomized double blind placebo controlled crossover trial, *Br Med J* 323:891–895, 2001.
Razvi S, IL, Keeka G, Oates C, McMillan C, Weaver JU: The beneficial effect of L-thyroxine on cardiovascular risk factors, endothelial function, and quality of life in subclinical hypothyroidism: randomized, crossover trial, *J Clin Endocrinol Metab* 92:1715–1723, 2007.
Report on myxoedema, Transactions of the Clinical Society of London, 1888.
Sachs BA, Wolfman L, Murthy G: Lipid and clinical response to a new thyroid hormone combination, *Am J Med Sci* 256:232–238, 1968.
Samuels MH, et al: Health status, mood, and cognition in experimentally induced subclinical hypothyroidism, *J Clin Endocrinol Metab* 92:2545–2551, 2007.
Saravanan P, et al: Psychological well-being in patients on "adequate" doses of L-thyroxine: results of a large, controlled community-based questionnaire study, *Clin Endocrinol* 57:577–585, 2002.
Sarne D, DeGroot LJ: Effects of the environment, chemicals and drugs on thyroid function. *Endocrine Education, Inc.* www.thyroidmanager.org, 2012.
Sawka AM, et al: Does a combination regimen of thyroxine (T_4) and 3,5,3'-triiodothyronine improve depressive symptoms better than T_4 alone in patients with hypothyroidism? Results of a double-blind, randomized, controlled trial, *J Clin Endocrinol Metab* 88:4551–4555, 2003.
Selenkow HA, Wool MS: A new synthetic thyroid hormone combination for clinical therapy, *Ann Intern Med* 67:90–99, 1967.
Smith RN, Taylor SA, Massey JC: Controlled clinical trial of combined triiodothyronine and thyroxine in the treatment of hypothyroidism, *Br Med J* 4:145–148, 1970.
Taylor S, Kapur M, Adie R: Combined thyroxine and triiodothyronine for thyroid replacement therapy, *Br Med J* 2: 270–271, 1970.
Tremont G, RA S: Use of thyroid hormone to diminish the cognitive side effects of psychiatric treatment, *Psychopharmacol Bull* 33:273–280, 1997.
van der Deure WM, et al: Polymorphisms in the brain-specific thyroid hormone transporter OATP1C1 are associated with fatigue and depression in hypothyroid patients, *Clin Endocrinol (Oxf)* 69:804–811, 2008.
Vigario P, et al: Perceived health status of women with overt and subclinical hypothyroidism, *Med Princ Pract* 18: 317–322, 2009.
Walsh JP, et al: Combined thyroxine/liothyronine treatment does not improve well-being, quality of life, or cognitive function compared to thyroxine alone: a randomized controlled trial in patients with primary hypothyroidism, *J Clin Endocrinol Metab* 88:4543–4550, 2003.
Whybrow PC: The therapeutic use of triiodothyronine and high dose thyroxine in psychiatric disorders, *Acta Med Aust* 21:47–52, 1994.

CHAPTER 42

DISORDERS OF SEXUAL DIFFERENTIATION

Anil Piya and Robert H. Slover

1. Describe the first level of sexual differentiation.

The first level of sexual differentiation is the establishment of chromosomal sex. Most infants are 46,XX females or 46,XY males. Genetic sex determines gonadal sex. Gonadal structures differentiate from the "bipotential," or primordial, gonadal ridge. The Y chromosome contains an area known as the sex-determining region, or SRY. The SRY gene product initiates the differentiation of the bipotential gonad into a testis. In its absence, the gonad becomes an ovary.

2. What is the next level of sex determination?

The next level of sex determination involves the genital duct structures. The genital duct structures are initially identical in the male and female. In the normal male, testicular Leydig cells produce testosterone, which is necessary to maintain ipsilateral wolffian duct structures (e.g., vas deferens, epididymis, seminal vesicles). The Sertoli cells of the testis produce müllerian-inhibiting factor (MIF), which acts ipsilaterally to cause regression of müllerian duct structures (fallopian tubes, uterus, upper third of the vagina). In the absence of testosterone and MIF, müllerian duct structures are preserved, and wolffian duct structures regress.

3. Discuss the development of the external genitalia.

Male and female external genitalia arise from the same embryologic structures. In the absence of androgen stimulation, these structures remain in the female pattern, whereas the presence of androgens causes male differentiation (virilization). For complete virilization, testosterone must be converted to dihydrotestosterone (DHT) by the enzyme 5-alpha-reductase, and androgen receptors must be functional. Excessive androgens virilize a female. Inadequate androgen production, inability to convert testosterone to DHT, or inability to respond to androgens, as in androgen receptor defects, results in undervirilization of a male.

4. What is testis-determining factor (TDF)?

The TDF promotes differentiation of the bipotential gonad into a testis; SRY was eventually characterized as the TDF. SRY belongs to a family of DNA binding proteins. Specific manipulations have shown that the introduction of SRY results in sex reversal of XX mice, and site-directed mutagenesis of the *SRY* gene in XY mice yields an XY female. The activation of SRY is influenced by the Wilms' tumor suppressor gene, *WT1.* Other genes that play a role downstream of SRY include *SOX9, SF-1, DAX1,WNT4, DMRT1, ATRX, DHH,* and *GATA4.*

5. Describe the Lyon hypothesis. In which cells are two X chromosomes necessary for normal development?

Dr. Mary Lyon addressed the question of the extra X chromosomal material in females. Simply put, if two X chromosomes are necessary in each cell, how can males be developmentally normal? Lyon suggested that in each cell, one of the two X chromosomes is inactive, and in any given cell line, which X is active is randomly determined. In fact, the inactive X may be identified in many cells as a clump of chromatin at the nuclear membrane (Barr body). The important exception is in the ovary, where two functional X chromosomes are necessary for normal sustained ovarian development. Without two X chromosomes per cell (as in 45 XO Turner syndrome), the ovary involutes and leaves only fibrous tissue.

6. Discuss normal male sexual differentiation.

The fetus is sexually bipotential. Figure 42-1 shows schematically how male development is accomplished. The undifferentiated gonad is derived from coelomic epithelium, mesenchyme, and germ cells, which, in the presence of SRY, give rise to Leydig cells, Sertoli cells, seminiferous tubules, and spermatogonia. Testes are formed at 7 weeks. Testicular production of testosterone (Leydig cells) leads to wolffian duct development, whereas MIF (Sertoli cells) leads to müllerian duct regression. Masculinization of the external genitalia is mediated by DHT, which is produced from testosterone by the action of the enzyme 5-alpha-reductase.

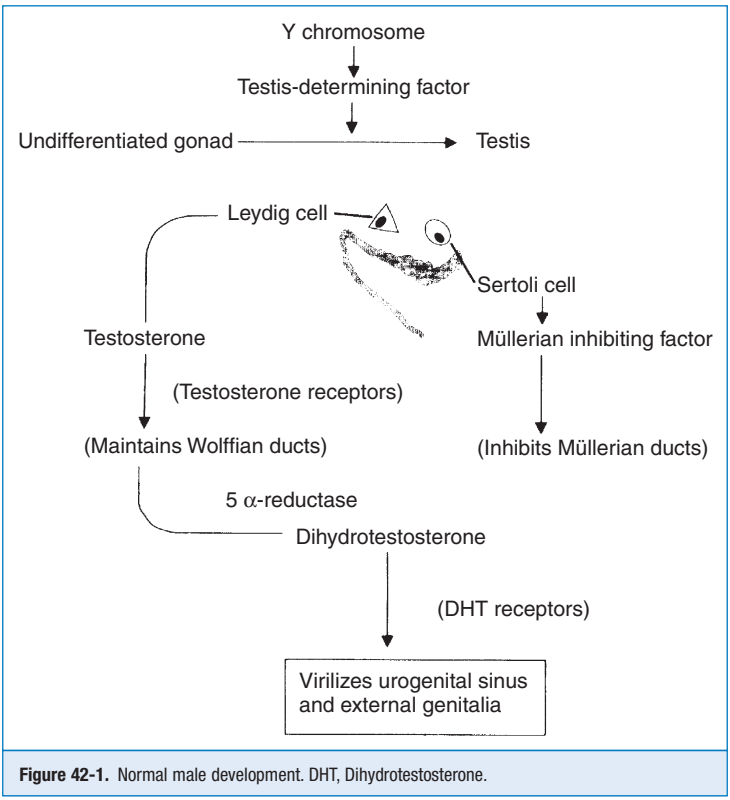

Figure 42-1. Normal male development. DHT, Dihydrotestosterone.

7. Describe normal female sexual differentiation.

In the absence of SRY, the undifferentiated gonad gives rise to follicles, granulosa cells, theca cells, and ova. Ovarian development occurs in the thirteenth to sixteenth week of gestation. Lack of testosterone and MIF allows regression of the wolffian ducts and maintenance of the müllerian ducts, respectively. Lack of DHT results in the maintenance of female external genitalia.

8. How is external genital development determined?

The external genitalia arise from the urogenital tubercle, urogenital swelling, and urogenital folds. In females, these become the clitoris, labia majora, and labia minora, respectively. In males, under the influence of DHT, the genital tubercle becomes the glans of the penis, the urogenital folds elongate and fuse to form the shaft of the penis, and the genital swellings fuse to form the scrotum. Fusion is completed by 70 days of gestation, and penile growth continues to term.

Female differentiation does not require ovaries or hormonal influence, whereas normal development of male genitalia requires normal testosterone synthesis, conversion to DHT by 5-alpha-reductase, and normal androgen receptors (Fig. 42-2).

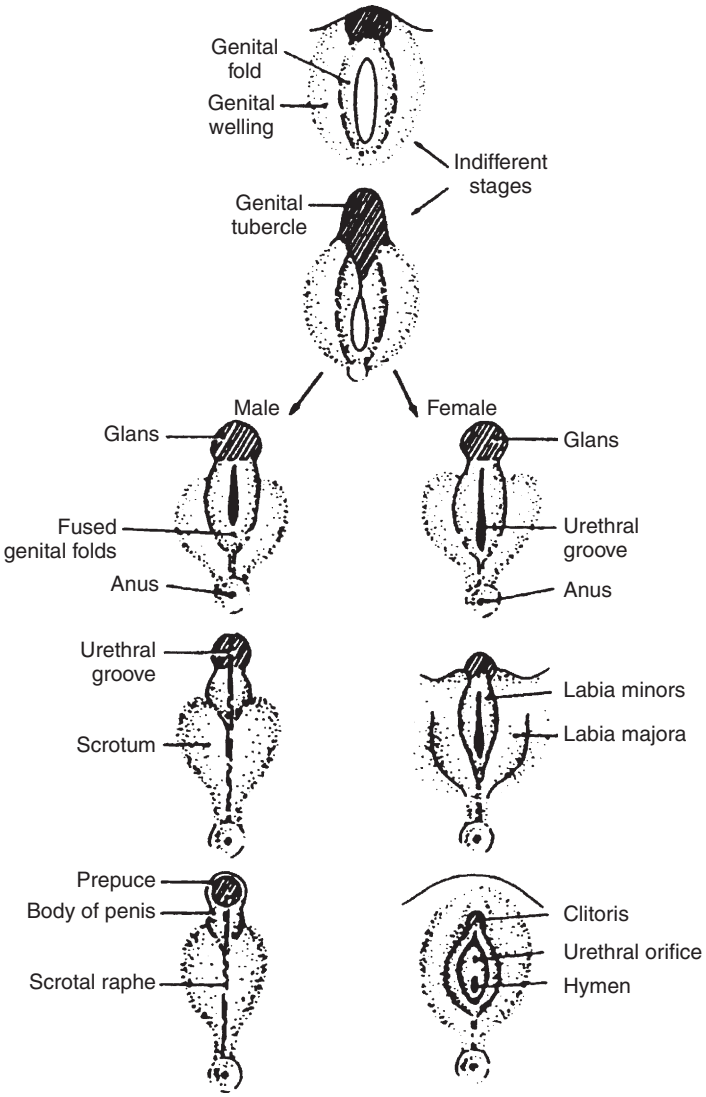

Figure 42-2. Differentiation of the external genitalia of male and female.

9. The differential diagnosis of disorders of sexual differentiation (DSD) is complex, but it may be simplified by an approach based on an understanding of the process of sexual differentiation. Can you devise such a classification?

KEY POINTS 1: DISORDERS OF SEXUAL DIFFERENTIATION

1. Sexual ambiguity in a newborn must be seen as a medical, social, and psychological emergency requiring a multidisciplinary team approach to assign a sex of rearing. Members of the team include the pediatric endocrinologist, urologist, geneticist, pediatrician, appropriate counselors, and an ethicist.
2. Evaluation of ambiguity must consider the four major categories of children presenting with this problem: virilized 46,XX females, undervirilized 46,XY males, disorders of gonadal differentiation, and unclassified forms (cryptorchidism, hypospadias, developmental anomalies).
3. The most common cause of sexual ambiguity in newborns is congenital adrenal hyperplasia secondary to 21-hydroxylase deficiency.
4. As a general rule, gonadal tissue containing Y chromosomal material is at higher risk for development of malignancy. Consideration must be given to surgical removal of such gonads at some point.

There are three large categories of ambiguity (Table 42-1):

- Sex chromosome DSD
- 46,XY DSD
- 46,XX DSD

TABLE 42-1. NEW CLASSIFICATION OF DISORDERS OF SEXUAL DIFFERENTIATION (CHICAGO CONSENSUS)

Sex Chromosome DSD	45,X (Turner syndrome and variants)
	47,XXY (Klinefelter syndrome and variants)
	45,X/46,XY (mixed gonadal dysgenesis, ovotesticular DSD)
	46,XX/46,XY (chimeric, ovotesticular DSD)
46,XY DSD	Disorders of testicular development (complete and partial gonadal dysgenesis, gonadal regression and ovotesticular DSD)
	Disorders of androgen biosynthesis, complete and partial androgen insensitivity, disorders of antimüllerian hormone (AMH)/receptor, LH receptor defects
	Other (severe hypospadias, cloacal exstrophy)
46,XX DSD	Disorders of ovarian development (testicular DSD, gonadal dysgenesis)
	Androgen excess (fetal [21-hydroxylase and 11-hydroxylase deficiency], fetoplacental [aromatase deficiency, POR], maternal [exogenous, luteoma])
	Other (vaginal atresia, cloacal exstrophy)
REVISED NOMENCLATURE	
New	**Old**
DSD	Intersex
46,XY DSD	Male pseudohermaphrodite, undervirilization of an XY male and undermasculinization of an XY male
46,XX DSD	Female pseudohermaphrodite, overvirilization of an XX female, and masculinization of an XX female
Ovotesticular DSD	True hermaphrodite
46,XX testicular DSD	XX male or XX sex reversal
46,XY complete gonadal dysgenesis	XY sex reversal

DSD, Disorders of sexual differentiation; LH, luteinizing hormone; POR, P450 Oxidoreductase.

10. What is a virilized female?

A virilized female (previously called female pseudohermaphroditism) is characterized by a 46,XX karyotype, ovaries, normal müllerian duct structures, absent wolffian duct structures, and virilized genitalia resulting from exposure to androgens during the first trimester. See Table 42-2.

TABLE 42-2. PRADER CLASSIFICATION: DEGREE OF VIRILIZATION OF EXTERNAL GENITALIA

Type 1	Clitoral hypertrophy
Type 2	Clitoral hypertrophy, urethral and vaginal orifices present, but very near
Type 3	Clitoral hypertrophy, single urogenital orifice, posterior fusion of the labia majora
Type 4	Penile clitoris, perineoscrotal hypospadias, complete fusion of the labia majora
Type 5	Complete masculinization (normal-looking male genitalia) but no palpable testes

11. What is the most common cause of a virilized female?

The most common cause is congenital adrenal hyperplasia (CAH) resulting from 21-hydroxylase deficiency. In fact, this disorder is the single most common cause of sexual ambiguity. In this condition, the gene responsible for encoding the 21-hydroxylase enzyme is inactive. This enzyme blockage occurs along the pathway to cortisol and aldosterone. Because of low or absent levels of cortisol, the feedback mechanism produces increased adrenocorticotropic hormone (ACTH), which drives the pathway further and results in accumulation of precursor hormones, the measurement of which is useful for making a diagnosis. Increased ACTH also drives the production of excess adrenal androgens, which result in virilization. Virilization may also be caused by maternal ingestion of androgens or synthetic progesterones during the first trimester of pregnancy.

12. How do virilized female infants present?

Affected infants may present with a wide spectrum of ambiguity, ranging from clitoromegaly alone to complete fusion of the labial swellings to form a scrotum and large phallus. (Beware the infant with bilaterally undescended testes.) Even in the most virilized girls, a penile urethra is rare.

13. What is an undervirilized male?

An undervirilized male (previously called male pseudohermaphroditism) refers to a 46,XY male who has ambiguous or female external genitalia. The abnormality may range from hypospadias to a completely female phenotype. Such disorders result from deficient androgen stimulation of genital development and most often are secondary to Leydig cell agenesis, testosterone biosynthetic defects, 5-alpha-reductase deficiency, and partial or total androgen resistance (androgen receptor defects).

14. Which boys with hypospadias should be evaluated for sexual ambiguity?

First-degree (coronal or glandular) hypospadias as the sole presenting genital abnormality has no apparent endocrine basis and need not be evaluated. The incidence of this anomaly is between 1 and 8 in 1000 births. In contrast, perineoscrotal hypospadias is a feature of many causes of sexual ambiguity, and a child with this finding should be fully evaluated as sexually ambiguous.

15. What is gonadal dysgenesis?

Patients with Y-related chromosomal or genetic disorders that cause maldevelopment of one or both testes are said to have gonadal dysgenesis. They present with ambiguous genitalia and may have hypoplasia of wolffian duct structures and inadequate virilization. MIF may be absent, thus allowing müllerian duct structures to persist. Duct asymmetry is therefore common. The Y-containing dysgenetic testes are at risk for developing gonadoblastomas and must be removed.

16. An infant is born with ambiguous genitalia, and the sex of the infant is uncertain. How do you proceed?

Honesty and diplomacy are essential. Explain that the genitalia are not yet fully developed and that further testing is necessary to determine the infant's sex. Reference to more commonly understood birth defects may be useful. Explain that while several days may be necessary to complete the testing and that a team will participate to make an accurate diagnosis and a considered recommendation, completion of the birth certificate should not be postponed, and sex assignment should not be delayed.

17. What history is necessary to evaluate the infant?

Maternal history is particularly important and should include illnesses, drug ingestion, alcohol intake, and ingestion of hormones during pregnancy. Was progestational therapy used for threatened abortion or androgens for endometriosis? Does the mother have signs of excessive androgen? Explore family history for occurrence of ambiguity, neonatal deaths, consanguinity, or infertility.

18. How should you direct the physical examination?

The diagnosis of the origin of sexual ambiguity can rarely be made by examination alone, but physical findings can help to direct further evaluation. Look for the following:

- Are gonads present? Are they normal in size, consistency, and position? Because gonadal descent is tied to müllerian duct regression, a palpable gonad implies MIF action on that side.
- What is the phallic length? Measure along the dorsum of the phallus from the pubic ramus to the tip of the glans. At term, a stretched phallic length of 2.5 cm is 2.5 SD below the mean. Assess phallic width and development.
- Note the position of the urethral meatus, and look for evidence of hypospadias and chordee (ventral curvature secondary to shortened urethra).
- What is the degree of fusion of the labioscrotal folds? The folds may range from normal labia majora to a fully fused scrotum. In subtle cases, the ratio of the distance from the posterior fourchette to the anus is compared with the total distance from the urethral meatus.
- Is there an apparent vaginal orifice?

19. What other areas should be evaluated?

Certain forms of CAH may cause dehydration, hypertension, or areolar or genital hyperpigmentation. Turner's stigmata may be present, including webbed neck, low hairline, and edema of hands and feet. Other associated congenital anomalies may indicate a complex that includes sexual ambiguity.

20. Explain which radiographic studies are necessary.

Structural studies are needed to address the presence of gonads and müllerian structures. Pelvic ultrasound examination by qualified and experienced personnel should be performed as soon as possible to look for a uterus. The presence of gonads, fallopian tubes, and a vaginal vault may also be determined. If necessary, a genitogram may be performed by inserting contrast material into the urogenital orifice (or vaginal orifice) to define vaginal size, presence of a cervix, and any fistulas.

21. Explain the role of karyotyping.

A karyotype is essential and must be obtained expeditiously. Buccal smears are absolutely contraindicated because they are inaccurate. In many laboratories, a karyotype can be completed within 48 to 72 hours. Some laboratories can also perform rapid fluorescence in situ hybridization analysis for the presence of the *SRY* gene.

22. What laboratory test is very helpful in almost all cases?

Because 21-hydroxylase deficiency is a common cause of sexual ambiguity, the level of 17-hydroxyprogesterone (17-OHP) should be assessed in all such infants who do not have palpable gonads.

23. How is further evaluation directed?

Further evaluation must be directed by information provided through the history, examination, and initial studies. Determining the presence or absence of palpable gonads (presumably testes), the presence or absence of a uterus, and the karyotype allows classification of the infant as a virilized female, an undervirilized male, having a disorder of gonadal differentiation, or having one of the unclassified forms.

24. The infant has no palpable gonads and has fused labioscrotal folds and a prominent phallus. The ultrasound scan reveals a uterus and tubes with possible ovaries. The karyotype is 46,XX. How do you proceed now?

The infant is a virilized female. If there is no history of maternal androgen ingestion or virilization, the infant has one of three forms of CAH. Of these, 21-hydroxylase deficiency is most common and is confirmed by finding an elevated serum level of 17-OHP. In 11-beta-hydroxylase deficiency, 11-deoxycortisol is elevated, whereas 17-hydroxypregnenolone and dehydroepiandrosterone (DHEA) are elevated in 3-beta-hydroxysteroid dehydrogenase deficiency. The baseline levels are usually diagnostic but can be confirmed by an ACTH stimulation test. The electrolyte disturbances seen with such disorders do not usually occur until 8 to 14 days of life; however, plasma renin activity is elevated earlier and should be measured as a marker of salt wasting. Screening of newborns for CAH with measurement of a 17-OHP level is now mandated in all 50 of the United States and in many countries throughout the world.

25. An undervirilized male represents a more complex diagnostic dilemma. In an infant with palpable gonads, no müllerian structures, and a 46,XY karyotype, how do you proceed?

Defects in testosterone synthesis include three enzyme blocks common to the adrenal and testicular pathways (StAR defect, 3-beta-hydroxysteroid dehydrogenase deficiency, and 17-alpha-hydroxylase deficiency). Enzyme blocks are diagnosed with ACTH stimulation testing and measurement of steroid precursors. Infants with StAR defects have no measurable precursors but show high levels of ACTH and a low cortisol response. Infants with 3-beta-hydroxysteroid dehydrogenase deficiency have elevated levels of 17-hydroxypregnenolone and DHEA. Patients with 17-alpha-hydroxylase deficiency have elevated levels of progesterone, desoxycorticosterone, and corticosterone, with associated hypertension (Fig. 42-3).

26. Discuss the two remaining defects that involve deficiencies of testicular, but not adrenal, enzymes.

The two remaining defects in testosterone synthesis involve deficiencies of specific testicular rather than adrenal enzymes: 17,20-lyase and 17-beta-hydroxysteroid dehydrogenase. Thus they are not associated with elevations of ACTH or electrolyte disturbances. Both deficiencies are diagnosed by measuring the precursor response to administration of human chorionic gonadotropin (hCG). Infants with 17,20-lyase deficiency have elevated levels of 17-hydroxypregnenolone and 17-OHP, whereas infants with 17-beta-hydroxysteroid dehydrogenase deficiency have elevated levels of DHEA and androstenedione.

27. What other possibilities should be investigated?

Infants with Leydig cell hypoplasia have low levels of testosterone before and after hCG stimulation but normal adrenal function. Testicular biopsy reveals normal seminiferous tubules and Sertoli cells but absent or few Leydig cells.

Stimulation with hCG also allows measurement of the testosterone-to-DHT ratio. If the ratio is elevated, 5-alpha-reductase deficiency should be suspected and may be confirmed by cultures of genital skin fibroblasts.

Finally, normal testosterone levels with no abnormalities in ACTH and hCG test results lead to the diagnosis of partial androgen insensitivity (androgen receptor defects). The diagnosis is made by demonstrating abnormal androgen binding in cultures of genital skin fibroblasts in a research laboratory or by molecular analysis.

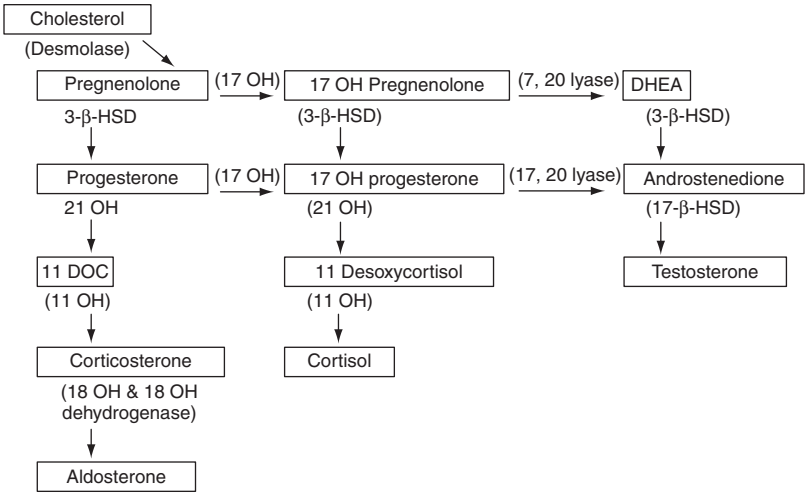

Figure 42-3. Testosterone synthesis pathway. DHEA, Dihydroepiandrostenedione; DOC, desoxycortisol; HSD, hydroxysteroid dehydrogenase.

28. What is complete androgen insensitivity?

The androgen receptor, encoded on the X chromosome, binds testosterone and, more avidly, DHT. Androgen insensitivity results from abnormalities of the androgen receptor. Complete androgen resistance occurs with a frequency of 1 in 20,000 to 1 in 64,000 XY individuals.

29. How do infants with complete androgen insensitivity present?

Complete androgen insensitivity (testicular feminization) rarely manifests as ambiguity in the newborn period or early childhood. Unless the testes have descended and are palpable in the labia majora, affected infants appear as phenotypically normal females.

Affected children grow as normal females until puberty. They feminize with normal breast development at puberty because high levels of testosterone are aromatized to estrogen, but they have no pubic or axillary hair and no menses. Because they produce MIF, they lack müllerian duct structures. Wolffian duct structures are also rudimentary or absent because these patients lack normal testosterone receptors. Gender identity is usually female. Patients come to medical attention because of primary amenorrhea. The diagnosis is therefore frequently made when patients are in their middle to late teens.

30. When should intraabdominal testicular tissue be removed?

The intraabdominal testes of androgen insensitivity or XY gonadal dysgenesis are at risk for malignancy (up to 20% in some series), particularly after the onset of puberty. Timing of gonadectomy is debated. Because the risk of malignancy is low until puberty, some clinicians prefer to leave the gonads intact until spontaneous pubertal development; however, because carcinoma in situ has been found in prepubertal patients, other practitioners recommend early removal. If the testes are removed before puberty, estrogen therapy is necessary for normal pubertal progression. Because the upper section of the vagina is müllerian in origin, affected individuals may have shortened vaginas and require plastic surgical repair.

31. Summarize the physiologic results of 5-alpha-reductase deficiency.

Deficiency of 5-alpha-reductase impairs the conversion of testosterone to DHT and leads to incomplete virilization and differentiation of the external genitalia, which are dependent on the action of

DHT. The disorder is particularly well documented in large kindreds in the Dominican Republic and Gaza, in whom it is inherited as an autosomal recessive condition.

32. Describe the clinical picture in children with 5-alpha-reductase deficiency.

Male infants with 5-alpha-reductase deficiency are born with sexual ambiguity. External genitalia range from a penis with simple hypospadias to a blind vaginal pouch and clitoris-like phallus. The most common presentation is a urogenital sinus with a blind vaginal pouch. During puberty, affected boys undergo virilization; affected females are normal.

Traditionally, infants with 5-alpha-reductase deficiency were raised as females until puberty, then continued life as males, and, in some cases, achieved fertility. More recently, however, the condition has been recognized early in life, and affected males are now raised from infancy as boys.

33. What is an ovotesticular DSD "true hermaphrodite"?

Ovotesticular DSD, previously known as true hermaphroditism, is a disorder of gonadal differentiation in which individuals have both ovarian and testicular elements. Affected children may have bilateral ovotestes, an ovary or testis on one side with an ovotestis on the other, or an ovary on one side and testis on the other. Because the effects of MIF and testosterone on duct structures are ipsilateral and localized, internal duct development is often asymmetric. Thus, a fallopian tube and unicornuate uterus, with absent or vestigial male duct structures, may develop on the side without testicular elements, whereas an epididymis, vas deferens, and seminal vesicles without müllerian structures may develop on the side with testicular elements. The genitalia may be male, female, or ambiguous, depending on the amount of functioning testicular tissue.

34. Why is a multidisciplinary team necessary in approaching an infant with sexual ambiguity?

Sexual ambiguity is a complex issue. An accurate diagnosis is essential and may take some time. Sex of assignment must be based not only on the underlying diagnosis and karyotype but also on the potential for adult sexual function, fertility, and psychological health. For these reasons, input from several specialties, including endocrinology, genetics, neonatology, psychology, urology, and an ethicist, is important. All members of the team must communicate adequately with each other. Parents must fully understand the medical recommendation for sex assignment and required therapy. They must wholeheartedly agree and support the assigned sex to avoid ambivalence, which can lead to gender confusion and psychological trauma for the child.

35. How is the decision about sex assignment made?

Exogenous and endogenous hormones are clearly important, as is the appearance of the genitalia. The decision about sex assignment must be carefully made, taking into consideration each "level" of sex determination. Sex assignment also depends on fetal sex hormone exposure, the potential for adult sexual function, and psychological and cultural considerations. It is vital that parents completely understand and support the decision because ambivalence about sex of rearing may result in gender confusion and psychological trauma.

36. After the cause of sexual ambiguity has been determined in an infant, what factors should be considered in assigning a sex of rearing?

Arriving at a precise diagnosis provides the treating team an understanding of potential risks and benefits of either sex assignment. For example, in poorly virilized males, the difference in outcomes among children with defects in testosterone synthesis, complete androgen insensitivity, and 5-alpha-reductase deficiency is enormous. A child with defective synthesis of testosterone may be raised male or female, depending on other factors; a child with complete androgen insensitivity should be raised female; and a boy with 5-alpha-reductase deficiency usually is raised male. Yet children affected by any of the three conditions have 46,XY karyotypes.

37. What other factors must be considered?

- What is the potential for unambiguous genital appearance?
- What is the potential for normal sexual function?
- Is there a potential for fertility?
- What was the in utero hormone exposure, with particular reference to exposure of the developing brain to excess androgen?
- What are the factors likely to affect gender identity and psychological health?
- Phallic size, urethral position, vaginal anatomy, and the presence or absence of müllerian or wolffian duct structures, as well as gonadal characteristics and karyotype, must all be considered.
- Parental backgrounds and expectations, broader family dynamics, social factors, and ethnic or cultural influences also must be considered.

38. To which gender are virilized females usually assigned?

Virilized females are usually assigned a female sex. They have normal ovaries as well as müllerian structures and, with surgical correction and steroid replacement, can have normal sexual function and achieve fertility. However, severely virilized females should be assigned a male sex.

39. How is sex assignment determined in undervirilized males?

Undervirilized males are often infertile, and sex assignment has usually been based on phallic size. Because a stretched penile length of 2.5 cm is 2.5 SD below the mean, an infant with a phallus smaller than 2.5 cm may be assigned a female sex of rearing. However, phallic size (penis or clitoris) has been challenged as a major factor in decisions of gender assignment. Adult social and fulfilling sexual function should be the primary goals of gender assignment. If male sex assignment is contemplated, a trial of depot testosterone (25 mg every 3-4 weeks) for 1 to 3 months indicates whether phallic growth is possible.

40. Summarize the factors that determine sex assignment in patients with gonadal dysgenesis.

In patients with gonadal dysgenesis and Y chromosomal material, gonadectomy is necessary, and fertility is not possible. Internal duct structure is also frequently deranged. Small phallic size usually leads to a female sex assignment.

41. How is sex assignment determined in ovotesticular DSD?

True hermaphrodites who have a unilateral ovary and müllerian structures may have spontaneous puberty and normal fertility and may be raised as females. External genital size and structure may allow male assignment, but more commonly, external genitalia are poorly virilized, and affected infants are assigned a female sex.

42. What principles should be kept in mind when sex assignments are made?

We have much to learn about gender identity and must consider which decisions may be made later than previously thought (e.g., surgery). Some surgical interventions are cosmetic, and some affected patients have expressed the wish to make the decisions in adolescence or adulthood. This field challenges many of our perceptions of sex and gender and our role as physicians. Although the infant with genital ambiguity presents a medical and social emergency, decisions should be made carefully, cautiously, and with all necessary biochemical and anatomic information available. Most important, the multidisciplinary team approach must involve the parents in an open and honest discussion of the options. In the end, it is the parents who come first in decision making on sex assignment.

BIBLIOGRAPHY

Brown J, Warne G: Practical management of the intersex infant, *J Pediatr Endocrinol Metab* 18:3–23, 2005.

Douglas G, Axelrad ME, Brandt ML et al: Guidelines for evaluating and managing children born with disorders of sexual development, *Pediatr Ann* 41:4, 2012.

Eugenides J: *Middlesex* [novel], New York, 2003, Picador.

Goodall J: Helping a child to understand her own testicular feminization, *Lancet* 337:33–35, 1991.

Houk CP, Lee PA: Intersexed states: diagnosis and management, *Endocrinol Metab Clin North Am* 34:791–810, 2005.

Jasso N, Boussin L, Knebelmann B, et al: Anti-müllerian hormone and intersex states, *Trends Endocrinol Metab* 2: 227–233, 1991.

Kaplan S: *Clinical Pediatric Endocrinology*, Saunders: Philadelphia, 1990.

Lee PA, Houk CP, Ahmed SF, Hughes IA: Consensus statement on management of intersex disorders, *Pediatrics* 118: e488–e500, 2006.

Low Y, Hutson JM: Murdoch Children's Research Institute Sex Study Group: rules for clinical diagnosis in babies with ambiguous genitalia, *J Paediatr Child Health* 39:406–413, 2003.

McGillivray BC: The newborn with ambiguous genitalia, *Semin Perinatol* 16:365–368, 1992.

Mieszczak J, Houk CP, Lee PA, et al: Assignment of the sex of rearing in the neonate with a disorder of sex development, *Curr Opin Pediatr* 21:541–547, 2009.

Meyers-Seifer CH, Charest NJ: Diagnosis and management of patients with ambiguous genitalia, *Semin Perinatol* 16: 332–339, 1992.

Mulaikal RM, Migeon CJ, Rock JA, et al: Fertility rates in female patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency, *N Engl J Med* 316:178–182, 1987.

Pagona R: Diagnostic approach to the newborn with ambiguous genitalia, *Pediatr Clin North Am* 34:1019–1031, 1987.

Penny R: Ambiguous genitalia, *Am J Dis Child* 144:753, 1990.

Prader Von A, et al: Der genitalbefund beim Pseudohermaproditismus femininus des kongenitalen adrenogenitalen Syndroms. Morphologie, Hausfigkeit, Entwicklung und Vererbung der verschiedenen Genitalformen, *Helv. Pediatr. Acta* 9:231–248, 1954.

Rangecroft L: British Association of Paediatric Surgeons working party on the surgical management of children born with ambiguous genitalia: surgical management of ambiguous genitalia, *Arch Dis Child* 88:799–801, 2003.

Thigpen AE, Davis DL, Gautier T, et al: Brief report: the molecular basis of steroid 5 alpha-reductase deficiency in a large Dominican kindred, *N Engl J Med* 327:1216–1219, 1992.

Warne GL, Kanumakala S: Molecular endocrinology of sex differentiation, *Semin Reprod Med* 20:169–180, 2002.

Zucker KJ, et al: Psychosexual development of women with congenital adrenal hyperplasia, *Horm Behav* 30:300–31, 1996.

DISORDERS OF PUBERTY

Scott A. Clements and Sharon H. Travers

CHAPTER 43

1. What physiologic events initiate puberty?

Reactivation of the hypothalamic-pituitary-gonadal axis initiates puberty. Several neurotransmitters, including kisspeptin, stimulate the hypothalamic secretion of gonadotropin-releasing hormone (GnRH) in pulses during sleep and eventually during waking hours as well. GnRH pulses stimulate the pituitary gland to secrete pulses of gonadotropins, luteinizing hormone (LH), and follicle-stimulating hormone (FSH), of which there is an LH predominance. In response to the increased secretion of gonadotropins, increased secretion of gonadal hormones leads to the progressive development of secondary sexual characteristics and gametogenesis. In both sexes, puberty requires maturation of gonadal function and increased secretion of adrenal androgens.

2. How is pubertal development measured?

Sexual maturity is determined by physical examination and is described in a scale devised by John Tanner in 1969 (Table 43-1). Because of the distinct actions of adrenal androgens and gonadal steroids, it is important to distinguish between pubic hair and breast development in girls and between pubic hair and testicular development in boys. In all cases, Tanner stage I is prepubertal and Tanner stage V is complete maturation. In addition to the physical examination, the tools to assess pubertal development may include determination of bone age, growth velocity, growth pattern, and specific endocrine studies.

TABLE 43-1. TANNER STAGES OF PUBERTAL DEVELOPMENT

STAGE	CHARACTERISTICS	CHARACTERISTICS
	Girls: Breast Development	**Girls: Pubic Hair Development**
I.	Prepubertal; elevation of papilla only	Prepubertal; no pubic hair
II.	Breast buds are noted or palpable; enlargement of areola	Sparse growth of long, straight, or slightly curly, minimally pigmented hair, mainly of labia
III.	Further enlargement of breast and areola, with no separation of their contours	Considerably darker and coarser hair spreading over mons pubis
IV.	Projection of areola and papilla to form secondary mound above level of breast	Thick, adult-type hair that does not yet spread to medial surface of thighs
V.	Adult contour breast with projection of papilla only	Hair adult in type and distributed in classic inverse triangle
	Boys: Genital Development	**Boys: Pubic Hair Development**
I.	Prepubertal; testicular length < 2.5 cm	Prepubertal; no pubic hair
II.	Testes > 2.5 cm in longest diameter, scrotum thinning and reddening	Sparse growth of slightly pigmented, slightly curly pubic hair, mainly at base of penis
III.	Growth of penis in width and length and further growth of testes	Thicker, curlier hair, spread to mons pubis
IV.	Penis further larger, with enlarged testes; darker scrotal skin color	Adult-type hair that does not yet spread to medial surface of thighs
V.	Genitalia adult in size and shape	Adult-type hair spread to medial thighs

Data from Marshall WE, Tanner JM: Variations in the pattern of pubertal changes in girls. *Arch Dis Child* 44:291–303, 1969; Variations in the pattern of pubertal changes in boys. *Arch Dis Child* 45:13–23, 1970.

3. What is adrenarche?

Adrenarche refers to the time during puberty when the adrenal glands increase their production and secretion of adrenal androgens. Plasma concentrations of dehydroepiandrosterone (DHEA) and DHEA-sulfate (DHEA-S), the most important adrenal androgens, begin to increase in children by approximately 6 to 8 years. However, the signs of adrenarche, such as pubic hair, axillary hair, acne, and body odor do not typically occur until early puberty to midpuberty. The control of adrenal androgen secretion is not clearly understood, but it appears to be separate from GnRH and the gonadotropins.

4. What controls the pubertal growth spurt?

In both boys and girls, the pubertal growth spurt is primarily controlled by the gonadal steroid estrogen. In both sexes, gonadal (and adrenal) androgens are aromatized to estrogens. Estrogens augment growth hormone (GH) and insulin-like growth factor I (IGF-I) secretion. Estrogens also suppress osteoclast activity and prolong the life span of osteoblasts and osteocytes. Androgens have a small independent role in maintenance of adequate bone mineral density. At the end of puberty, linear growth is nearly complete as a result of the effects of gonadal steroids on skeletal maturation and epiphyseal fusion.

5. What is the normal pattern of puberty in boys?

The mean age of puberty onset in boys is 11.8 years, with a range of 9 to 14 years. Black boys may start puberty as early as 8 years of age. The first evidence of puberty in the majority of boys is enlargement of the testes to a volume greater than 4 mL or a length greater than 2.5 cm. It is not until midpuberty, when testosterone levels are rapidly rising, that boys experience voice change, axillary hair, facial hair, and the peak growth spurt. Spermatogenesis is mature at a mean age of 13.3 years.

6. What is the normal pattern of puberty in girls?

Girls normally begin puberty between age 8 and 13 years (mean age: 10.4 years for white girls, 9.8 years for Hispanic girls, and 9.5 years for black girls). The initial pubertal event is typically the appearance of breast buds, although a small percentage of girls will develop pubic hair first. In an even smaller percentage of girls, menstrual cycling may appear first. Initial breast development often occurs asymmetrically and should not be of concern. Breast development is primarily under the control of estrogens secreted by the ovaries, whereas growth of pubic hair and axillary hair results mainly from adrenal androgens. Unlike in boys, the pubertal growth spurt in girls occurs at the onset of puberty. Menarche usually occurs 18 to 24 months after the onset of breast development (mean age: 12.5 years). Although most girls have reached about 97.5% of their maximum height potential at menarche, this can vary considerably. Consequently, age of menarche is not necessarily a good predictor of final adult height.

7. What constitutes sexual precocity in boys and girls?

Precocious puberty is defined as pubertal development occurring below the limits of age set for normal onset of puberty. In girls, this is puberty before 8 years in white girls, 6.6 years in black girls, and 6.8 years in Hispanic girls. For boys, precocious puberty is development occurring before 9 years in white and Hispanic boys and 8 years in black boys. Girls showing signs of puberty between 6 and 8 years often have a benign, slowly progressing form that requires no intervention. Consequently, evaluation and treatment of girls who start puberty between 6 and 8 years should depend on factors such as family history, rapidity of development, the presence of central nervous system (CNS) symptoms, and family concern. Girls who are short and start puberty between 6 and 8 years may also benefit from evaluation. In children who present with early pubertal signs, precocious puberty must be distinguished from normal variants of puberty, such as benign premature thelarche and benign premature adrenarche.

8. Which two common benign conditions in girls are often confused with precocious puberty?

Benign premature thelarche is defined as isolated breast development in girls without other signs of puberty such as linear growth acceleration and signs of adrenarche, such as pubic hair, axillary hair,

body odor, and acne. Benign premature adrenarche, which occurs in both sexes, is defined as the early development of pubic hair with or without axillary hair, body odor, and acne. There are no signs of gonadarche in benign premature adrenarche; girls have no breast development, and boys have no testicular enlargement.

9. How is benign premature thelarche diagnosed?

Several characteristics of benign premature thelarche distinguish it from the breast development that occurs in precocious puberty. First of all, benign premature thelarche is most common in girls who are either less than 2 years old or between 6 and 8 years of age. Girls with benign premature thelarche may have a history of slowly progressing breast development or waxing and waning of breast size. Growth rate and bone age are not accelerated, and on physical examination, the breast tissue rarely develops beyond Tanner stage II or III. GnRH stimulation may provoke an FSH-predominant response, as opposed to the typical LH-predominant response seen in true central puberty.

10. How is benign premature thelarche treated?

The natural course of benign premature thelarche is for the breast tissue to regress or fail to progress. Because of the benign nature of this condition, treatment is not necessary except for reassurance and follow-up. Follow-up is critical because premature thelarche occasionally is the first sign of what later becomes apparent as central precocious puberty. Measurement of breast tissue diameter during the clinic visit can be helpful for comparison at a later visit.

11. How is benign premature adrenarche diagnosed?

Benign premature adrenarche is caused by early secretion of the adrenal androgens, primarily DHEA and DHEA-S, and is suspected when clinical signs of androgen exposure are present, such as pubic hair, axillary hair, acne, or body odor. A child who has benign premature adrenarche and Tanner stage II pubic hair development will have adrenal androgen values similar to those normally found in a pubertal child at the same stage of development. As in premature thelarche, growth rate and bone age are typically not accelerated. If signs of puberty are rapidly progressing, or if there is evidence of increased linear growth and advanced bone age, measurement of androgens (DHEA-S, androstenedione, and testosterone) is performed to evaluate for a serious virilizing disorder such as congenital adrenal hyperplasia (CAH) or an adrenal tumor. A 17-hydroxyprogesterone (17-OHP) level may also be drawn as the first screen for late-onset CAH.

12. How is benign premature adrenarche treated?

The natural course of benign premature adrenarche is a slow progression of the signs of adrenarche with no effect on the timing of true puberty. Because pubic hair development may be the first sign of puberty, follow-up is necessary to evaluate for evidence of gonadarche (i.e., breast development or testicular enlargement).

13. What clinical findings are associated with precocious puberty?

Precocious puberty, regardless of the cause, is associated with accelerated linear growth and skeletal maturation secondary to elevated sex steroid levels. Children with precocious puberty are often tall for their age during childhood. However, skeletal maturation may become more advanced than stature, thus leading to premature fusion of the epiphyseal growth plates and a compromised final adult height. In addition to the physical consequences of early puberty, social and psychological aspects may need to be considered.

14. In which sex is precocity more prevalent?

Precocious puberty predominantly affects girls. The disparity in overall prevalence of precocity is explained by the large numbers of girls with central idiopathic precocity, a condition that is less common in boys. At least 80% of all precocious puberty in girls is central idiopathic. The prevalence of organic causes of precocious puberty (CNS lesions, gonadal tumors, and specific underlying diseases) is similar in both sexes.

15. How is the diagnosis of precocious puberty made?

The diagnosis of precocious puberty requires the appearance of the physical signs of puberty before the defined age limits, as discussed previously. In both boys and girls, a complete history should be taken, with careful consideration of any exposure to exogenous steroids or estrogen receptor agonists (e.g., lavender oil or tea tree oil), onset of pubertal signs and rate of progression, presence or history of CNS abnormalities, and pubertal history of other family members. Height measurements should be plotted on a growth chart to determine growth pattern and growth velocity. A physical examination should be performed with a focus on Tanner staging, the presence of café-au-lait spots, and neurologic signs. One of the early steps in evaluating a child with early pubertal development should be to obtain a radiograph of the left hand and wrist to determine skeletal maturity (bone age). If the bone age is advanced, further evaluation is warranted. Sex steroid levels should be measured, especially in boys, because testosterone levels higher than the prepubertal range ($>$ 10 ng/dL) confirm pubertal status. For girls, estradiol measurements are less reliable indicators of puberty, because most commercial assays are not sufficiently specific or sensitive to demonstrate an increase during early puberty.

16. How does GnRH-dependent (central) precocious puberty differ from GnRH-independent (peripheral) precocious puberty?

It is usually difficult to distinguish GnRH-dependent (central) from GnRH-independent (peripheral) precocity on physical examination. Central precocious puberty involves activation of the GnRH pulse generator, an increase in gonadotropin secretion, and a resultant increase in the production of sex steroids. Consequently, the sequence of hormonal and physical events in central precocious puberty is identical to the progression of normal puberty. Peripheral precocious puberty occurs independent of gonadotropin secretion. Although the possible causes of peripheral precocious puberty are more numerous (Box 43-1), central precocity accounts for most cases.

BOX 43-1. CAUSES OF PRECOCIOUS PUBERTY

Central (GnRH-Dependent)
Idiopathic true precocious puberty
CNS tumors (hamartomas, hypothalamic tumors)
CNS disorders (meningitis, encephalitis, hydrocephalus, trauma, abscesses, cysts, granulomas, radiation therapy)

Peripheral (GnRH-Independent)
Males
Human chorionic gonadotropin (hCG)-secreting tumors (CNS, liver)
CAH (21-hydroxylase, 3-beta-hydroxysteroid dehydrogenase, or 11-hydroxylase deficiency)
Adrenal tumors
Leydig cell testicular tumors
Familial gonadotropin-independent Leydig cell maturation (testotoxicosis)
McCune-Albright syndrome (polyostotic fibrous dysplasia)

Females
Follicular cysts
Ovarian tumors
Adrenal tumors
CAH (21-hydroxylase, 3-beta-hydroxysteroid dehydrogenase, or 11-hydroxylase deficiency)
Exogenous estrogen
McCune-Albright syndrome (polyostotic fibrous dysplasia)

CAH, Congenital adrenal hyperplasia; *CNS,* central nervous system; *GnRH,* gonadotropin-releasing hormone; *hCG,* human chorionic gonadotropin.

17. What is the single most important test in establishing a specific diagnosis?

The GnRH stimulation test is the single most important test to determine whether gonadotropin responses are consistent with central or peripheral precocious puberty. The diagnosis of central precocious puberty is made by demonstrating a pubertal LH response to GnRH. Measurement of random gonadotropins is typically not helpful because of overlap between prepubertal and early pubertal values until at least Tanner stage III. If random gonadotropins are measured, a third-generation assay is recommended because it has better discrimination between prepubertal and pubertal levels.

18. When is a magnetic resonance imaging (MRI) study of the brain indicated?

In girls younger than 6 years, and boys of any age, who are diagnosed with central precocious puberty, an MRI study of the brain should be performed to evaluate for CNS lesions. It is unlikely that an abnormality will be found in girls between 6 and 8 years old, so the need for an MRI in this age group should be assessed individually.

19. How is central idiopathic precocious puberty treated?

Children with central precocious puberty can be treated with GnRH agonists, such as leuprolide. GnRH agonists disrupt the endogenous pulsatile GnRH, thus downregulating pituitary GnRH receptors and decreasing gonadotropin secretion. The most important clinical criteria for GnRH agonist therapy is documented progression of pubertal development, which is based on the recognition that many girls with central precocious puberty, especially those between 6 and 8 years old, have a slowly progressive form and reach a normal adult height without intervention. With GnRH agonist treatment, physical changes of puberty regress or cease to progress, and linear growth slows to a prepubertal rate. Pubic hair and axillary hair typically do not regress. Projected final adult height often increases because of a slowing of skeletal maturation. GnRH agonists are generally given as a monthly depot intramuscular injection, and side effects are rare. There is also a small hydrogel implant that can be placed under the skin that releases a GnRH agonist (histrelin) continuously for about 1 year. Children receiving GnRH agonists should be monitored every 4 to 6 months to evaluate for pubertal regression or treatment failure. After discontinuation of therapy, pubertal progression resumes, and normal rates of fertility are expected.

20. What findings suggest peripheral precocious puberty?

In peripheral precocious puberty, basal serum FSH and LH levels are low, and the LH response to GnRH stimulation is suppressed by feedback inhibition of the hypothalamic-pituitary axis by the autonomously secreted gonadal steroids. Girls with ovarian cysts, ovarian tumors, or McCune-Albright syndrome generally have signs of estrogen excess such as breast development and possibly vaginal bleeding. In these girls, a pelvic ultrasound scan is diagnostic, and estradiol levels are markedly elevated. In boys with peripheral precocious puberty, laboratory studies should include serum testosterone, human chorionic gonadotropin (hCG), DHEA-S, and androstenedione levels. Elevated adrenal androgens could indicate an adrenal tumor or CAH. To evaluate further for CAH, measurement of baseline or adrenocorticotropic hormone (ACTH)-stimulated steroid intermediates (e.g., 17-OHP, 17-hydroxypregnenolone, 11-deoxycortisol) is recommended. Asymmetric or unilateral enlargement of the testes suggests a Leydig cell tumor.

21. What is McCune-Albright syndrome?

McCune-Albright syndrome is a triad consisting of GnRH-independent precocious puberty, irregular (coast-of-Maine) café-au-lait lesions, and polyostotic fibrous dysplasia, but only two of these are necessary to make the diagnosis. It can affect both sexes, but it is seen infrequently in boys. In girls, breast development and vaginal bleeding occur with sporadic increases in estradiol from autonomously functioning ovarian cysts. Serum gonadotropin levels are low, and GnRH testing elicits a prepubertal response. With time, however, increased estradiol may mature the hypothalamus, thus leading to true central GnRH-dependent precocity. The syndrome can be associated with other endocrine dysfunction including hyperthyroidism, GH excess, and hypercortisolism. In affected tissues, there is an activating mutation in the gene that encodes the alpha-subunit of Gs, the G-protein that

stimulates adenylate cyclase. Endocrine cells with this mutation have autonomous hyperfunction and secrete excess amounts of their respective hormones.

22. How is McCune-Albright syndrome treated?

Girls with McCune-Albright syndrome are generally treated with a medication that inhibits the aromatization of testosterone to estrogen, such as letrozole. Other trials have been performed using tamoxifen, an estrogen receptor antagonist. In boys, treatment consists of either inhibiting androgen production with ketoconazole or using a combination of an aromatase inhibitor that blocks the conversion of androgen to estrogen and an antiandrogen that antagonizes the effects of androgens at the receptor.

23. What is testotoxicosis, and how is it treated?

Familial testotoxicosis is a male-limited autosomal dominant, gonadotropin-independent form of male precocious puberty. Boys with this condition begin to develop true precocity with bilateral testicular and phallic enlargement and growth acceleration by 4 years of age. Serum testosterone levels are high, but serum gonadotropins are low, and GnRH testing shows a prepubertal response. By midadolescence to adulthood, GnRH stimulation demonstrates a more typical LH-predominant pubertal response. This condition is caused by an activating mutation in the gene encoding the LH receptor. The mutant LH receptors in the testes are constitutively overactive and do not require LH binding for their activity, but they produce testosterone autonomously. Treatment options are the same as for boys with McCune-Albright syndrome. If central precocious puberty has been induced, GnRH agonists may also be part of the treatment plan.

24. How does 21-hydroxylase-deficient CAH manifest?

The most common adrenogenital syndrome is 21-hydroxylase deficiency. Girls usually develop virilization in utero, resulting in a degree of sexual ambiguity. They are discovered at birth and should be diagnosed within the first few days of life by finding a greatly elevated serum 17-OHP level. Boys have normally formed genitalia and therefore are not identified on physical examination at birth. In the more common salt-losing form of the disease, boys present with vomiting, shock, and electrolyte disturbances at 7 to 10 days. Fortunately, with neonatal screening for 21-hydroxylase deficiency, boys are being diagnosed before they develop life-threatening electrolyte abnormalities. Small subsets of affected boys and girls do not waste salt and may present in early or late childhood with signs of adrenarche, such as pubic hair, acne, body odor, acceleration of linear growth, and skeletal maturation.

25. How is CAH treated?

Treatment for all forms of CAH is directed at reducing serum androgen levels by replacing glucocorticoids to reduce pituitary secretion of ACTH. Insufficient glucocorticoid replacement leads to a compromise in final adult height secondary to advanced skeletal maturation, whereas excessive glucocorticoid replacement leads to short stature because of the direct effects of glucocorticoids on bone. Serum markers, growth curves, and bone age radiographs must be carefully monitored. In salt-wasting CAH, the mineralocorticoid fludrocortisone is also required. This is not necessary in the non–salt-wasting forms of CAH.

26. What is the association of hypothyroidism with precocity?

Rarely, severe primary hypothyroidism may cause breast development in girls and increased testicular size in boys. The exact mechanism is unclear, but one theory is that thyroid-stimulating hormone (TSH), which is elevated in primary hypothyroidism, can stimulate the FSH receptor on the gonads. These children generally present with growth deceleration as typically seen in hypothyroidism, rather than growth acceleration as typically seen in precocious puberty. Bone age is usually delayed. Thyroid hormone replacement results in regression of pubertal changes, and no other therapy is necessary.

27. What is adolescent gynecomastia? When and how should it be treated?

Normal boys often have either unilateral or bilateral breast enlargement during puberty. Breast development generally starts during early puberty and resolves within 2 years. The cause of gynecomastia is not clearly understood, but it may be related to an elevated ratio of estradiol to testosterone. Treatment consists primarily of reassurance and support. However, if resolution does not occur or if breast enlargement is excessive, surgery may be warranted. Surgery should be avoided until puberty is complete, to avoid recurrence of gynecomastia. Pathologic conditions associated with gynecomastia include Klinefelter syndrome and various other testosterone-deficient states. Tea tree oils and lavender oils have been associated with gynecomastia in boys. Some prescription medications, such as atypical antipsychotics, may cause gynecomastia and galactorrhea. Evidence is mixed regarding the connection of cannabis abuse and gynecomastia.

28. At what age does failure to enter puberty necessitate investigation?

Delayed puberty should be evaluated if there are no pubertal signs by 13 years in girls and by 14 years in boys. An abnormality in the pubertal axis may also manifest as a lack of normal pubertal progression, which is defined as more than 4 years between the first signs of puberty and menarche in girls or more than 5 years for completion of genital growth in boys.

29. How do body habitus and lifestyle influence the timing of puberty?

There is a high incidence of delayed puberty and primary amenorrhea in girls with anorexia nervosa and in girls who are highly competitive athletes. These girls have hypogonadotropic hypogonadism that appears to be directly related to their low body fat. Girls with a low body mass index (BMI) also have low circulating leptin and estrogen levels and are more likely to have delayed puberty or menstrual dysfunction. Leptin is a hormone produced by adipocytes that is important in hypothalamic-pituitary-gonadal feedback signaling. Leptin deficiency has been associated with both anorexia and obesity, with hypogonadotropic hypogonadism present in both phenotypes. There appears to be a minimum leptin level that is permissive for pubertal development. When severely underweight girls improve their BMI, puberty ensues and progresses to menarche appropriately.

30. What is constitutional growth delay, and how does it affect puberty?

Constitutional growth delay is the most common cause of delayed puberty. Children with this growth pattern generally have a fall-off in their linear growth within the first 2 years of life. After this, growth returns to normal, but along a lower growth channel than would be expected for parental heights. Skeletal maturation is also delayed, and the onset of puberty is commensurate with bone age rather than chronologic age. For example, a 14-year-old boy with a bone age of 11 years will start puberty when his bone age is closer to 11.5 to 12 years. This delay in puberty postpones the pubertal growth spurt and closure of growth plates, so that the child continues to grow after his or her peers have reached their final adult height. A key feature of this growth pattern is normal linear growth after 2 years of age. There is often a family history of "late bloomers."

31. When is hypogonadism diagnosed?

Functional or permanent hypogonadism should be considered when there are no signs of puberty and bone age has advanced to beyond the normal ages for puberty to start. A eunuchoid body habitus is often evident in children with abnormally delayed puberty; a decreased ratio of upper to lower body and a long arm span characterize this habitus. As a rule, serum gonadotropin levels are measured first to determine whether the child has hypogonadotropic hypogonadism (gonadotropin deficiency) or hypergonadotropic hypogonadism (primary gonadal failure). If a child's bone age is less than the normal age for puberty to start, gonadotropin levels are not a reliable means of making an accurate diagnosis.

32. What are the causes of hypogonadotropic hypogonadism?

Normal or suppressed gonadotropins indicate a failure of the pituitary to stimulate gonadal steroid production. Chronic illness, malnutrition, excessive exercise, or anorexia can cause a functional

deficiency of gonadotropins that reverses when the underlying condition improves. Hyperprolactinemia can also manifest as delayed puberty, and only 50% of the time will there be a history of galactorrhea. Other endocrinopathies such as diabetes mellitus, glucocorticoid excess, and hypothyroidism can cause hypogonadotropic hypogonadism when untreated. Permanent gonadotropin deficiency is suspected if these conditions are ruled out and gonadotropin levels are low. Gonadotropin deficiency may be associated with other pituitary deficiencies from conditions such as septo-optic dysplasia, tumors such as craniopharyngioma, trauma, empty sella syndrome, pituitary dysgenesis, Rathke pouch cysts, or cranial irradiation. Various syndromes, such as Kallmann syndrome, Laurence-Moon-Bardet-Biedl syndrome, and Prader-Willi syndrome are also associated with gonadotropin deficiency, so a karyotype or other genetic testing may be necessary. Drug abuse, particularly with heroin or methadone, has been associated with hypogonadotropic hypogonadism. Isolated gonadotropin deficiency (i.e., occurring without another pituitary deficiency) is often difficult to diagnose because hormonal tests do not absolutely distinguish whether a child can produce enough gonadotropins or whether he or she simply has very delayed puberty. If gonadotropin deficiency cannot be clearly distinguished from delayed puberty, a short course of sex steroids can be given. Patients with constitutional delay often enter puberty after such an intervention. If spontaneous puberty does not occur after this treatment or after a second course, the diagnosis of gonadotropin deficiency may be made.

33. What is Kallmann syndrome?

Kallmann syndrome is one of a class of disorders referred to as idiopathic hypogonadotropic hypogonadism or idiopathic hypothalamic hypogonadism. It occurs as frequently as 1 in 10,000 boys and 1 in 50,000 girls. The classic form is characterized by hypogonadotropic hypogonadism with hyposmia or anosmia. It is caused by aplasia or hypoplasia of the olfactory bulbs and is associated with hypoplasia or aplasia of other structures of the rhinencephalon (e.g., cleft lip or cleft palate, congenital deafness, and color blindness). Undescended testes and gynecomastia are common.

34. What are the causes of hypergonadotropic hypogonadism?

Elevated gonadotropin levels indicate a failure of the gonads to produce enough sex steroids to suppress the hypothalamic-pituitary axis. These levels are diagnostic for gonadal failure at two periods of time: before 2 to 3 years of age and after the bone age is at or beyond the normal age for puberty to start. If hypergonadotropic hypogonadism is diagnosed, a karyotype should be performed. Potential causes include the following:

- Variants of ovarian or testicular dysgenesis: Turner syndrome, Klinefelter syndrome, Noonan syndrome, pure XX or XY gonadal dysgenesis
- Gonadal toxins: chemotherapy (particularly alkylating agents), radiation treatment
- Androgen enzymatic defects: 17-alpha-hydroxylase deficiency in the genetic male or female, 17-ketosteroid reductase deficiency in the genetic male
- Complete or partial androgen insensitivity syndrome
- Galactosemia (in girls only)
- Other miscellaneous disorders: infections, gonadal autoimmunity, vanishing testes, trauma, surgery, torsion

35. What is Klinefelter syndrome?

Klinefelter syndrome is the most common cause of testicular failure and results from at least one extra X chromosome; the most common karyotype is 47,XXY. The incidence is 1 in 1000 male births, and eunuchoid body proportions are often present from early childhood. Associated features include gynecomastia, tall stature, small testes, low testosterone, and elevated serum gonadotropins. Learning disabilities and behavioral problems may also be present. Many boys with Klinefelter syndrome have spontaneous onset of pubic hair growth, but they fail to progress completely through puberty. Testosterone supplementation is indicated in many boys over time, and in some it is required to initiate puberty. Leydig cell function (testosterone production) is variable, but seminiferous tubular function is almost always abnormal. This generally results in infertility, and many of these men are not diagnosed until they are seen in an infertility clinic.

36. How is gonadal failure evaluated in girls?

In girls with gonadal failure (indicated by elevated gonadotropin levels) and no apparent cause, a karyotype evaluation should be performed because Turner syndrome is the most likely explanation. 46,XX gonadal dysgenesis can also occur and may be inherited as an autosomal recessive trait. A karyotype would also identify 46,XY gonadal dysgenesis in a phenotypic female who is actually a genetic male. In this condition, there is complete lack of testicular development, and consequently, except for the absence of gonads, normal female sexual differentiation occurs. If the karyotype is normal, then the evaluation should look for causes of premature ovarian failure, as discussed in question 34.

37. What is Turner syndrome?

Any consideration of pubertal delay in girls must include the possibility of Turner syndrome. An absent or structurally abnormal second X chromosome characterizes Turner syndrome. The incidence of Turner syndrome is approximately 1 in 2000 live female births. However, the chromosomal abnormality is actually more common than this. Ninety percent or more of conceptuses with Turner syndrome do not survive beyond 28 weeks of gestation, and the 45,XO karyotype occurs in 1 out of 15 miscarriages. In the absence of a second functional X chromosome, oocyte degeneration is accelerated, leaving fibrotic streaks in place of normal ovaries. Because of primary gonadal failure, serum gonadotropin levels rise and are elevated at birth and again at the normal time of puberty.

38. What are the clinical findings in patients with Turner syndrome?

See Table 43-2.

39. What features are present in the history of an adolescent with pubertal delay?

The history should include questions regarding the presence of chronic illnesses, autoimmune disorders, nutritional disorders, exercise history, galactorrhea, sense of smell, family history of infertility, and timing of puberty in parents and siblings. Weight gain or loss should also be noted.

40. What features are present in the physical examination of an adolescent with pubertal delay?

Physical examination should include measurement of arm span and upper-to-lower-segment ratio. Eunuchoid body proportions occur early in patients with Klinefelter syndrome and late in those with other forms of hypogonadism. Signs of any chronic illness, malnutrition, anorexia, hypothyroidism, glucocorticoid excess, or features of Turner syndrome (girls) or Klinefelter syndrome (boys) should be noted. A careful examination should be made for any signs of puberty, such as pubic hair, axillary hair, acne, testicular size (boys), penile length (boys), or breast development (girls). Pubic hair may represent only adrenal androgen production. Testicular volume greater than 4 mL (length $>$ 2.5 cm) indicates gonadotropin stimulation. Breast development and vaginal maturity are indicators of estrogen exposure. In addition, visual fields and olfaction should be evaluated (80% of boys with Kallmann syndrome have a reduced, or absent, sense of smell). The growth chart should be analyzed to evaluate for short stature and to determine whether linear growth has been normal.

41. How are radiographic studies and gonadotropin levels helpful in the diagnosis of pubertal delay?

Assessment of bone age is critical in determining biologic age and the time of expected pubertal development. If linear growth is normal and the bone age is less than the normal age for pubertal onset, the diagnosis is likely to be constitutional growth delay. If linear growth is impaired and the bone age is delayed, it may be necessary to evaluate GH or thyroid function. If the bone age has advanced beyond the age for normal puberty, gonadotropin levels are helpful to distinguish between gonadotropin deficiency and primary gonadal failure.

42. What other laboratory tests may be needed?

Additional laboratory studies may include a chemistry panel, complete blood cell count, celiac testing, thyroid function tests, estradiol (girls), testosterone (boys), and prolactin levels. If gonadotropins are

TABLE 43–2. CLINICAL FINDINGS IN PATIENTS WITH TURNER SYNDROME

PRIMARY DEFECTS	SECONDARY FEATURES	INCIDENCE (%)
Physical Features		
Skeletal growth disturbances	Short stature	100
	Short neck	40
	Abnormal upper-to-lower segment ratio	97
	Cubitus valgus	47
	Short metacarpals	37
	Madelung deformity	7.5
	Scoliosis	12.5
	Genu valgum	35
	Characteristic facies with micrognathia	60
	High arched palate	36
Lymphatic obstruction	Webbed neck	25
	Low posterior hairline	42
	Rotated ears	Common
	Edema of hands and feet	22
	Severe nail dysplasia	13
	Characteristic dermatoglyphics	35
Unknown factors	Strabismus	17.5
	Ptosis	11
	Multiple pigmented nevi	26
Physiologic Features		
Skeletal growth disturbances	Growth failure	100
	Otitis media	73
Germ cell chromosomal defects	Gonadal failure	96
	Infertility	99.9
	Gonadoblastoma	4
Unknown factors: embryogenic	Cardiovascular anomalies	55
	Hypertension	7
	Renal and renovascular anomalies	39
Unknown factors: metabolic	Hashimoto thyroiditis	34
	Hypothyroidism	10
	Alopecia	2
	Vitiligo	2
	Gastrointestinal disorders	2.5
	Carbohydrate intolerance	40

Data from Hall J, Gilchrist D: Turner syndrome and its variants. *Pediatr Clin North Am* 37:1421, 1990.

elevated, chromosome analysis is indicated for both genders to evaluate for Turner syndrome (girls) or Klinefelter syndrome (boys). In the case of low gonadotropin levels, olfactory testing and cranial MRI are recommended.

43. How is delayed puberty managed?

The treatment of delayed puberty depends on the underlying cause. If the delayed pubertal development is secondary to anorexia, hypothyroidism, or illness, treatment of these underlying conditions results in spontaneous onset of puberty. Puberty also begins spontaneously, albeit late, in constitutional growth delay, so reassurance alone to the patient and family may be sufficient. In some patients with constitutional growth delay, treatment to induce puberty may be appropriate. For boys, a 4- to 6-month course of low-dose depot testosterone (50–100 mg intramuscularly every 4 weeks)

can be offered if the bone age is at least 11 to 12 years. This treatment results in some early virilization, without adversely affecting final adult height. Spontaneous puberty usually begins, as evident by testicular enlargement, 3 to 6 months after the end of the testosterone course. For girls, a 3-month course of low-dose estradiol (0.25–0.5 mg orally every day) can be offered if the bone age is at least 10 to 11 years. Therapy is then stopped, and physical changes are evaluated. Withdrawal bleeding is unusual after one course of estrogen therapy, but it may occur with subsequent courses.

44. What is the treatment of hypogonadism in boys?

In boys with hypogonadotropic hypogonadism for whom fertility is not an immediate issue, and in all boys with primary hypogonadism, long-term testosterone therapy is required. While the patient is growing, careful attention must be paid to growth velocity and bone age. Most commonly, depot testosterone esters (enanthate or cypionate) are used in 25- to 50-mg doses intramuscularly every 3 to 4 weeks for the first 1 to 2 years of therapy. By the second or third year of therapy, the dose is raised to 50 to 100 mg every 3 to 4 weeks. The adult maintenance dose is 200 to 300 mg every 3 to 4 weeks. Alternatively, a transdermic testosterone patch or gel may be used.

45. How is estrogen treatment given for girls with hypogonadism?

Estrogen replacement therapy in hypogonadal girls is begun with very low-dose unopposed estrogen treatment for 12 to 18 months. The dosage used varies depending on height projections and individual response. Following this period of unopposed estrogen, progesterone is added for 10 to 12 days of each month, and eventually a birth control pill may be prescribed. Progesterone therapy is necessary to counteract the effects of estrogen on the uterus; unopposed estrogen can cause endometrial hyperplasia and carcinoma. Replacement of gonadal steroids in both sexes is also necessary for normal bone mineralization and to prevent osteoporosis.

46. How is Turner syndrome treated?

Approximately 10% to 20% of girls with Turner syndrome have some ovarian function at puberty that allows for early breast development. A small percentage of this group will have normal periods, and an even smaller percentage ($<$ 1% of all girls with Turner syndrome) will actually be fertile. Most girls with Turner syndrome require exogenous gonadal steroid replacement. Low-dose unopposed estradiol, followed by cycling with estrogen and progestin, allows for development of secondary sexual characteristics. The timing for initiation of estrogen is critical and should be decided by an endocrinologist through discussions with each patient and her family. This decision depends on several factors, including height and psychosocial factors. The short stature of girls with Turner syndrome is treated with GH. Final adult height in girls with Turner syndrome is related to when GH is initiated, with better outcomes in girls who are started at a younger age. Consequently, early diagnosis of Turner syndrome is essential.

47. What is amenorrhea?

A girl who has not had menarche by 16 years of age, or within 4 years after the onset of puberty, is considered to have primary amenorrhea. Secondary amenorrhea is diagnosed if more than 6 months have elapsed since the last menstrual period, or if more than the length of three previous cycles has elapsed with no menstrual bleeding.

48. How do you evaluate a girl with amenorrhea?

To sort out the many causes of amenorrhea, it is helpful to distinguish girls who produce sufficient estrogen from those who do not by performing a progesterone challenge. Girls who are producing estrogen will have withdrawal bleeding after 5 to 10 days of oral progesterone, whereas those who are estrogen-deficient will have very little or no bleeding. Those who do not have bleeding should be evaluated for hypogonadism as described previously. However, in two situations, girls who have sufficient estrogen will not have withdrawal bleeding: obstruction of the cervix and absence of the cervix or uterus. In Rokitansky syndrome, maldevelopment of the müllerian structures leads to an absent or hypoplastic uterus or cervix (or both). Complete androgen insensitivity syndrome (testicular

feminization) in a genetic male results in a phenotypic female who has normal breast development because of the aromatization of testosterone to estrogen. The production of antimüllerian hormone in patients with androgen insensitivity syndrome leads to regression of the müllerian structures and thus the absence of a uterus. The absence of a cervix is a diagnostic finding in both Rokitansky syndrome and complete androgen insensitivity syndrome. Consequently, a pelvic examination should be considered in all girls who present with amenorrhea, especially primary amenorrhea.

49. What causes amenorrhea in girls who are producing estrogen and do not have an outflow tract obstruction?

Amenorrhea in girls who are producing normal or even elevated amounts of estrogen is a manifestation of anovulatory cycles. Irregular menses may also be a sign of chronic anovulation given that estrogen production, unopposed by progesterone, leads to endometrial hyperplasia and intermittent shedding. Because menarche is normally followed by a period of anovulatory cycles and irregular menses, many adolescents with a pathologic cause of amenorrhea may be missed. Consequently, it is important to evaluate all girls who do not have regular menses by 3 years after menarche. The most common cause of chronic anovulation is polycystic ovarian syndrome (PCOS), a disorder characterized by increased ovarian androgen production. The clinical presentation of PCOS varies and may include amenorrhea, oligomenorrhea, dysfunctional uterine bleeding, hirsutism, acne, or obesity. PCOS is further discussed in a separate chapter.

KEY POINTS 1: DISORDERS OF PUBERTY

1. Central precocious puberty occurs more frequently in girls than boys. Boys with central precocity, however, have a much higher incidence of underlying central nervous system disorders.
2. Precocious puberty must be distinguished from normal variants of early development, such as benign premature thelarche and benign premature adrenarche.
3. The most useful diagnostic test to evaluate precocious puberty is a gonadotropin-releasing hormone stimulation test.
4. Children with delayed puberty and normal linear growth will most likely have constitutional growth delay.
5. Bone age assessment is the first step in evaluating a child with delayed puberty.
6. After it has been determined that a child has abnormally delayed puberty, gonadotropin levels should be obtained. If gonadotropins are elevated, obtaining chromosomes is generally the next step.

BIBLIOGRAPHY

Bondy CA: Care of girls and women with Turner syndrome: a guideline of the Turner Syndrome Study Group, *J Clin Endocrinol Metab* 92:10–25, 2007.

Carel JC, et al: Consensus statement on the use of gonadotropin-releasing hormone analogs in children, *Pediatrics* 123: e752–e762, 2009.

Durbin KL: Van Wyk and Grumbach syndrome: an unusual case and review of the literature, *J Pediatr Adolesc Gynecol* 24:1083–3188, 2011.

Eugster EA: Peripheral precocious puberty: causes and current management, *Horm Res* 71(Suppl 1):64–67, 2009.

Eugster EA, Clarke W, Kletter GB, et al: Efficacy and safety of histrelin subdermal implant in children with central precocious puberty: a multicenter trial, *J Clin Endocrinol Metab* 92:1697–1704, 2007.

Gordon CM: Functional hypothalamic amenorrhea, *N Engl J Med* 363:365–371, 2010.

Grumbach MM, Styne DM: Puberty: ontogeny, neuroendocrinology, physiology, and disorders. In JD Wilson, Foster DW, Kronenberg HM, Larsen PR, editors: *Williams textbook of endocrinology,* ed 9, Saunders: Philadelphia, pp 1509–1625.

Grumbach MM: The neuroendocrinology of human puberty revisited, *Horm Res* 57(suppl 2):2–14, 2002.

Herman-Giddens ME, Slora EJ, Wasserman RC, et al: Secondary sexual characteristics and menses in young girls seen in office practice: a study from the Pediatric Research in Office Setting network, *Pediatrics* 99:505–512, 1997.

Ibanez L, Virdis R, Potau N, et al: Natural history of premature pubarche and auxological study, *J Clin Endocrinol Metab* 74:254, 1992.
Kaplan S, Grumbach M: Pathophysiology and treatment of sexual precocity, *J Clin Endocrinol Metab* 71:785, 1990.
Kaplowitz: PB Link between body fat and the timing of puberty, *Pediatrics* 121(Suppl 3):208–217, 2008.
Kulin H, Rester E: Managing the patient with a delay in pubertal development, *Endocrinologist* 2:231, 1992.
Layman LC: Hypogonadotropic hypogonadism, *Endocrinol Metab Clin North Am* 36:283–296, 2007.
Levine M: The McCune-Albright syndrome: the whys and wherefores of abnormal signal transduction, *N Engl J Med* 325:1738–1740, 1991.
Magiakou MA, Manousaki D, Papadaki M, et al: The efficacy and safety of gonadotropin-releasing hormone analog treatment in childhood and adolescence: a single center, long-term follow-up study, *J Clin Endocrinol Metab* 95: 109–117, 2010.
Matejek N, Weimann E, Witzel C, et al: Hypoleptinaemia in patients with anorexia nervosa and in elite gymnasts with anorexia athletica, *Int J Sports Med* 20:451–456, 1999.
Nathan BM, Palmert MR: Regulation and disorders of pubertal timing, *Endocrinol Metab Clin North Am* 34:617–641, 2005.
Nelson LM: Clinical practice: primary ovarian insufficiency, *N Engl J Med* 360:606–614, 2009.
Oakley AE, Clifton DK, Steiner RA: Kisspeptin signaling in the brain, *Endocr Rev* 30:713–743, 2009.
Pasquino AM, Pucarelli I, Accardo F, et al: Long-term observation of 87 girls with idiopathic central precocious puberty treated with gonadotropin releasing hormone analogs: impact on adult height, body mass index, bone mineral content, and reproductive function, *J Clin Endocrinol Metab* 93:190–195, 2008.
Root AW: Precocious puberty, *Pediatr Rev* 21:10–19, 2000.
Rosenfield R: Diagnosis and management of delayed puberty, *J Clin Endocrinol Metab* 70:559–562, 1990.
Wu T, Mendola P, Buck GM. Ethnic differences in the presence of secondary sex characteristics and menarche among US girls: the Third National Health and Nutrition Examination Survey, 1988–1994, *Pediatrics* 110:752–757, 2002.
Wheeler M, Styne DM: Diagnosis and management of precocious puberty, *Pediatr Clin North Am* 37:1255–1271, 1990.
Williams RM, Ward CE, Hughes IA: Premature adrenarche, *Arch Dis Child* 97:250–254, 2012.

CHAPTER 44

MALE HYPOGONADISM

Sky D. Graybill, and Robert A. Vigersky

1. What is male hypogonadism?

Male hypogonadism is the clinical and/or laboratory syndrome that results from a failure of the testis to work properly. The normal testis has two functions: synthesis and secretion of testosterone from the Leydig cells and production of sperm from the seminiferous tubules. Deficiency of one or both functions is termed *male hypogonadism*. This condition can result from a disruption at one or more levels of the hypothalamic-pituitary-gonadal axis. Depending on the stage of development, hypogonadism may have varied manifestations.

2. What are the manifestations of in utero hypogonadism?

In utero androgen deficiency leads to a female phenotype or ambiguous genitalia, most commonly caused by a block in the production of testosterone secondary to congenital testosterone biosynthetic enzyme defects. Rarely, peripheral tissues cannot respond normally to testosterone, thereby resulting in the androgen insensitivity syndromes of testicular feminization (complete) and Reifenstein's syndrome (incomplete). Other manifestations include micropenis, hypospadias, and cryptorchidism.

3. What are the manifestations of peripubertal hypogonadism?

Childhood androgen deficiency results in delayed, incomplete, or absent pubertal development. Common manifestations include the following:

- Eunuchoid proportions (ratio of pubis to vertex/pubis to floor is < 0.9 and/or arm span is > 5 cm more than height; this phenotype results from the delayed closure of the epiphyses)
- Small testes (< 20 mL or $< 4.5 \times 3.0$ cm)
- Decreased body hair
- Gynecomastia
- Reduced peak bone mass
- Reduced male musculature
- Persistently higher-pitched voice

4. What are the manifestations of hypogonadism in early adulthood?

In early adulthood, a decrease in sperm output (azoospermia or oligospermia) without deficient production of testosterone is common and results in male infertility; thus, infertility is a form of male hypogonadism. A decrease in production of testosterone in adulthood is usually accompanied by a decline in production of sperm. When it is not, the term *fertile eunuch* (eunuchoid proportions, low levels of luteinizing hormone [LH], low levels of testosterone, normal levels of follicle-stimulating hormone [FSH], and spermatogenesis) is appropriately applied. Libido and/or potency may be diminished.

5. What are the manifestations of hypogonadism in middle to late adulthood?

The most frequent circumstance in which adult hypogonadism occurs is in the middle-aged or senescent man complaining of decreased libido or potency. Semen analysis is rarely performed in these men because they are usually not concerned with fertility. Other findings may include osteoporosis, diminished androgen production, and small prostate. If the onset of hypogonadism is acute, the patient may experience hot flushes and sweats.

6. How is the production of testosterone normally regulated?

LH is episodically secreted from the anterior pituitary in response to pulses of gonadotropin-releasing hormone (GnRH), thus stimulating production of testosterone by Leydig cells. Once testosterone is secreted into the bloodstream, it is bound by sex hormone–binding globulin (SHBG) and albumin. The non–SHBG-bound (or "free") testosterone provides negative feedback to the hypothalamic-pituitary unit and thus inhibits output of LH. This classic endocrine feedback loop serves to maintain serum testosterone at a predetermined level; if serum testosterone falls below the set point, the pituitary is stimulated to secrete LH, which, in turn, stimulates testicular output of testosterone until serum levels return to the set point. Conversely, if serum testosterone rises above the set point, decreased output of LH results in decreased testicular output of testosterone until serum levels have declined to the set point. Although most automated total testosterone assays are reliable and are generally able to distinguish hypogonadal from eugonadal men, abnormalities in the SHBG level may give falsely low or high total testosterone levels. Equilibrium dialysis is the gold standard for measuring the free testosterone, but it is not commonly available and should be ordered to be performed only in a reliable reference laboratory. Liquid chromatography–mass spectrometry or gas chromatography–mass spectrometry is used by some reference laboratories to measure testosterone. This is a very accurate but expensive method. Analog methods for determining free testosterone are more widely available but are not accurate in the low ranges.

7. What are some conditions associated with decreased or increased serum SHBG levels?

Moderate obesity, nephrotic syndrome, hypothyroidism, and the use of certain medications (notably glucocorticoids and androgenic steroids) decrease SHBG levels and give a low total serum testosterone level, whereas aging, anticonvulsant use, estrogen use, herbal preparations for "prostate health" that contain plant-derived estrogens, hepatic cirrhosis, human immunodeficiency virus (HIV) infection, and hyperthyroidism may all increase SHBG and cause a high total level of testosterone.

8. How is sperm production normally regulated?

The regulation of sperm production is complex and less clearly understood than is the regulation of testosterone production. Both hormonal and nonhormonal factors are important. The Sertoli cells within the seminiferous tubules seem to play an important coordinating role. Sertoli cells respond to FSH by producing inhibin (secreted into the blood) and androgen-binding protein, transferrin, and other proteins (secreted into the seminiferous tubular lumen). Inhibin appears to inhibit the output of FSH from the pituitary gland, thus completing a feedback loop. In theory, if spermatogenesis declines, production of inhibin also should decline; thus the negative feedback effect on the pituitary would be reduced, leading to an increased output of FSH, which would then presumably stimulate spermatogenesis. However, not all aspects of this feedback loop (FSH-inhibin-spermatogenesis) have been verified experimentally. Moreover, spermatogenesis depends on intratesticular production of testosterone mediated by androgen receptors within Sertoli cells. Initiation of spermatogenesis during puberty requires both LH and FSH. However, reinitiation of the process if it is disrupted by exogenous factors (see the following) requires only LH (or human chorionic gonadotropin [hCG]), although FSH may be needed to produce a normal number of sperm.

9. What is the difference between primary and secondary hypogonadism?

Failure of testicular function may result from a defect either at the testis or at the hypothalamic-pituitary level. Testicular disorders leading to hypogonadism are termed *primary hypogonadism* (Fig. 44-1), whereas disorders of hypothalamic-pituitary function leading to hypogonadism are termed *secondary hypogonadism* (Fig. 44-2). This distinction has therapeutic implications. In men with secondary hypogonadism, fertility can generally be restored with appropriate hormonal treatment. Men with primary hypogonadism have fewer options and more limited success with improvement in fertility. In addition, the evaluation of secondary hypogonadism can reveal a pituitary mass or systemic illness as the underlying cause.

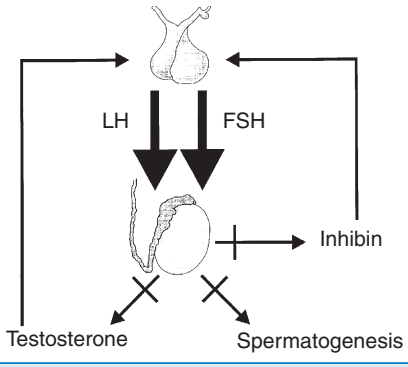

Figure 44-1. Primary hypogonadism. FSH, Follicle-stimulating hormone; LH, luteinizing hormone.

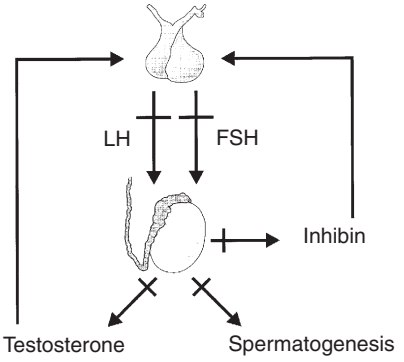

Figure 44-2. Secondary hypogonadism. FSH, Follicle-stimulating hormone; LH, luteinizing hormone.

10. What is the initial laboratory workup for hypogonadism?

Primary hypogonadism resulting from a testicular disorder leads to a decline in production of testosterone and sperm, a consequent decrease in the negative feedback effects on the pituitary, and a corresponding increase in serum levels of LH and FSH. Conversely, in secondary hypogonadism resulting from a hypothalamic-pituitary disorder, serum LH and FSH may be subnormal or "inappropriately" normal (explainable, in part, by decreased bioactivity) despite a low testosterone level. A subnormal sperm count and a normal testosterone level with a normal LH and elevated FSH suggest primary hypogonadism with a dysfunction of the seminiferous tubules and sperm production but intact Leydig cell function. An algorithm for the logical evaluation of hypogonadism is shown in Figure 44-3.

11. What are congenital causes of primary hypogonadism?

- Klinefelter's syndrome (47,XXY and mosaics)
- Microdeletions of azoospermia factor (AZF) regions of Yp telomere (15% of men with nonobstructive azoospermia; 5% to 10% of those with oligospermia)

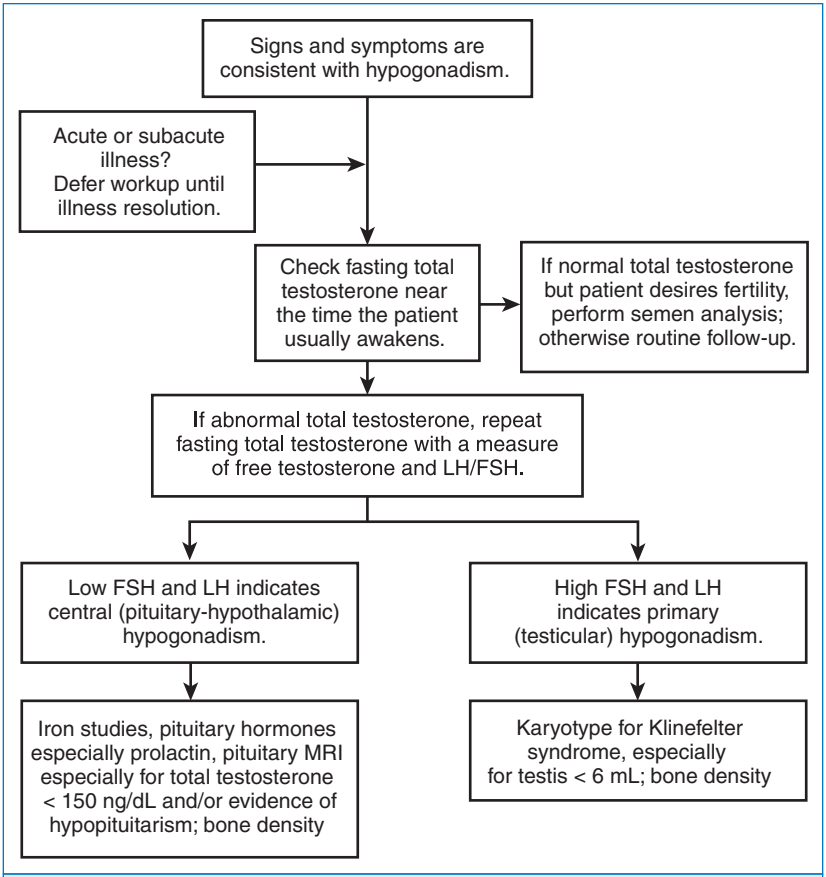

Figure 44-3. Initial workup for hypogonadism. FSH, Follicle-stimulating hormone; LH, luteinizing hormone.

- Cryptorchidism
- Myotonic dystrophy
- Testosterone biosynthetic enzyme deficiencies (3-beta-hydroxysteroid dehydrogenase, 17-alpha-hydroxylase, or 17-beta-hydroxysteroid dehydrogenase)
- Androgen receptor gene mutation (qualitative or quantitative)
- LH receptor mutations (male phenotype, if mild; female phenotype, if severe)

12. What are acquired causes of primary hypogonadism?

- Cancer therapy: chemotherapy (alkylating agents more than cisplatin and carboplatin) and radiation therapy (may be permanent with external radiation; usually transient with radioactive iodine)
- Drugs (e.g., ketoconazole, 5-alpha-reductase inhibitors)
- Testicular injury
- Hyperthyroidism
- Infiltrative disease (e.g., hemochromatosis)
- Infections (e.g., HIV [may be multifactorial], mumps orchitis)
- Systemic illness (e.g., uremia, cirrhosis); may be multifactorial

13. Is normal aging associated with primary hypogonadism?

Symptomatic hypogonadism, defined by at least three sexual symptoms and a low total testosterone (< 320 ng/dL) and/or low free testosterone (< 64 pg/mL) level, is present in about 2% of men between 40 and 79 years of age. When only biochemical criteria are used, the prevalence is higher (2%–6%) in that age range and 18% to 30% in men more than 70 years old. Multiple cross-sectional studies have noted that older men have mildly reduced levels of total serum testosterone but significantly reduced levels of free testosterone (because of a rise in SHBG with age) compared with younger men. This decline is associated with a rise in LH and FSH, a finding suggesting a primary gonadal cause. Studies have demonstrated an average 1% to 2% decline in total serum testosterone and an even greater reduction in free testosterone (because of elevations in SHBG) per year associated with normal aging. Further complicating the situation is the observation that there has been a population-level decrease in serum testosterone levels in men in the United States since the early 1990s.

14. What are the causes of secondary hypogonadism?

Any disease that affects the hypothalamic-pituitary axis can cause secondary hypogonadism. Involvement of the hypothalamus or pituitary stalk interferes with the secretion of GnRH or the ability of GnRH to communicate with the pituitary. Various anatomic lesions of the pituitary cause secondary hypogonadism by interfering with the release of LH and FSH. Such lesions include benign tumors and cysts, malignant tumors (both primary central nervous system tumors and metastatic tumors from distant sources), vascular aneurysms, infiltrative diseases (e.g., hemochromatosis), pituitary hemorrhage, and pituitary trauma. Certain inflammatory diseases (e.g., sarcoidosis and histiocytosis) can also affect the hypothalamus and pituitary and decrease testosterone production. Congenital disorders, in which output of LH and FSH is impaired, such as Kallmann's syndrome (see later), also lead to secondary hypogonadism. Both obesity and HIV/acquired immunodeficiency syndrome (AIDS) are associated with secondary hypogonadism as well. Drugs commonly used in the treatment of benign prostatic hypertrophy, the 5-alpha-reductase inhibitors finasteride and dutasteride, are among the iatrogenic causes of hypogonadism. Other drug-related causes include the use of narcotic analgesics and the abuse of anabolic steroids by athletes.

15. What assessment for congenital hypogonadotropic hypogonadism (CHH) should be done?

The sense of smell in the patient (and his relatives) should be assessed by direct questioning. A quantitative or semiquantitative method is olfactometry. In addition, magnetic resonance imaging (MRI) can be performed to assess the olfactory bulb. If the sense of smell is normal and there does not appear to be a syndromic form of CHH (i.e., Kallmann's syndrome), then the most common gene abnormalities are *GNRHR, KISS1R, GnRH1, TAC3,* and *TACR3.* If the sense of smell is decreased or absent in a man with CHH, then the diagnosis is Kallmann's syndrome. *KAL1* mutations occur in Kallmann's syndrome, especially in men with mirror movements (bimanual synkinesis), renal agenesis, and an X-linked pattern of inheritance. *FGFR1* mutations occur more often in patients with Kallmann's syndrome and midline abnormalities (e.g., cleft lip or palate, short metacarpals and/or metatarsals), but they can occur in normosmic CHH. *FGF8, PROK2,* or *PROKR2* mutations are more common in Kallmann's syndrome but can also occur in normosmic CHH.

16. What is the most common pituitary tumor in adults?

The most common pituitary tumor found in adults is a prolactin-secreting adenoma. These tumors primarily cause hypogonadism as a result of local destruction and compression, thus inhibiting the production and release of LH and FSH. Elevated prolactin levels can also interrupt secretion of GnRH, although this is usually of much less significance in men than is the mass effect.

17. How do other pituitary adenomas cause hypogonadism?

Pituitary adenomas that produce growth hormone (acromegaly) or adrenocorticotropic hormone (Cushing's disease) and nonfunctioning pituitary tumors may similarly cause secondary hypogonadism by their mass effects.

18. What clinical symptoms are seen in male hypogonadism?

Loss of the sperm-producing function of the testis leads to infertility, usually defined as failure of a normal female partner to conceive after 12 months of unprotected intercourse. Loss of the testosterone-producing function of the testis may lead to loss of libido and erectile dysfunction, as well as diminution of secondary sexual characteristics, such as facial and pubic hair, and decrease in testicular volume. Decreased production of testosterone also may cause more generalized symptoms, such as decreased muscle mass and strength, malaise, and fatigue. In boys who develop hypogonadism before sexual maturation, delay or absence of the onset of puberty is typical. Tender gynecomastia is frequently seen in hypogonadism. Numerous nonspecific symptoms are also commonly associated with hypogonadism, such as normochromic normocytic anemia, poor concentration, depressed mood, and increased body fat and body mass index.

19. What questions are most helpful in determining whether a man may have hypogonadism?

When the condition is associated with a low total or free testosterone level, the following questions are useful in establishing a diagnosis of clinical hypogonadism:

- How frequently have you awakened with a full erection in the past month?
- Are you able to get and keep an erection sufficient for sexual intercourse?
- How often do you think about sex?

20. How does hypogonadism affect bone architecture?

Osteoporosis is now a well-recognized result of both primary and secondary hypogonadism. Trabecular architecture (and bone strength) is even more severely disturbed than bone density in men with hypogonadism. Thus, it is not surprising that hypogonadism is found in up to 30% of men with vertebral fractures. Estradiol that is aromatized from testosterone may be the most important factor in preserving bone architecture and density in both men and women. However, androgen receptors are also found in bone and may explain the sexual dimorphism of bone density.

21. What laboratory tests help to confirm a suspected diagnosis of male hypogonadism?

The main functions of the testis, production of sperm and production of testosterone, are readily assessed by semen analysis and measurement of serum testosterone, respectively. Normal semen analysis values in men following 2 to 3 days of abstinence are 20 million sperm/mL and more than 60% motility of the sperm. Because sperm density is highly variable from day to day in all men, accurate assessment usually involves several semen analyses done with the same abstinence period each time. The best initial test for testosterone production is measurement of the fasting morning serum total testosterone level. Serum testosterone also varies considerably from moment to moment and from morning to night in response to LH secretion; again, several samples may be needed to establish an accurate measurement. In addition, most testosterone in serum is bound to plasma proteins, particularly SHBG; thus, in patients who have increased or decreased SHBG levels (see earlier) and in those men in whom plasma protein levels may be disrupted, measurement of the physiologically active "free" testosterone may prove informative. Bone density measurement using a dual-energy x-ray absorptiometry (DXA) scan may provide helpful baseline information and assist in deciding whether to provide androgen replacement therapy.

22. What other diagnostic tests are useful in defining the cause of male hypogonadism?

Additional diagnostic testing should be based on clinical suspicion and the results of preliminary testing. For example, in cases of secondary hypogonadism, measurement of serum prolactin and pituitary radiography, preferably MRI with gadolinium, should be done. Computed tomography (CT) of the sella turcica usually detects macroadenomas ($>$ 1.0 cm) but misses many clinically significant microadenomas and is therefore less preferable than MRI. Plain skull or sella turcica films are not adequate for diagnosis. Measurement of other pituitary hormones also may be appropriate to assess either possible tumoral hypersecretion (e.g., Cushing's disease, acromegaly) or tumor-related hypopituitarism. Visual

field testing is indicated if a macroadenoma is present or there is suprasellar extension. Similarly, the initial findings in primary hypogonadism may suggest additional tests. For example, small firm testes, gynecomastia, azoospermia, modestly reduced serum testosterone levels, and high levels of serum LH and FSH in a young man should lead to chromosome analysis to confirm a presumptive diagnosis of Klinefelter's syndrome. Measurement of serum estradiol levels may be helpful when feminization is prominent clinically, as in secondary hypogonadism related to production of estrogen by testicular or adrenal tumors. If infertility is the primary issue and no hormonal abnormality is found, genetic causes should be investigated. This includes testing for Y chromosome microdeletion syndromes. Testis biopsy rarely provides information that is useful in establishing a specific diagnosis, prognosis, or treatment.

23. What is a hermaphrodite?

Hermaphrodite refers to someone who has both ovarian and testicular elements in the body. These patients usually have a 46,XX or 46,XX/46,XY karyotype. Such individuals may have an ovary and a testis or an ovotestis. They most often have ambiguous genitalia.

24. What is a pseudohermaphrodite?

Pseudohermaphrodite refers to someone whose external genitalia are not consistent with his or her gonadal sex. A male pseudohermaphrodite, for example, has a 46,XY karyotype and testes but has either ambiguous genitalia or a complete female phenotype. Most often this results from genetic disorders of testosterone biosynthetic enzymes, the androgen receptor, or the 5-alpha-reductase enzyme; the severity of the phenotype depends on the severity of the genetic defect. A female pseudohermaphrodite, in contrast, has a 46,XX karyotype and ovaries but has ambiguous external genitalia. The most common cause of this is congenital adrenal hyperplasia, which results in virilization of the female fetus in utero.

25. How do you treat hypogonadism?

Testosterone deficiency is easily treated with testosterone replacement therapy (TRT) (Table 44-1). An alternative approach to TRT is oral clomiphene citrate, which blocks estrogen feedback on the hypothalamic-pituitary axis and thereby increases LH and FSH secretion, with a resultant increase in testosterone production. In general, the treatment goal for TRT in primary hypogonadism is to provide sufficient testosterone doses to normalize the serum LH, which may take normal to high-normal serum testosterone levels. For patients with secondary hypogonadism, the goal is a serum total testosterone level in the midnormal range. The treatment goal in elderly men is a low-normal to midnormal range serum testosterone without regard to the LH level.

There is currently considerable controversy over whether men with age-associated hypogonadism should be treated with TRT. Although some short-term studies have demonstrated treatment benefits, long-term large studies are lacking and are needed to clarify the criteria for treatment, as well as the risks and benefits associated with TRT in this population. One study in older men with hypogonadism and impaired mobility was stopped early because of an increase in cardiovascular events. Some older men with testosterone deficiency are unconcerned about sexual function and may not desire TRT. In testosterone-deficient men of any age, osteopenia or osteoporosis and/or reduced hematopoiesis may be indications for TRT even in the absence of decreased libido or erectile dysfunction, although low bone mass may be more safely improved with a bisphosphonate. Testosterone preparations are currently designated as schedule III drugs by the Anabolic Steroid Control Act because of their potential for abuse by athletes and others.

26. What are the potential adverse effects of TRT?

Gynecomastia and acne are rare symptoms that may occur in the first few months after initiating TRT; these side effects may resolve with continued treatment, although temporary dose reductions may be helpful. Abnormalities of liver function tests are uncommon with currently used injectable and transdermal preparations, but they can be seen with seldom-used oral preparations. A testosterone-induced increase in hematocrit is common, especially when testosterone injections are used, although clinically significant polycythemia is quite rare unless the drug is being abused. TRT may also precipitate or worsen sleep apnea; marked increases in hematocrit may be a clue to this side effect. Skin reactions are commonly seen in patients using the transdermal patch and are occasionally, but much less frequently, seen

TABLE 44-1. TESTOSTERONE REPLACEMENT THERAPY

FORMULATION	REGIMEN	ADVANTAGES	DISADVANTAGES
Testosterone Gel	Apply 20-100mg daily to clean, dry, intact skin but not to genitals	Good skin tolerability; flexibility of dosing; ease of application	Potential of transfer to others by direct skin-to-skin contact; occasion skin irritation; moderately high DHT levels
Testosterone Topical Solution	Apply 30 mg to each axilla daily	Good skin tolerability; flexibility of dosing; uses an applicator	Potential of transfer to others by direct skin-to-skin contact; occasion skin irritation
Testosterone Patch	Apply 2-6 mg daily to clean, dry, intact skin but not to genitals	Ease of application	Frequent skin irritation at the application site
Testosterone enanthate or cypionate in oil	75-100 mg IM per week or 50-400 mg IM every 2-4 weeks	Relatively inexpensive; flexibility of dosing	IM injection resulting in supraphysiologic serum T levels which then decline into the hypogonadal range
Testosterone Pellets	150-450 mg subcutaneous implant every 3-6 months	Ensures compliance	Requires surgical incision for insertions; pellets may extrude spontaneously
Buccal Testosterone	Apply 30 mg every 12 hours to gums above the incisor teeth		Gum-related adverse events in 16%

DHT, Dihydrotestosterone; IM, intramuscular(ly).

with the gels. In boys who have not yet gone through puberty, the rapid increase in serum testosterone after initial treatment may lead to considerable psychological difficulties and physically aggressive behavior; initiating treatment with smaller doses may be helpful. TRT has no adverse effect on lipid profiles compared with eugonadal men, but overtreatment can lead to several lipid abnormalities, including decreases in high-density lipoprotein cholesterol level. There does not appear to be a significant increase in cardiovascular disease associated with physiologic TRT, and some studies have even suggested a treatment benefit. However, patients with class III or IV heart failure should be given TRT cautiously.

27. Does TRT affect the prostate in older men?

In older men, TRT effects on the prostate must be considered, including the possibility of precipitating urinary retention secondary to testosterone-induced prostate enlargement. Short-term studies have not shown any histologic or gene expression effects of TRT. However, prostate volume increases with long-term TRT to a level comparable to eugonadal men without any significant associated increases in symptoms, urine flow rates, or residual volumes. Individual men may experience voiding symptoms along with this enlargement, which they should be advised to monitor. Although TRT with a scrotal patch or gel (but not a nonscrotal patch) increases dihydrotestosterone more than testosterone and it is the former that stimulates the prostate, it is advisable to perform a digital rectal examination (DRE) of the prostate and monitor prostate-specific antigen (PSA) in middle-aged and older men before and annually while they are receiving any TRT. Although no compelling evidence indicates that TRT causes prostate carcinoma, the potential for testosterone stimulation of occult prostate carcinoma growth exists. Men with an elevated PSA level or an abnormal DRE should be evaluated further, potentially including a prostate biopsy, before initiation of TRT.

28. How does one treat deficient sperm production in primary hypogonadism?

In men with primary hypogonadism, as manifested by elevated levels of serum FSH, there seems to be no effective pharmacologic treatment for increasing the sperm count. Anatomic lesions, such

as varicoceles and ejaculatory duct obstructions, can be corrected surgically, but improvement in spermatogenesis may not result. If one plans to use a medication that is known to cause hypogonadism (e.g., cancer chemotherapeutic agents), it may be desirable to cryopreserve semen specimens before treatment, provided that treatment is not unduly delayed.

29. How does one treat deficient sperm production in secondary hypogonadism?

The outlook is much less pessimistic with secondary hypogonadism, particularly if the condition developed after puberty. Treatment with gonadotropins (hCG with or without added FSH) may be successful in restoring production of sperm, as well as testosterone. The pretreatment size of the testis is often a clue to prognosis; larger testis size is associated with a better outcome. Production of testosterone and sperm in men with secondary hypogonadism also may be enhanced with pulsatile administration of GnRH via a portable infusion pump, provided that the pituitary retains the capability to make gonadotropins. Treatment with gonadotropins or GnRH tends to be both costly and prolonged.

30. What alternative is available to men with hypogonadism who do not respond to therapy with an increase in spermatogenesis?

In men with primary or secondary hypogonadism who have not responded to specific therapy when appropriate and who have preservation of some germ cells in either ejaculate or testis, intracytoplasmic sperm injection (ICSI) may offer some hope, although at a high financial cost. The prognosis for successful ICSI is dependent on the site and extent of microdeletions on the Y chromosome. If microdeletions are found, the patient should be counseled about the possibility of transmittal to his male child. Microsurgical testicular sperm extraction (micro-TESE) is a surgical method for harvesting sperm. Fertility options that should be discussed also include donor sperm and adoption.

31. What are the advantages and disadvantages of the various forms of androgen replacement therapy?

The available forms of testosterone treatment are shown in Table 44-1.

32. What parameters should be monitored in men receiving TRT?

The following should be determined at baseline, at 3 months after initiation of TRT, and then followed at least yearly, once the patient is stabilized:

- Hematocrit and hemoglobin
- Prostate size by digital rectal examination
- Serum PSA
- Liver function tests
- Development of gynecomastia, acne, or edema
- Serum testosterone levels in all forms of treatment
- Serum dihydrotestosterone levels in patients receiving scrotal patches or gel
- Development of or worsening of sleep apnea
- Bone mineral density (at baseline and at 1- to 2-yearly intervals)

33. In what conditions is testosterone therapy absolutely or relatively contraindicated?

Absolute contraindications:

- Carcinoma of the prostate
- Uncontrolled obstructive sleep apnea
- Polycythemia vera
- Symptomatic and/or severe benign prostatic hypertrophy
- Breast carcinoma

Relative contraindications:

- Prostate nodule that has not been biopsied
- Elevated serum PSA level
- Class III or IV congestive heart failure

WEBSITES

1. The Endocrine Society's clinical guidelines: http://www.endo-society.org/guidelines/final/upload/FINAL-Androgens-in-Men-Standalone.pdf
2. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hypogonadism in adult male patients: 2002 update: https://www.aace.com/files/hypogonadism.pdf
3. Medline Plus article on hypogonadotropic hypogonadism: http://www.nlm.nih.gov/medlineplus/ency/article/000390.htm
4. Hormone health article on rare endocrine disorders: adrenal insufficiency, hormone imbalance, and more: http://www.hormone.org/public/other.cfm
5. Mayo Clinic article on male hypogonadism: http://www.mayoclinic.com/health/male-hypogonadism/DS00300

KEY POINTS 1: MALE HYPOGONADISM

1. The manifestations of hypogonadism vary depending on the patient's stage of development when the hypogonadism occurs.
2. A reduction in testicular volume to less than 20 mL is the most common manifestation of hypogonadism and is seen in nearly all cases of long-standing hypogonadism.
3. Classify hypogonadism as primary (a disorder at the level of the testes) or secondary (a disorder at the level of the hypothalamus or pituitary).
4. Therapeutic goals are generally to correct testosterone to the midnormal range by topical preparations or by injection.
5. Monitor patients receiving testosterone replacement therapy for polycythemia, sleep apnea, gynecomastia, psychological difficulties, prostate symptoms and size, and increases in prostate-specific antigen.

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BIBLIOGRAPHY

Adamopoulos DA, Lawrence DM, Vassilopoulos P, et al: Pituitary-testicular relationships in mumps orchitis and other viral infections, *BMJ* 1:1177, 1978.

Armory JK, Wang C, Swerdloff RS, et al: The effect of 5 reductase inhibition with dutasteride and finasteride on semen parameters and serum hormones in healthy men, *J Clin Endocrinol Metab* 92:1659–1665, 2007.

Araujo AB, Esche GR, Kupelian V, et al: Prevalence of symptomatic androgen deficiency in men, *J Clin Endocrinol Metab* 92:4241–4247, 2007.

Bagatell CJ, Bremner WJ: Androgens in men: uses and abuses, *N Engl J Med* 334:707–714, 1996.

Baker HWG, Burger HF, DeKretser DM, et al: Changes in the pituitary-testicular system with age, *Clin Endocrinol* 5:349, 1976.

Basaria S, Coviello AD, Travison TG, et al. Adverse events associated with testosterone administration, *N Engl J Med* 363:109–122, 2010.
Bannister P, Handley T, Chapman C, Losowsky MS: Hypogonadism in chronic liver disease: impaired release of luteinising hormone, *BMJ* 293:1191, 1986.
Bhasin S, Cunningham GR, Hayes FJ, et al: Testosterone therapy in adult men with androgen deficiency syndromes: an Endocrine Society Clinical practice guideline, *J Clin Endocrinol Metab* 91:1995–2010, 2006.
Bhasin S. Approach to the infertile man, *J Clin Endocrinol Metab* 92:1995–2004, 2007.
Byrne M, Nieschlag E. Testosterone replacement therapy in male hypogonadism, *J Endocrinol Invest* 26:481–489, 2003.
Castro-Magana M, Bronsther B, Angulo MA: Genetic forms of male hypogonadism, *Urology* 35:195, 1990.
Dada R, Gupta NP, Kucheria K: Molecular screening for Yq microdeletion in men with idiopathic oligospermia and azoospermia, *J Biosci* 28:163–168, 2003.
Gambineri A, Pelusi C, Vicennati V, Pagotto U, Pasquali R. Testosterone in ageing men, *Expert Opin Investig Drugs* 10: 477–492, 2001.
Griffin JL, Wilson JD: The syndromes of androgen resistance, *N Engl J Med* 302:198, 1980.
Gromoll J, Eiholzer U, Nieschlag E, Simoni M: Male hypogonadism caused by homozygous deletion of exon 10 of the luteinizing hormone (LH) receptor: differential action of human chorionic gonadotropin, *J Clin Endocrinol Metab* 85:2281, 2000.
Guo CY, Jones TH, Eastell R: Treatment of isolated hypogonadotropic hypogonadism effect on bone mineral density and bone turnover, *J Clin Endocrinol Metab* 82:658–665, 1997.
Harman SM, Metter EJ, Tobin JD, et al: Longitudinal effects of aging on serum total and free testosterone levels in healthy men: Baltimore Longitudinal Study of Aging, *J Clin Endocrinol Metab* 86:724–731, 2001.
Hayes FJ, Seminara SB, Crowley WF: Hypogonadotropic hypogonadism, *Endocrinol Metab Clin North Am* 27:739–763, 1998.
Hopps CV, Mielnik A. Goldstein M, et al: Detection of sperm in men with Y chromosome microdeletions on the AZFa, AZFb and AZFc regions, *Hum Reprod* 18:1660–1665, 2003.
Hsueh WA, Hsu TH, Federman DD: Endocrine features of Klinefelter's syndrome, *Medicine* 57:447, 1978.
Kalyani RR, Gavini S, Dobs AS: Male hypogonadism in systemic disease, *Endocrinol Metab Clin North Am* 36:333–348, 2007.
Kidd GS, Glass AR, Vigersky RA: The hypothalamic-pituitary-testicular axis in thyrotoxicosis, *J Clin Endocrinol Metab* 48:798–802, 1979.
Layman LC: Hypogonadotropic hypogonadism, *Endocrinol Metab Clin North Am* 36:283–296, 2007.
Lee PA, O'Dea LS: Primary and secondary testicular insufficiency, *Pediatr Clin North Am* 37:1359, 1990.
Lieblich JM, Rogol AD, White BJ, Rosen SW: Syndrome of anosmia with hypogonadotropic hypogonadism (Kallman syndrome): clinical and laboratory studies in 23 cases, *Am J Med* 73:506, 1982.
Marks LS, Mazer NA, Mostaghel E, et al: Effect of testosterone replacement therapy on prostate tissue in men with late-onset hypogonadism, *JAMA* 296:2351–2361, 2006.
Matsumoto AM, Bremner WJ: Endocrinology of the hypothalamic-pituitary-testicular axis with particular reference to the hormonal control of spermatogenesis, *Baillieres Clin Endocrinol Metab* 1:71, 1987.
Rhoden EL, Morgentaler A: Risks of testosterone-replacement therapy and recommendations for monitoring, *N Engl J Med* 350:482–492, 2004.
Schwartz ID, Root AW: The Klinefelter syndrome of testicular dysgenesis, *Endocrinol Metab Clin North Am* 20:153, 1991.
Seminara SB, Hayes FJ, Crowley WF Jr: Gonadotropin-releasing hormone deficiency in the human (idiopathic hypogonadotropic hypogonadism and Kallmann's syndrome): pathophysiological and genetic considerations, *Endocr Rev* 19:521, 1998.
Silveira LF, MacColl GS, Bouloux PM: Hypogonadotropic hypogonadism, *Semin Reprod Med* 20:327–338, 2002.
Snyder PJ, et al: Effects of testosterone replacement in hypogonadal men, *J Clin Endocrinol Metab* 85:2670, 2000.
Swerdloff RS, Wang C, et al: Long-term pharmacokinetics of transdermal testosterone gel in hypogonadal men, *J Clin Endocrinol Metab* 85:4500–4510, 2000.
Szulc P, Munoz F, Claustrat B, et al: Bioavailable estradiol may be an important determinant of osteoporosis in men: the MINOS study, *J Clin Endocrinol Metab* 86:192, 2001.
Tenover JL: Male hormone replacement therapy including "andropause." *Endocrinol Metab Clin North Am* 27:969–987, 1998.
Whitcomb RW, Crowley WF: Male hypogonadotropic hypogonadism, *Endocrinol Metab Clin North Am* 22:125, 1993.
Wu FCW, Tajar A, Beynon JM, et al: Identification of late-onset hypogonadism in middle-aged and elderly men, *N Engl J Med* 363:123–135, 2010.
Young J: Approach to the male patient with congenital hypogonadotropic hypogonadism, *J Clin Endocrinol Metab* 97: 707–718, 2012.

IMPOTENCE

Peter Z. McIntyre and Robert A. Vigersky

1. What is impotence?

A more descriptive term for impotence is erectile dysfunction (ED). Classically, ED has been defined as the inability to attain and maintain an erection of sufficient rigidity for sexual intercourse in at least 50% of attempts. This definition is important to consider because any normal man can have occasional ED, and treating men with only occasional symptoms is not without risk.

2. Do men with ED have disturbances in other sexual functions?

Most men with ED are able to ejaculate. Premature ejaculation may precede the development of impotence and is sometimes associated with drug therapy. Sexual desire (libido) is also usually preserved; loss of libido is suggestive of hypogonadism or severe systemic or psychiatric illness.

3. Is impotence common?

At least 10 million American men and perhaps as many as 20 million are impotent. Another 10 million may suffer from partial ED. The prevalence of impotence increases with age; about 2% of 40-year-old, 20% of 55-year-old, and 50% to 75% of 80-year-old men are impotent. There is a libido-potency gap in that many elderly men continue to have active libidos, but only 15% of them engage in sexual activity.

4. How does a normal erection occur?

Erection is primarily a vascular event that results from the complex interplay of the hormonal, vascular, and peripheral and central nervous systems. There is considerable psychiatric interplay in that underlying psychiatric conditions or medications can cause decreased erectile function. Conversely, undesired sexual symptoms can also adversely affect mood and self-perception.

5. Explain the role of the nervous system in achieving erection.

Erection is usually initiated by various psychological and/or physiologic stimuli in the cerebral cortex. The stimuli are modulated in the limbic system and other areas of the brain, integrated in the hypothalamus, transmitted down the spinal cord, and carried to the penis via both autonomic and sacral spinal nerves. (For the few remaining Latin scholars, these are the nervi erigentes derived from the verb *erigo, erigere, erexi, erectus*.) Sensory nerves from the glans of the penis enhance the message and help to maintain erection during sexual activity via a reflex arc.

6. Explain the hormonal aspects of erection.

Nervous system stimuli release neurotransmitters that reverse the tonic smooth muscle constriction maintained by norepinephrine, endothelin, and other vasoconstrictive factors. The most important of these are the potent vasodilators nitric oxide (NO) and prostaglandin E_1 (PGE_1). In addition to neural sources, NO is derived from endothelial cells, and this may explain why endothelial integrity may be necessary for maintenance of an erection. NO works by increasing cyclic guanosine monophosphate (cGMP) and causing a decrease in intracellular calcium. This results in relaxation of vascular smooth muscle cells secondary to dissociation of actin-myosin. The role of testosterone in erectile function remains complex and controversial. Testosterone has a critical role in stabilizing intracavernosal NO synthase, and for fully satisfactory sexual function, a "normal" quotient of testosterone must be present. Testosterone is also the main hormonal mediator of male libido; this means that deficiency can have a psychologic impact on erectile function. Regardless, some men with testosterone levels below the reference limit still have

normal erections. Testosterone replacement is therefore not guaranteed to cure ED in hypogonadal men, nor is it indicated in men with normal testosterone levels but impaired sexual function.

7. What vascular changes in the penis result in erection?

Within the two spongy corpora cavernosa of the penis are millions of tiny spaces called lacunae, each lined by a wall of trabecular smooth muscle. As neurotransmitters dilate cavernosal and helicine arteries to the penis and relax the trabecular smooth muscle, the lacunar spaces in the penis become engorged with blood. This results in entrapment of outflow vessels between the expanding trabecular walls and the rigid tunica albuginea that surrounds the corpora cavernosa, thereby greatly reducing venous outflow from the penis. This venoocclusive mechanism accounts for both rigidity and tumescence. Failure of venous occlusion (venous leak) is one of the intractable causes of impotence.

8. What types of nerves and neurotransmitters play a role in penile erection?

At least three neuroeffector systems play a role in penile erection. Adrenergic nerves generally inhibit erection; cholinergic nerves and nonadrenergic, noncholinergic (NANC) substances enhance erection as follows:

- Sympathetic nerves (via beta-adrenergic receptors) constrict cavernosal and helicine arteries and contract trabecular smooth muscle.
- Parasympathetic nerves (via cholinergic receptors) inhibit adrenergic fibers and stimulate NANC fibers.
- NANC messengers (NO, vasoactive intestinal polypeptide, and prostaglandins or other endothelium-derived factors) dilate cavernosal and helicine arteries and relax trabecular smooth muscle.

9. How does detumescence occur?

Phosphodiesterase 5 (PD5), by causing a decrease in cGMP, allows for reversal of the process (i.e., detumescence), thus making PD5 inhibitors, such as sildenafil, vardenafil, and tadalafil, important therapeutic agents for the treatment of impotence (see the following).

10. What are the common causes of impotence?

The frequency of the various causes of impotence is difficult to assess because of the large number of patients who do not report the problem, confusion regarding the diagnosis, and variability in the sophistication of the initial evaluation. Primary causes of impotence in men presenting to a medical outpatient clinic are approximated as follows:

- Endocrine factors (including hyperthyroidism and hypothyroidism): 30%
- Diabetes mellitus and metabolic syndrome: 15%
- Medications: 20%
- Systemic disease and alcoholism: 10%
- Primary vascular causes: 5% (Alterations of blood flow are thought to play a role in many causes of impotence, but specific lesions amenable to therapy are relatively rare.)
- Primary neurologic causes: 5%
- Psychogenic or unknown causes: 15%

11. What lifestyles are associated with impotence?

- Low levels of physical activity
- Overeating and obesity
- Smoking
- Excessive television viewing
- Alcohol consumption

12. Besides diabetes mellitus, what are the three most common endocrine causes of impotence?

- Primary (hypergonadotropic) hypogonadism (increased luteinizing hormone [LH] and decreased testosterone)

- Secondary (hypogonadotropic) hypogonadism ("inappropriately" normal or actually decreased LH combined with decreased testosterone)
- Hyperprolactinemia

Less common causes include hyperthyroidism, hypothyroidism, adrenal insufficiency, and Cushing's syndrome.

13. Describe the most common drugs known to induce impotence.

Nonprescription drugs, such as alcohol (as the porter says to Macduff in Act II, Scene 3 of *Macbeth,* "It provokes the desire but takes away the performance"), and illicit drugs, such as cocaine, methadone, and heroin, can cause impotence. The prescription drugs most commonly associated with impotence include the following:

- Antihypertensive agents, especially methyldopa, clonidine, beta-blockers, vasodilators (e.g., hydralazine), thiazide diuretics, and spironolactone
- Antipsychotic medications
- Antidepressants and tranquilizers
- Others (especially cimetidine, digoxin, phenytoin, carbamazepine, ketoconazole, metoclopramide, and megestrol)

14. Which antihypertensive agents should be used in patients with impotence?

Virtually every blood pressure medication has been associated with impotence. Although there is little overall difference in the rate of erectile problems among the commonly prescribed antihypertensive agents, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and calcium channel blockers are the agents least likely to affect erectile ability. When beta-blockade is required, selective beta-antagonists, such as atenolol or acebutolol, are preferred because they have minimal impact on sexual function.

15. What is "stuttering" impotence? What is its significance?

Impotence alternating with periods of entirely normal sexual function is termed stuttering impotence. Multiple sclerosis (MS) is the most significant organic cause of stuttering impotence. It may be the initial manifestation of MS and may be present in up to 50% of men with the disease.

16. What historical information helps to separate organic from psychogenic impotence?

True psychogenic impotence is uncommon and should be a diagnosis of exclusion. Questions that may help to separate psychogenic from organic impotence are listed in Table 45-1. A detailed history assessing for contributing physical and psychiatric conditions can also help with this distinction. These include obesity, hypertension, hyperlipidemia, atherosclerosis, diabetes mellitus or other

TABLE 45-1. ORGANIC VERSUS PSYCHOGENIC IMPOTENCE

	ORGANIC	PSYCHOGENIC
Was onset abrupt?	No	Yes
Is impotence stress dependent?	No	Yes
Is libido preserved?*	Yes	No
Do you have morning erections?	No	Yes
Do you have orgasms?	Yes	No
Can you masturbate?	No	Yes
Does impotence occur with all partners?	Yes	No

*There is a general relationship of libido with hypogonadal levels of testosterone in populations, but on an individual basis, libido may not be a reliable discriminator.

endocrinopathy, neurologic disease, prior pelvic surgery or irradiation, trauma, Peyronie's disease, substance abuse, depression, or the aforementioned medications. A detailed social history is also important and includes assessment of stressors and the patient's coping mechanisms, concomitant psychosexual problems such as premature ejaculation, and relationship dynamics with partners.

17. Name the essential components of a physical examination in a man complaining of impotence.

- Secondary sexual characteristics, such as muscle development, hair pattern, and presence of breast tissue
- Vascular examination, especially of the femoral and lower extremity pulses and the presence of bruits
- Focused neurologic examination, including assessing the presence of peripheral neuropathy with vibratory and light touch sensation and of autonomic neuropathy using the cremasteric reflex, anal sphincter tone and/or the bulbocavernosus reflex, evaluation of standing and supine blood pressure, and measurement of the heart rate response to deep breathing and Valsalva maneuver (diabetic patients rarely have autonomic neuropathy as a cause of impotence in the absence of peripheral neuropathy)
- Examination of the genitalia to determine penile size, shape, presence of plaque or fibrous tissue (Peyronie's disease); size and consistency of the testes; prostate examination; normal testis size is more than 5 $\times$ 3 cm or 20 mL (by orchidometer)
- Thyroid-relevant examination including size, the presence of nodularity, and abnormal reflexes

18. What is the appropriate laboratory assessment for men with impotence?

Laboratory assessment should be based on history and physical examination findings. It can discover previously unknown disease in 6% of men. Generally, it should include the following:

- Complete blood count
- Urinalysis
- Fasting plasma glucose and (in known diabetic patients) hemoglobin A_{1C} (HbA_{1C})
- Fasting serum lipid profile
- Serum creatinine
- Serum free thyroxine and thyrotropin
- Serum testosterone, LH, and follicle-stimulating hormone

19. Should prolactin levels be measured in all impotent men?

Whether serum prolactin should be measured in all men with impotence is somewhat controversial. In general, patients with normal levels of testosterone and LH and a normal neurologic examination do not require measurement of prolactin. However, if testosterone is low and associated with low or low-normal LH or if history or examination suggests a pituitary lesion, prolactin should be measured. Because prolactin interferes with the action of testosterone, prolactin status should be assessed in hypogonadal men unresponsive to testosterone replacement therapy. Hypothyroidism and renal failure also may elevate prolactin.

20. What is a penile brachial index?

Comparison of the penile and brachial systolic blood pressure allows a general assessment of the vascular integrity of the penis. This technique is not highly sensitive, but it is noninvasive and easy to perform and may help to identify men who require more extensive vascular studies. Penile systolic blood pressure obtained with Doppler ultrasound should be the same as brachial systolic pressure (i.e., ratio approximately 1.0). An index lower than 0.7 is highly suggestive of vasculogenic impotence. Diagnostic yield is increased if the penile brachial index is repeated after exercising the lower extremities for several minutes. This maneuver may uncover a pelvic steal syndrome (loss of erection resulting from pelvic thrusting) that is characterized by a difference of more than 0.15 between the resting and exercise ratios.

21. What is nocturnal penile tumescence monitoring?

Most men experience three to six erections during the night that are entrained to rapid eye movement (REM) sleep. By monitoring such events, one can assess the frequency, duration, and, with some instruments, even the rigidity of erection. This procedure helps to distinguish organic from psychogenic impotence. This can be done at home either semiquantitatively (using a Snap-Gauge) or more quantitatively (using the RigiScan).

22. What are the therapeutic options in the treatment of impotence?

Once drugs with a high likelihood of causing impotence are discontinued and other underlying conditions are aggressively treated (e.g., diabetes mellitus, hypercholesterolemia), specific therapy is instituted. The broad categories of available medical and surgical therapy are summarized in Table 45-2. Important adjuncts include the following:

- Medical treatment, including lifestyle modifications and/or weight reduction
- External mechanical aids and vacuum or suction devices
- Psychological therapy (especially in the absence of an obvious organic cause)

23. What options are available for medical treatment?

- Testosterone replacement in hypogonadal men with a goal of achieving a midnormal level of serum testosterone (see Chapter 44)
- Dopamine agonists (bromocriptine or cabergoline) to reduce hyperprolactinemia in men with normal testosterone unresponsive to testosterone treatment
- PD5 inhibitors, such as sildenafil citrate (Viagra), vardenafil (Levitra), or tadalafil (Cialis) (Table 45-3)
- Adrenergic receptor blockers (e.g., yohimbine, 5-10 mg three times daily)
- Herbal remedies (e.g., Korean red ginseng)
- Selective serotonin reuptake inhibitor (SSRI) for premature ejaculation

24. Summarize the role of intracavernosal injections.

Intracavernosal injection of vasoactive substances (PGE, papaverine, and phentolamine) individually or in combination (Trimix) may be effective for men in whom PD5 inhibitors have failed or are contraindicated.

25. List the surgical procedures used to treat impotence.

- Revascularization procedures
- Obliteration of venous shunts
- Surgical penile implants

26. How effective are PD5 inhibitors?

The introduction of the selective PD5 inhibitors sildenafil citrate (Viagra), vardenafil (Levitra), and tadalafil (Cialis) produced a paradigm shift in the approach to the treatment of impotence by reducing the relevance of finding a specific cause of the problem. There appears to be no tachyphylaxis to their effect for at least 5 years. Given 1 hour before anticipated sexual activity (and for sildenafil and vardenafil avoiding a fatty meal, which inhibits absorption by one third), they are successful in up to 80% of men with organic impotence (although only in about 50% to 70% of diabetic men and 50% of elderly men). Newer studies indicate that once daily tadalafil may have efficacy and safety equivalent to those of "as needed" dosing. Unfortunately, well-performed comparisons of the available treatments for ED are not available. The literature on PD5 inhibitors, in particular, is limited by inconsistencies in study designs, inclusion and exclusion criteria, dosages, treatment durations, randomization, and crossover. When assessing "success" of ED therapy, it is important to consider more than the quality of the erection or the frequency of vaginal penetration because effective but invasive interventions (i.e., intracavernosal injections) are not uniformly preferred by patients. In terms of PD5 inhibitors, maximum doses are generally preferred to submaximum doses, and longer treatment durations are generally preferred to shorter durations. Younger men with a psychogenic

TABLE 45-2. TREATMENT OPTIONS FOR IMPOTENCE

	ORAL PD5 INHIBITORS	INTRAURETHRAL ALPROSTADIL	INTRACAVERNOUS INJECTION (ALPROSTADIL, PAPAVERINE, PHENTOLAMINE)	PENILE PROSTHESIS IMPLANTATION
Mechanism of Action	Inhibit PD5, potentiate vasodilation by nitric oxide–generated cGMP, metabolized by CYP450, require hepatic dosing	Synthetic vasodilator identical to PGE_1, relaxes arterial smooth muscle, inhibits platelet aggregation	Agent specific, relaxes smooth muscle	Available in inflatable and noninflatable versions
Contraindications	Nitrate use within 24 hr (48 hr for tadalafil), prolonged QT (vardenafil), caution if using alpha-blockers, caution if penile deformity Caution in liver or kidney disease	Sickle cell anemia, multiple myeloma, leukemia, penile deformities, penile implants	Sickle cell anemia, multiple myeloma, leukemia, penile deformity, penile implant	Active systemic, cutaneous, or urinary infection
Side Effects	Flushing, nasal congestion, headache, dyspepsia, visual side effects (sildenafil and vardenafil), back pain, mild QT prolongation (vardenafil), hypotension, syncope, MI, angina, stroke	Hypotension, syncope, priapism, GU pain	Priapism, penile fibrosis, hypotension, hematoma, ecchymosis, penile pain, bleeding, angulation/ Peyronie's disease	Infection, erosion, mechanical failure (6%-16% at 5 yr), penile shortening, reduced efficacy of medical therapy if prosthesis fails, autoinflation
Monitoring Parameters	Creatinine at baseline	Initial dose under supervision (risk of syncope)	Initial dose under supervision, train for management of priapism	Physical examination

cGMP, Cyclic guanosine monophosphate; GU, genitourinary; MI, myocardial infarction; PD5, phosphodiesterase 5; PGE_1, prostaglandin E_1.

TABLE 45-3. COMPARISON OF PHOSPHODIESTERASE 5 INHIBITORS*

	SILDENAFIL (VIAGRA)	VARDENAFIL (LEVITRA)	TADALAFIL (CIALIS)
Onset	20 min	10 min	20 min
T_{max}	1 hr	45 min	2 hr
$T_{1/2}$	3-5 hr	4-5 hr	17.5 hr
Initial dose	50 mg (25 mg if > 65 yr old)	10 mg (5 mg if > 65 yr old)	10 mg
Maximum dose	100 mg	20 mg	20 mg
Notes	Original PD5 inhibitor; most data on safety and efficacy; avoid high-fat meals when dosing	Avoid high-fat meals when dosing	Comparable efficacy and safety when given 2.5-5 mg daily for men with intercourse more than twice/wk; no dietary restriction needed

*Comparative efficacy data on the three available agents are lacking. Failure of one agent is not a contraindication to trial of a different PD5 inhibitor.
PD5, Phosphodiesterase 5; T_{max}, time to maximum plasma concentration, $T_{1/2}$, half-life.

origin of ED tend to prefer tadalafil for its greater duration of action, whereas older men with moderate or severe organic ED tend to prefer sildenafil or vardenafil for better efficacy and side effect profiles. Switching from one PD5 inhibitor to another is sometimes beneficial for nonresponders. There may also be a place for testosterone "rescue" in patients who do not respond to PD5 inhibitors and who also have low testosterone levels.

27. Discuss the side effects of PD5 inhibitors.

The few immediate side effects associated with PD5 inhibitors (headache, flushing, dyspepsia, and a blue haze in vision) rarely cause discontinuation of their use. Tadalafil causes less crossover inhibition of retinal PD6 and therefore is associated with fewer visual side effects. Because PD5 inhibitors cause vasodilatation similar to that of nitrates, they are contraindicated in men taking any form of nitrates. The long half-life of tadalafil (the so-called "weekend pill") may prove to be particularly troublesome if a patient develops angina within 72 to 96 hours of taking the drug. Priapism may occur as a result of using PD5 inhibitors.

28. What drug interactions are associated with PD5 inhibitors?

Because PD5 inhibitors are metabolized via CYP3A4, any drugs that block that enzyme (e.g., erythromycin and other macrolide antibiotics; ketoconazole and other antifungal drugs; human immunodeficiency virus [HIV] protease inhibitors, such as saquinavir and ritonavir; and cimetidine) increase the plasma concentrations of PD5 inhibitors. In such cases, PD5 inhibitors should be started at one fourth to one half of the usual dose. Because PD5 inhibitors may potentiate the hypotensive effect of beta-adrenergic blocking agents, they should be given in lower doses (sildenafil) or not at all (vardenafil) in men taking alpha-blockers for control of blood pressure or for benign prostatic hypertrophy.

29. When are intracavernosal or intraurethral injections recommended?

Injection of vasodilatory substances directly into the corpora cavernosa of the penis should be reserved for men in whom PD5 inhibitors are ineffective, contraindicated, or limited by intolerable adverse effects. Such "PD5 salvage" therapy results in erection satisfactory for intercourse in some

men with impotence. PGE_1 (Caverject), papaverine, and phentolamine may be used alone or in combination (Trimix).

30. Discuss the side effects of intracavernosal and intraurethral injections.

Side effects, which depend on the types and quantities of substances injected, include hypotension, elevation of liver enzymes, and headache. Local complications include hematoma, swelling, inadvertent injection into the urethra, and local fibrosis with long-term use. The most serious local complication is priapism (a sustained erection) for more than 4 hours, which may necessitate injection of alpha-adrenergic agonists or corpora cavernosal aspiration. PGE_1 is also available as an intraurethral suppository (medicated urethral system for erection [MUSE]) and, because it is less invasive and easier to use, may be a more appropriate second-line agent than intracavernosal injection. No controlled studies have evaluated the success of either approach in PD5 inhibitor failures.

31. Does the onset of impotence have other health implications?

The development of impotence is associated with a 45% increased risk of cardiovascular events. This is in the same range as other well-known risk factors such as current smoking and a family history of a myocardial infarction (MI). This association has implications on management because treatment of ED carries a 2.5-fold risk of nonfatal MI. This is comparable to having had a prior MI, after which the risk of a subsequent MI is increased 2.9-fold. The risk increase in ED treatment is probably the result of the increased level of exertion (approximately 3–4 METS) associated with intercourse. Despite these observations, the absolute risk of MI while receiving ED treatment is still extremely low (20 cases per million per hour of use) in patients with a prior MI, and so known cardiac disease is not a strict contraindication to treatment. High-risk patients, however, should be stabilized before treatment of ED:

- Unstable or refractory angina
- Uncontrolled hypertension
- Congestive heart failure
- MI or stroke in the past 2 weeks
- High-risk arrhythmias
- Hypertrophic or other cardiomyopathy
- Moderate to severe valvular disease

32. What other modalities are available to treat impotent men?

Vacuum erection devices provide a noninvasive, mechanical solution for impotence. They are somewhat cumbersome to use and require the placement of an occlusive ring at the base of the penis to prevent venous outflow. They may be particularly effective in those men who have a "venous leak" as the cause of their impotence. The constrictive ring prevents antegrade ejaculation because of the urethral constriction. Surgical revascularization has a limited place in the treatment of impotent men because of its invasiveness and limited success rate. Similarly, penile prosthesis insertion is rarely done because of the availability of several effective and noninvasive alternatives. In men in whom premature ejaculation is the major problem, intermittent use of topical anesthetic agents or SSRI use has been efficacious in delaying time to ejaculation.

33. What future treatments may be forthcoming?

Newer PD5 inhibitors are in trials. In particular, avanafil is shorter acting and thus may permit use more than once a day. Taking another approach is the use of centrally acting melanocortin receptor agonists. These drugs can be administered by nasal spray and are in clinical trials. They appear to be effective alone or in combination with PD5 inhibitors. Finally, a novel use of metformin as an adjunct to sildenafil may improve ED in patients without diabetes but who have insulin resistance.

KEY POINTS 1: IMPOTENCE

1. Erections are mediated by neural and endothelial release of nitric oxide that induce vasodilation.
2. The specific cause of impotence can be diagnosed in 85% of men.
3. The antihypertensives that are least likely to cause impotence are angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers.
4. Consider the role of risk factor and lifestyle modification and psychological counseling in all patients with impotence.
5. Consider the possibility of concomitant cardiovascular disease in patients with impotence, and treat unstable cardiac conditions before initiation of therapy of erectile dysfunction.
6. Phosphodiesterase 5 inhibitors (sildenafil, vardenafil, and tadalafil) are the most effective drugs in treating nonhormonal impotence.

WEBSITES

1. http://www.endo-society.org/guidelines/final/upload/FINAL-Androgens-in-Men-Standalone.pdf. Link is no longer available.
2. http://www.impotence.org: Center for Reconstructive Urology.
3. http://kidney.niddk.nih.gov/kudiseases/pubs/impotence/index.htm: National Kidney and Urologic Diseases Information Clearinghouse (NKUDIC).
4. http://www.hormone.org/public/other.cfm: Hormone Health Network.
5. http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines.cfm: American Urological Association.

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BIBLIOGRAPHY

Adams MA, Banting BD, Maurice DH, et al: Vascular control mechanism in penile erection: phylogeny and the inevitability of multiple overlapping systems, *Int J Impotence Res* 9:85–95, 1997.

Andersson K-E: Erectile physiological and pathophysiological pathways involved in erectile dysfunction, *J Urol* 170: S6–S14, 2003.

Bhasin S, Cunningham GR, Hayes FJ, et al: Testosterone therapy in adult men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline, *J Clin Endocrinol Metab* 91:1995–2010, 2006.

Bagatell CJ, Bremner WJ: Androgens in men: use and abuses, *N Engl J Med* 334:707–714, 1997.

Cohan P, Korenman SG: Erectile dysfunction, *J Clin Endocrinol Metab* 86:2391–2394.

Cookson MS, Nadig PW: Long-term results with vacuum constriction device, *J Urol* 149:290–294, 1993.

Esposito K, Giugliano F, Di Palo C, et al: Effect of lifestyle changes on erectile dysfunction in obese men: a randomized controlled trial, *JAMA* 291:2978–2984, 2004.

Esposito K, Giugliano F, Martedi E, et al: High proportions of erectile dysfunction in men with the metabolic syndrome, *Diabetes Care* 28:1201–1203, 2005.

Feldman HA, Goldstein I, Hatzichristou DJ, et al: Impotence and its medical and psychosocial correlates: results of the Massachusetts male aging study, *J Urol* 151:54–61, 1994.

Goldstein I, Lue TF, Padma-Nathan H, et al: Oral sildenafil in the treatment of erectile dysfunction, *N Engl J Med* 338:1397–1404, 1998.
Goldstein I, Young JM, Fischer J, et al: Vardenafil, a new phosphodiesterase type 5 inhibitor, in the treatment of erectile dysfunction in men with diabetes: a multicenter double-blind placebo-controlled fixed-dose study, *Diabetes Care* 26:777–783, 2003.
Grimm RH Jr, Grandits GA, Prineas RJ, et al (for the TOHMS Research Group): Long-term effects on sexual function of five antihypertensive drugs and nutritional hygienic treatment in hypertensive men and women: Treatment of Mild Hypertension Study (TOHMS), *Hypertension* 29:8–14, 1997.
Guay A, et al: American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of male sexual dysfunction: a couple's problem–2003 update, *Endocr Pract* 9:77–95, 2003.
Hanash KA: Comparative results of goal oriented therapy for erectile dysfunction, *J Urol* 157:2135–2139, 1997.
Herrmann HC, Chang G, Klugherz BD, Mahoney PD: Hemodynamic effects of sildenafil in men with severe coronary artery disease, *N Engl J Med* 342:1622–1626, 2000.
Hong G, Ji YH, Hong JH, et al: A double-blind crossover study evaluating the efficacy of Korean red ginseng in patients with erectile dysfunction: a preliminary report, *J Urol* 168:2070–2073, 2002.
Krane RJ, Goldstein I, DeTejada JS: Impotence, *N Engl J Med* 321:1648–1659, 1989.
Krassas GE, Tziomalos K, Papadopoulou F et al: Erectile dysfunction in patients with hyper- and hypothyroidism: how common and should we treat? *J Clin Endocrinol Metab* 93:1815–1819, 2008.
Lerner SF, Melman A, Christ GJ: A review of erectile dysfunction: new insights and more questions, *J Urol* 149: 1246–1252, 1993.
Linet OI, Ogring FG, and the Alprostadil Study Group: Efficacy and safety of intracavernosal prostaglandin in men with erectile dysfunction, *N Engl J Med* 334:873–878, 1996.
Melman A: Gene therapy for male erectile dysfunction, *Urol Clin North Am* 34:619–630, 2007.
McMahon C: Comparison of the safety, efficacy, and tolerability of on-demand tadalafil and daily dosed tadalafil for the treatment of erectile dysfunction, *J Sex Med* 2:415–427, 2005.
McMahon C, Touma K: Treatment of premature ejaculation with paroxetine hydrochloride as needed: two single-blind placebo controlled crossover studies, *J Urol* 161:1826–1830, 1999.
McNamara ER, Donatucci CF: Newer phosphodiesterase inhibitors: comparison with established agents, *Urol Clin North Am* 38:155–163, 2011.
Montague D, et al: The management of erectile dysfunction: an AUA update, *J Urol* 174:230–239, 2005.
Morley JE, Kaiser FE: Impotence: the internists' approach to diagnosis and treatment, *Adv Intern Med* 38:151–168, 1993.
Mulhall J, et al: Evaluating preference trials of oral phosphodiesterase 5 inhibitors for erectile dysfunction, *Eur Urol* 49:30–37, 2006.
Neisler AW, Carey NP: A critical reevaluation of nocturnal penile tumescence monitoring in a diagnosis of erectile dysfunction, *J Nerv Ment Dis* 178:78–79, 1990.
NIH Consensus Conference: Impotence, *JAMA* 270:83–90, 1993.
Padma-Nathan H, Hellstrom WSG, Kaiser FE, et al [for the Medicated Urethral System for Erection (MUSE) Study Group]: Treatment of men with erectile dysfunction with transurethral alprostadil, *N Engl J Med* 336:1–7, 1997.
Park K, Ku JH, Kim SW, Paick J-S: Risk factors in predicting a poor response to sildenafil citrate in elderly men with erectile dysfunction, *BJU Int* 95:366–370, 2005.
Porst H, Padma-Nathan H, Giuliano F, et al: Efficacy of tadalafil for the treatment of erectile dysfunction at 24 and 36 hours after dosing: a randomized controlled trial, *Urology* 62:121–125, 2003.
Rajfer J, Aronson WJ, Bush PA, et al: Nitric oxide as a mediator of relaxation of the corpus cavernosum in response to nonadrenergic, noncholinergic neurotransmission, *N Engl J Med* 326:90–94, 1992.
Rendell MS, Rajfer J, Wicker PA, et al: Sildenafil for treatment of erectile dysfunction in men with diabetes: a randomized controlled trial, *JAMA* 281:421–426, 1999.
Rey Valzacchi GR, Costanzo PR, Finger LA, et al: Addition of metformin to sildenafil treatment for erectile dysfunction in eugonadal non-diabetic men with insulin resistance: a prospective, randomized, double blind pilot study, *J Androl* 19:268–272, 2012.
Rosenthal BD, May NR, Metro MJ, et al: Adjunctive use of Androgel (testosterone gel) with sildenafil to treat erectile dysfunction in men with acquired androgen deficiency syndrome after failure using sildenafil alone, *Urology* 67: 571–574, 2006.
Sidi AA: Vasoactive intracavernous pharmacotherapy, *Urol Clin North Am* 15:95–101, 1988.
Thompason IM, Tangen CM, Goodman PJ, et al: Erectile dysfunction and subsequent cardiovascular disease, *JAMA* 294:2996–3002, 2005.
Witherington R: Mechanical aids for treatment of impotence, *Clin Diabetes* 7:1–22, 1989.

GYNECOMASTIA

Mark Bridenstine, Brenda K. Bell, and Micol S. Rothman

1. Define gynecomastia.

Gynecomastia is defined as the presence of palpable breast tissue in a male. True gynecomastia resulting from enlargement of glandular tissue should be distinguished from excess adipose accumulation (i.e., pseudogynecomastia).

2. How does gynecomastia manifest clinically?

Gynecomastia usually manifests as a palpable, discrete button of tissue radiating from beneath the nipple and areola. Gynecomastia feels "gritty" when the breast is pinched between the thumb and forefinger. Fatty tissue, unlike gynecomastia, will not cause resistance until the nipple is reached. If doubt remains, soap and water on the breast can facilitate the examination by decreasing skin friction.

3. What is the significance of painful gynecomastia?

Gynecomastia is frequently asymptomatic and incidentally discovered. Pain or tenderness implies recent, rapid growth of breast tissue. This may indicate a pathologic cause of the gynecomastia and should prompt further evaluation.

4. Is gynecomastia always bilateral?

The involvement tends to be bilateral, but asymmetry is common. Unilateral enlargement is present in 5% to 25% of patients and may be a preliminary stage in the development of bilateral disease. In autopsy studies, unilateral enlargement is often found to be bilateral gynecomastia histologically.

5. Summarize the pathophysiology of gynecomastia.

Gynecomastia results from an imbalance between the stimulatory effect of estrogen on ductal proliferation and the inhibitory effect of androgen on breast development. The imbalance is most commonly caused by increased production of estrogens, decreased production of testosterone, or increased conversion of androgens to estrogens in peripheral tissue. Disorders of sex hormone–binding globulin or with androgen receptor binding and function can also result in gynecomastia.

6. Where are estrogens produced in the male?

Direct testicular production of estrogens accounts for less than 15% of male estrogen production. Most estrogens come from the conversion of adrenal and testicular androgens to estrogens in peripheral tissues, particularly adipose tissue and the liver.

7. What is the most common cause of gynecomastia?

Asymptomatic palpable breast tissue is common in normal males, particularly in the neonate (60%–90%), at puberty (60%–70%, ages 12 and 15 years), and with increasing age (20%–65%, $>$50 years). Prevalence of histopathologically confirmed gynecomastia is up to 40% in autopsy series. Because of this high prevalence, gynecomastia is considered a relatively normal finding during these periods of life. Gynecomastia is often called physiologic or idiopathic at these ages.

8. Why does gynecomastia occur so commonly during these stages of life?

Neonatal gynecomastia results from placental transfer of estrogens. During early puberty, production of estrogens begins sooner than testosterone production, thus causing an imbalance in the ratio of

estrogens to androgens. With aging, testosterone production decreases, and peripheral androgen to estrogen conversion often increases because of an age-related increase in adipose tissue. There may also be a higher prevalence of offending medications and medical conditions in the elderly population.

9. What are the other causes of gynecomastia?

Idiopathic gynecomastia and pubertal gynecomastia make up the majority of cases. Drugs account for 10% to 20% of cases and hypogonadism for another 10%. Adrenal or testicular tumors account for less than 3% of cases; gynecomastia may precede the development of the testicular tumor. Other causes combined account for less than 10% of cases and include androgen-resistant disorders, malnutrition, cirrhosis, alcohol abuse, renal disease, congenital adrenal hyperplasia, extragonadal tumors, refeeding gynecomastia, and hyperthyroidism. Case reports of atypical infectious causes have been described (e.g., tuberculosis and filariasis).

10. What drugs cause gynecomastia?

Many drugs have been implicated, some with well-characterized steroid effects and others noted in case reports and without a clearly elucidated mechanism:

TABLE 46-1. DRUGS IMPLICATED IN GYNECOMASTIA

PROPOSED MECHANISM	REPORTED AGENTS
Altered Androgen/Estrogen Ratio	
Estrogen excess (exogenous)	Androgens and anabolic steroids (via aromatization of androgens to estrogens), estrogen creams and systemic formulations, hCG, digitoxin (via estrogen-like activity)
Androgen deficiency or inhibition of androgen synthesis	Finasteride, dutasteride, ketoconazole, metronidazole, methotrexate, various chemotherapeutic agents, GnRH agonists (e.g., leuprolide, goserelin)
Decreased androgen action	Spironolactone, cimetidine, ranitidine, antiandrogen prostate cancer therapies (e.g., bicalutamide, flutamide), marijuana, cyproterone acetate
Increased Prolactin	
Antidopaminergic agents	Haloperidol, risperidone, metoclopramide, domperidone, phenothiazines
Mechanism Unknown	
Angiotensin-converting enzyme inhibitors	Captopril, enalapril
Calcium channel blockers	Nifedipine, amlodipine, diltiazem, verapamil
Alpha-receptor blockers	Doxazosin, prazosin
Centrally acting agents	Clonidine, methyldopa, reserpine, diethylpropion, amphetamines
Statins (? inhibition of adrenal-gonadal steroid synthesis)	Rosuvastatin, lovastatin, pravastatin, simvastatin
Immunomodulatory agents	Thalidomide, imatinib, dasatinib
Antidepressants	Tricyclic antidepressants, duloxetine, fluoxetine
Antiepileptics	Phenytoin, diazepam, gabapentin
Antituberculosis agents	Isoniazid, ethionamide
Supplements	Lavender, tea tree oil, melatonin, dong quai, hCG diet
Other	Amiodarone, protease inhibitors, proton pump inhibitors, growth hormone, fenofibrate, heroin, methadone, alcohol, minocycline, penicillamine, etretinate, theophylline, auranofin, sulindac

GnRH, Gonadotropin-releasing hormone; hCG, human chorionic gonadotropin.

11. How do testicular tumors cause gynecomastia?

Germ cell tumors can produce human chorionic gonadotropin (hCG). Like luteinizing hormone (LH), hCG increases testicular estradiol production. Leydig cell tumors may directly secrete estradiol.

12. What extragonadal tumors cause gynecomastia?

Pancreatic, gastric, and pulmonary tumors, transitional cell bladder carcinoma, and renal cell carcinoma have been associated with hCG production. Hepatomas may have increased aromatase activity that results in excess conversion of androgens to estrogens.

13. Who should undergo evaluation for gynecomastia?

History and physical examination are indicated in all cases and determine the cause in 30% to 40% of patients. Gynecomastia is so common, however, that many experts are cautious about attaching importance to the detection of a small amount of breast tissue in an otherwise asymptomatic man. In adolescents, there is no reason to consider endocrine testing unless the enlargement is massive or the gynecomastia persists longer than 2 years. Acute development of enlargement and tenderness in men who than 20 years old warrants additional evaluation, as do eccentric, hard masses and lesions larger than 4 cm.

14. What information is significant in the history?

BOX 46-1. SIGNIFICANT INFORMATION IN THE PATIENT'S HISTORY

- Age
- Thyroid symptoms
- Duration of enlargement
- Drugs, herbs, supplements
- Breast symptoms (tenderness, discharge)
- Alcohol and illicit drug use
- Family history of gynecomastia or breast cancer
- Other illnesses
- Congenital abnormalities
- Nutritional status and recent changes in weight
- Pubertal progression
- Impotence and libido

15. What should be noted on the physical examination?

Important features include characteristics of the breast tissue (size, irregularity, firmness, eccentric location, nipple discharge), overlying skin changes (ulceration, nipple retraction), testes (size, asymmetry), abdomen (liver enlargement, ascites, spider angiomas), secondary sexual characteristics, thyroid status (goiter, tremor, reflexes), and signs of excessive cortisol (buffalo hump, central obesity, hypertension, purple striae, moon facies), and body mass index or body habitus (bodybuilder physique, obesity).

KEY POINTS 1: GENERAL APPROACH TO GYNECOMASTIA

1. The most important differentiation is between gynecomastia and breast cancer. If doubt remains after physical examination, obtain a mammogram.
2. Most cases are bilateral, asymptomatic, and incidentally discovered. History, physical examination, and reevaluation in 3 to 6 months are appropriate for such men.
3. Rapid enlargement, size larger than 4 cm, pain, and age less than 10 years or between 20 and 50 years correlate with a systemic illness or pathologic cause of the gynecomastia. Such men should be evaluated thoroughly if the cause is not apparent after history and physical examination.
4. Malignant tumors can cause gynecomastia, although rarely. Consider testicular, pulmonary, and abdominal tumors (pancreatic, adrenal, gastric, and renal or bladder).

16. Should laboratory tests be ordered?

Some clinicians believe that hormonal testing is not cost-effective and favor checking testicular ultrasound alone to rule out the 3% incidence of feminizing tumors. Most practitioners, however, favor measuring liver enzymes, blood urea nitrogen, creatinine, thyrotropin (thyroid-stimulating hormone [TSH]), and testosterone (total and free). Estradiol, hCG, prolactin, LH, and follicle-stimulating hormone (FSH) may follow the initial screen. If the hCG or estradiol level is elevated, a testicular ultrasound scan is indicated. If this is negative, a chest radiograph and abdominal computed tomography (CT) scan should follow. For prepubertal patients, an adrenal CT scan precedes the testicular ultrasound examination.

17. What findings raise the suspicion of breast cancer?

Breast cancer is rare in men (0.2%). The risk is increased in Klinefelter's syndrome (3%–6%) and in male relatives of young women with breast cancer. Carcinoma is usually unilateral, painless, and nontender. Bloody discharge, ulceration, firmness, fixation to the underlying tissue, eccentric location, and adenopathy are suspicious findings. If doubt remains, a mammogram or biopsy should be considered. The sensitivity and specificity of mammogram for the diagnosis of male breast cancer approach 90%. The diagnostic accuracy of fine-needle aspiration cytology is greater than 90%. Excisional biopsy or mastectomy is recommended for malignant or suspicious cytology or mammogram appearance.

18. Will gynecomastia spontaneously regress?

Gynecomastia of recent onset and less than 3 cm in size regresses in 85% of patients. It may take 18 to 36 months for gynecomastia to resolve during puberty, but resolution occurs in more than 90% of pubertal boys. Persistence is uncommon after age 17 years. Gynecomastia resulting from a medication or underlying disease should also resolve after discontinuing the inciting agent or treating the underlying disease. Persistent tissue becomes more fibrous with time, however, and is less likely to remit spontaneously if it has been present for more than 12 months. More highly developed breast tissue (Tanner stages III, IV, and V) is also less likely to regress.

19. What is the treatment when gynecomastia does not regress?

Hormonal therapy can be attempted. Tamoxifen, clomiphene, danazol, dihydrotestosterone, testolactone, and anastrozole have all been used. Although studies are small and this is an off-label use, tamoxifen has the fewest side effects and the highest response rate for both improvement in tenderness and decrease in size. Partial regression can be seen in approximately 80% of patients and complete regression in about 60%. Medication is more likely to work if gynecomastia has been present for less than 4 months and the size of the tissue is less than 3 cm. Tamoxifen is given at a dosage of 10-20 mg daily with follow-up in 3 months to assess response. For recurrent or persistent gynecomastia greater than 3 cm, surgery is the recommended therapy. Liposuction or ultrasound-guided liposuction, excision, or both may be used. Low-dose bilateral breast irradiation and tamoxifen have also been studied in trials as prophylaxis to prevent the development of gynecomastia caused by estrogens and antiandrogens used in the treatment of prostate cancer.

KEY POINTS 2: TREATMENT OF GYNECOMASTIA

1. Most cases resolve spontaneously or after removal of the offending medication or treatment of the underlying disease.
2. Medical management with tamoxifen can be attempted for 3 to 6 months if desired.
3. The longer the tissue has been present and the larger the amount of tissue, the less likely a response to tamoxifen will be. Surgery is indicated for these cases.

BIBLIOGRAPHY

Bowers S, Pearlman N, McIntyre R, et al: Cost-effective management of gynecomastia, *Am J Surg* 176:638–641, 1998.
Braunstein G: Gynecomastia, *N Engl J Med* 357:1229–1237, 2007.
Braunstein G: Pathogenesis and diagnosis of gynecomastia, *UpToDate* 11:1–11, 2003.
Braunstein G: Prevention and treatment of gynecomastia, *UpToDate* 11:1–9, 2003.
Carlson HE: Approach to the patient with gynecomastia, *J Clin Endocrinol Metab* 96:15–21, 2011.
Ersoz H, Onde M, Terekeci H, et al: Causes of gynecomastia in young adult males and factors associated with idiopathic gynecomastia, *Int J Androl* 25:312–316, 2002.
Evans G, Anthony T, Appelbaum A, et al: The diagnostic accuracy of mammography in the evaluation of male breast disease, *Am J Surg* 181:96–100, 2001.
Fruhstorfer B, Malata C: A systematic approach to the surgical treatment of gynecomastia, *Br J Plast Surg* 56:237–246, 2003.
Gruntmanis U, Braunstein G: Treatment of gynecomastia, *Curr Opin Investig Drugs* 2:643–649, 2001.
Henley DV, Lipson N, Korach KS, et al: Prepubertal gynecomastia linked to lavender and tea tree oils, *N Engl J Med* 356:479–485, 2007.
Ismail A, Barth J: Endocrinology of gynaecomastia, *Ann Clin Biochem* 38:596–607, 2001.
Khan H, Blarney R: Endocrine treatment of physiological gynecomastia, *BMJ* 327:301–302, 2003.
Koh J, Tee A: Images in clinical medicine: tuberculous abscess manifesting as unilateral gynecomastia, *N Engl J Med* 361:2270, 2009.
Kolhi K, Jain S: Filariasis presenting as gynecomastia, *Breast J,* 18:83–84, 2012.
Narula HS, Carlson HE: Gynecomastia, *Endocrinol Metab Clin North Am* 36:497–519, 2007.
Widmark A, Fossa S, Lundmo P, et al: Does prophylactic breast irradiation prevent antiandrogen induced gynecomastia? *Urology* 61:145–151, 2003.
William MJ: Gynecomastia: its incidence, recognition and host characterization in 447 autopsy studies, *Am J Med* 34:103–112, 1963.
Yaturu S, Harrara E, Nopajaroonsri C, et al: Gynecomastia attributable to HCG secreting giant cell carcinoma of the lung, *Endocr Pract* 9:233–235, 2003.

CHAPTER 47

AMENORRHEA

Micol S. Rothman and Margaret E. Wierman

1. Define amenorrhea.

Amenorrhea is the absence of menstrual periods. Primary amenorrhea is the failure ever to begin menses; secondary amenorrhea refers to cessation of menstrual periods after cyclic menses have been established. Oligomenorrhea refers to lighter, irregular menses.

2. Describe the normal timing of puberty.

Puberty usually begins after age 8 years in girls and is heralded by the initiation of breast development. The average age for girls in the United States to begin menses is 12 years. This event generally signals the end of the pubertal process, occurring after the growth spurt and most somatic changes are completed. National Health and Nutrition Examination Survey (NHANES) data have noted the average age of menarche to be decreasing slightly, and African American girls have a mean earlier age of breast development onset when compared with white girls (8.9 years versus 10.0 years).

3. Summarize the underlying process of pubertal development.

The process is triggered by kisspeptin activation of gonadotropin-releasing hormone (GnRH)–induced episodic secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary gland. The pulsatile release of gonadotropins activates the ovaries and causes maturation of follicles and production of estrogen and, later, progesterone. These gonadal steroids give feedback at the level of the hypothalamus and pituitary to regulate GnRH and gonadotropin secretion. A final maturation event is the development of positive feedback by estradiol to induce the midcycle LH surge that stimulates ovulation. In many adolescents, menstrual cycles are anovulatory, and thus irregular, for the first 12 to 18 months. As the hypothalamic-pituitary-gonadal (HPG) axis matures, ovulatory cycles become more frequent. In normal adult women, all but one or two cycles per year are ovulatory.

4. What types of disorders cause primary amenorrhea?

Primary amenorrhea is defined as lack of menses by age 16 years or lack of secondary sexual characteristics by age 14 years. It usually results from abnormal anatomic development of the female reproductive organs or from a hormonal disorder involving the hypothalamus, pituitary gland, or ovaries (Box 47-1). The presence of normal secondary sexual characteristics in such patients suggests an anatomic problem, such as obstruction or failure of development of the uterus or vagina. In contrast, a lack of secondary sexual characteristics indicates a probable hormonal cause.

5. What are hypothalamic and pituitary causes of primary amenorrhea?

Idiopathic hypogonadotropic hypogonadism (IHH) can result from maturational arrest of GnRH-producing neurons during embryonic development (also called Kallmann syndrome when associated with anosmia) or failure of GnRH secretion at the time of puberty. The kisspeptin/Kiss receptor system has been shown to regulate GnRH secretion at puberty. Mutations in this pathway, as well as the GnRH receptor in the pituitary, may also cause failure of or impaired sexual maturation. Pituitary tumors, craniopharyngiomas, and Rathke pouch cysts can cause impaired LH and FSH secretion in adolescence that disrupts sexual maturation.

BOX 47-1. CAUSES OF PRIMARY AMENORRHEA

Anatomic
Congenital absence of ovaries, uterus, or vagina
Cervical stenosis
Imperforate hymen

Hormonal
Hypothalamic
Gonadotropin-releasing hormone deficiency
Hypothalamic tumor (craniopharyngioma)

Pituitary
Prolactinoma
Rathke cleft cyst
Panhypopituitarism from a genetic mutation

Ovarian
Gonadal dysgenesis (XO)
Chemotherapy or radiation damage of the ovaries
Androgen resistance syndromes (XY)

Other
Congenital adrenal hyperplasia

6. Summarize the ovarian causes of primary amenorrhea.

Ovarian function may be impaired because of gonadal dysgenesis secondary to Turner syndrome (45,XO karyotype) or destruction by chemotherapy or radiation before the completion of sexual maturation. The presence of ambiguous genitalia or palpable gonads in the labia or inguinal area may indicate a disorder of sexual differentiation, such as congenital adrenal hyperplasia (CAH) (21-hydroxylase deficiency) or an androgen resistance syndrome (testicular feminization) caused by mutations in the androgen receptor.

7. What disorders cause secondary amenorrhea?

Secondary amenorrhea, which is much more common than primary amenorrhea, occurs postpubertally. The causes are outlined in Box 47-2. Pregnancy should be excluded in all amenorrheic women. Onset of irregular menses after prior regular menses with associated hot flashes should suggest premature ovarian insufficiency (POI; i.e., premature menopause). Hypothalamic amenorrhea occurs in 3% to 5% of women and is caused by abnormal GnRH-induced gonadotropin secretion, often as a result of stress or eating disorders, but it is a diagnosis of exclusion. Hyperprolactinemia caused

BOX 47-2. CAUSES OF SECONDARY AMENORRHEA

Pregnancy
Hypogonadotropic hypogonadism
Hyperprolactinemia (from drugs or prolactinoma)
Pituitary tumor inhibiting gonadotropin production
Hypothalamic amenorrhea
Hypergonadotropic hypogonadism
Premature ovarian insufficiency (surgical or autoimmune)
Gonadotropin-producing pituitary tumors
Hyperandrogenic anovulation

by medications or tumors occurs in 10% of amenorrheic women. Pituitary tumors can also result in secondary amenorrhea. Hyperandrogenic anovulatory disorders such as polycystic ovary syndrome (PCOS), CAH, and, rarely, gonadal or adrenal tumors are usually associated with oligomenorrhea rather than amenorrhea and signs and symptoms of excess androgens, such as hirsutism and acne.

8. How do you evaluate a patient with amenorrhea?

One must determine whether the disorder is anatomic or hormonal, congenital or acquired, and where the defect is located. A complete history and physical examination provide the first essential clues. Pregnancy testing should always be ordered. Timed measurement of serum gonadotropin levels (LH and FSH) should be done within the first 5 days after the onset of spontaneous or induced menses. However, patients who have been taking birth control pills or other forms of hormonal contraceptives may need to wait a cycle to ensure accurate results. Patients with low or normal levels of LH and FSH (hypogonadotropic hypogonadism) have a disorder at the level of the hypothalamus or pituitary gland. In contrast, patients with high LH and/or FSH levels (hypergonadotropic hypogonadism) may have a defect at the level of either the ovary or the hypothalamic-pituitary unit (e.g., PCOS, in which the hypothalamic GnRH pulse generator is abnormally accelerated or a gonadotrope pituitary tumor that secretes the gonadotropins FSH and/or LH).

Other laboratory tests to consider include a prolactin level to exclude hyperprolactinemia and thyroid function tests to exclude thyroid disorders. In a patient with signs of excess androgens, dehydroepiandrosterone (DHEA) sulfate (DHEAS) and testosterone levels should be obtained. In the appropriate patient, Cushing syndrome should be excluded with a 24-hour urine free cortisol test, 1-mg dexamethasone suppression test, or late night salivary cortisol testing. Exclusion may require more than one test.

9. Discuss the major congenital causes of hypogonadotropic hypogonadism.

IHH results from GnRH deficiency. Female patients present with primary amenorrhea and lack of secondary sex characteristics. When associated with anosmia, the disorder is termed Kallmann syndrome. GnRH deficiency occurs in 1 in 8000 males and 1 in 40,000 females and may be X-linked, autosomal dominant, autosomal recessive, or sporadic. The X-linked form is associated with a mutation in the *KAL1* gene that encodes anosmin, a neural cell adhesion protein thought to be important in providing the scaffolding for GnRH neurons in their migration from the olfactory placode to the hypothalamus during embryonic development. Similarly, mutations in fibroblast growth factor-8 (FGF8) or its receptor (FGFR1) also disrupt neuronal and olfactory nerve migration. Thus GnRH neurons fail to reach their target in the hypothalamus. All other hypothalamic-pituitary function is normal. Investigators have found that mutations in the kisspeptin/Kiss receptor system that mediates GnRH secretion at puberty can also cause IHH. In these young women, estrogen administration is used to initiate the development of secondary sexual characteristics, and fertility can be attained using pulsatile GnRH or gonadotropin therapy.

10. What are the most frequent acquired forms of amenorrhea caused by hypogonadotropic hypogonadism?

- Hyperprolactinemia
- Hypothalamic amenorrhea

11. How does hyperprolactinemia cause amenorrhea?

Elevated prolactin levels may result from prolactinomas, hypothyroidism, medications (usually psychotropic drugs), or pregnancy. Hyperprolactinemia impairs the normal function of the HPG axis at multiple levels, but the major site of inhibition is the hypothalamic GnRH pulse generator. As prolactin levels rise, luteal phase defects develop, ovulation ceases, and menstrual cycles become shorter and irregular. Higher levels of prolactin are associated with amenorrhea. Treatment of the underlying cause of the elevated prolactin level usually normalizes menstrual cycles.

12. What is hypothalamic amenorrhea?

Hypothalamic amenorrhea refers to amenorrhea resulting from acquired disorders of the GnRH pulse generator. Excessive stress, exercise, and weight loss have been shown to act centrally to disrupt the

GnRH-induced pulsatile gonadotropin secretory pattern. In men, GnRH-induced LH pulses normally occur every 2 hours. In contrast, the LH pulse pattern in women must change across the menstrual cycle, accelerating from every 90 to 60 minutes across the follicular phase to every 30 minutes at ovulation and then slowing from every hour to every 4 to 8 hours across the luteal phase. Disruption of this precisely timed pattern results in anovulation, irregular menses, and, eventually, amenorrhea.

13. What types of GnRH pulse generator defects cause hypothalamic amenorrhea?

Hypothalamic amenorrhea may result from several types of gonadotropin secretory disorders. Some women with anorexia nervosa have absent GnRH-induced LH pulsations (prepubertal pattern), some have pulsations only at night (early pubertal pattern), and still others have LH pulses throughout the 24-hour period, but they are significantly reduced in amplitude or frequency.

14. How do you make a diagnosis of hypothalamic amenorrhea?

The diagnosis depends on excluding other causes of amenorrhea and then relies heavily on a history of weight loss, high levels of exercise or stress, or a combination of these. Supportive findings on physical examination include evidence of decreased estrogen effects and absence of other major illnesses. Laboratory testing usually reveals low serum estradiol and low or low-normal serum LH and FSH levels; the test for βhCG is negative, and the prolactin level is normal. Elevated FSH levels with low estradiol levels, in contrast, indicate probable POI.

15. What are the consequences of estrogen deficiency?

Short-term consequences of estrogen deficiency may include painful intercourse, hot flashes, and sleep disturbances. Among the more important long-term consequences are osteoporosis and premature coronary artery disease.

16. What treatment options are available for hypothalamic amenorrhea?

Interventions to reduce stress and balance nutritional intake with degree of exercise should be attempted initially. If these interventions are unsuccessful, estrogen replacement therapy (usually with oral contraceptives) can be instituted. However, data are mixed on the protective effect of estrogen on bone health in women with anorexia nervosa. Fertility, if desired, may be achieved by ovulation induction with clomiphene in mild cases or with human menopausal gonadotropins or pulsatile GnRH administration if the disorder is more severe.

17. What disorders cause amenorrhea with hypergonadotropic hypogonadism?

- Premature ovarian failure (high FSH, later high LH, and low estradiol)
- PCOS (low FSH, high LH, and normal estradiol)
- Gonadotropin-secreting pituitary tumors (high FSH and/or LH, often in postmenopausal women, low estradiol)

18. How do you make a diagnosis of premature ovarian failure?

POI, which is defined as menopause before age 40 years, may result from surgical removal or autoimmune destruction of the ovaries. Autoimmune destruction of the ovaries is characterized by a history of normal puberty and regular menses followed by the early onset of hot flashes, irregular menses, and eventual amenorrhea. Elevated serum FSH levels are the laboratory hallmark of gonadal failure secondary to loss of inhibin. To avoid misdiagnosis, blood for FSH and estradiol should be drawn in the early follicular phase (day 1-5 after onset of spontaneous or induced menses), because FSH levels rise along with LH at midcycle in normally ovulating women. Turner syndrome mosaics (XO/XX) may have several menses before they undergo menopause; therefore, a karyotype may be helpful if ovarian failure occurs in adolescence or the early 20s. Measurement of antimüllerian hormone (AMH) may predict the age of menopause and assess for POI. AMH is produced by granulosa cells in the ovary and decreases over time with eventual absence at the time of menopause.

19. What other disorders may coexist with POI?

Both patients and family members are at risk for other autoimmune disorders, including primary adrenal insufficiency (Addison disease), autoimmune thyroid disorders (Graves' disease, Hashimoto thyroiditis), type 1 diabetes mellitus, pernicious anemia (vitamin B_{12} deficiency), celiac sprue (often with vitamin D and iron deficiency), and/or rheumatologic disorders.

20. What are the treatment options for women with POI?

Estrogen therapy, usually in combination with progesterone, is used to decrease postmenopausal bone loss and premature coronary artery disease. Options for fertility in women with POI include incubation of donor eggs with the partner's sperm with in vitro fertilization protocols, along with sex hormonal preparation of the patient to enable her to carry the fetus in her uterus.

21. What is hyperandrogenic anovulation?

Hyperandrogenic anovulation refers to the cluster of disorders that manifest with irregular menses or amenorrhea and signs of androgen excess, such as hirsutism and acne. The disorders in this group include PCOS, androgen-secreting tumors of the ovaries or adrenal glands, Cushing syndrome, CAH (classic or attenuated form), and obesity-induced irregular menses. PCOS is the most common disorder of this type, described in 6% to 10% of reproductive age women.

22. How does the patient with PCOS manifest clinically?

Most patients with PCOS present in adolescence with a history of early menarche ($<$ 12 years) and persistently irregular menses. Hirsutism and acne beginning in the teenage years are other common features of the disorder. Approximately 60% of patients become overweight. Patients also frequently have signs of insulin resistance, including acanthosis nigricans, a velvety, hyperpigmented cutaneous lesion on the neck and in the axillae. Irregular, anovulatory menses lead to infertility, and the resultant unopposed estrogen exposure increases the risk of endometrial hyperplasia and carcinoma.

23. Describe the pathogenesis of PCOS.

Experts disagree on whether PCOS is a primary disorder of the central nervous system, the adrenal glands, or the ovaries or whether it is caused by insulin resistance. Existing data support the presence of an abnormal hypothalamic GnRH pulse generator at the time of puberty that is set too fast in PCOS, in contrast to hypothalamic amenorrhea, in which it is too slow. The pituitary gonadotropin response to GnRH is rate dependent; rapid GnRH pulses stimulate LH secretion but inhibit FSH production. The increased LH/FSH secretory ratio results in multiple ovarian follicle recruitment, but no dominant follicle development and an inability to trigger a GnRH-induced LH surge, thus causing anovulation and the appearance of multiple subcapsular cysts. The GnRH pattern triggers constant estrogen and enhanced androgen production by the ovaries. Other experts have suggested that a primary ovarian defect triggers the abnormal GnRH-induced LH pulse pattern. The ovarian prohormones (DHEA and androstenedione) and testosterone may be elevated; for unclear reasons, the adrenal androgens, DHEA and DHEAS, may be increased as well. High levels of circulating androgens decrease hepatic production of sex hormone–binding globulin (SHBG), thereby allowing more free androgen to target the skin and hair follicles and inducing the development of acne and hirsutism. Insulin resistance also plays a role in the ultimate picture; hyperinsulinemia augments ovarian androgen production to reduce SHBG levels further and increase the levels of free, biologically active androgens.

24. What are the criteria for the diagnosis of PCOS?

The 1990 National Institutes of Health criteria were modified by the Rotterdam criteria in 2003. The Rotterdam criteria include two of the following three features: oligoovulation or anovulation, clinical or biochemical signs of hyperandrogenism, and polycystic ovaries by ultrasound examination. Other causes such as Cushing syndrome, CAH, and androgen-secreting tumors should be excluded.

25. What are the treatment options for patients with PCOS?

The initial goals are to suppress androgen production and action and to ensure regular shedding of the endometrium, to decrease the risk of developing endometrial hyperplasia. Birth control pills are the treatment of choice; an antiandrogen, such as spironolactone, may be added if hirsutism is a major problem. Intermittent cycling with progesterone (Provera or Prometrium) is an alternative for endometrial protection, but it does not suppress the elevated androgens and their ultimate impact on ovarian morphology and function.

Fertility may be achieved with clomiphene citrate or human menopausal gonadotropins. Data show that clomiphene citrate is more efficacious than metformin for induction of ovulation and increased live births. There was a higher incidence of multiple births in the clomiphene group (5% versus 0%) than the metformin group. This trial was in contrast to other previous, smaller trials, which found similar rates in ovulation between the two medications but did not report live birth rates. The patients in this trial were also heavier, with an average body mass index (BMI) of 36.0 and 35.6 kg/m^2 in the clomiphene and metformin groups, respectively, although the results were not different in the subgroup of patients with a BMI lower than 30 kg/m^2.

26. Is there a role for insulin sensitizers in the treatment of women with PCOS?

Studies have shown that reducing insulin resistance and serum insulin levels with metformin results in modest decreases in serum androgen levels, decreased blood pressure, improved lipid levels, improvement in menstrual regularity, and improved ovulation in response to clomiphene citrate. The thiazolidinedione class of insulin sensitizers had shown promise, but weight gain and cardiovascular concerns limited their use. Small trials are investigating the potential of glucagon-like peptide-1 (GLP-1) therapy in PCOS. Predictors of responders to metformin may include patients with a family history of type 2 diabetes, history of rapid weight gain, and lack of severe obesity. Oral glucose tolerance testing and/or hemoglobin A_{1C} testing should be considered in all patients with PCOS.

27. What are the long-term consequences of PCOS?

Long-term consequences of PCOS include infertility, endometrial cancer, obesity, metabolic syndrome (hypertension, central adiposity, dyslipidemia, hyperglycemia), and type 2 diabetes. Epidemiologic studies have not yet defined a clear-cut increase in cardiovascular events, but long-term studies are under way.

28. How do tumors cause hyperandrogenic anovulation?

Androgen-producing ovarian and adrenal tumors are suggested by rapid progression of hirsutism and virilization (temporal hair recession, clitoris enlargement, breast atrophy, as well as high serum androgen levels [testosterone or DHEAS]). These tumors are usually associated with a serum testosterone level greater than 200 ng/dL or a DHEAS level greater than 1000 ng/mL. However, no level of testosterone or DHEAS absolutely confirms or excludes the diagnosis. The diagnosis of these tumors depends on accurate imaging studies.

29. What clinical and biochemical features suggest that a patient with hirsutism has CAH?

CAH (most commonly resulting from 21-hydroxylase deficiency) manifests in infancy with ambiguous genitalia in girls and occasionally with salt-wasting syndromes. Milder forms manifest in adolescence with early pubarche and irregular menses. Family history and ethnicity (Ashkenazi Jews, Italians, Hispanics, Eskimos) increase the suspicion for CAH. CAH is diagnosed by high basal ($>$ 2-3 ng/mL) or adrenocorticotropic hormone (ACTH)–stimulated ($>$ 10 ng/mL) levels of 17-hydroxyprogesterone with the test performed in the follicular phase.

30. When should you suspect obesity-induced hyperandrogenic anovulation?

Obesity-induced hyperandrogenic anovulation is suggested by a history of normal puberty and menses until progressive weight gain triggers the development of hirsutism, acne, oligomenorrhea, and, later, amenorrhea. Affected women have low serum levels of FSH and LH in the follicular phase, in contrast to women with PCOS (see subsequent discussion).

31. Describe the pathophysiology of obesity-induced hyperandrogenic anovulation.
Fat tissue contains aromatase and 5-alpha-reductase enzymes. Aromatase converts androgens to estrogens; when aromatase is present in increased amounts, as in obesity, constant (rather than fluctuating) serum estrogen levels are produced, inhibiting LH and FSH secretion and thereby impairing normal ovulation. Increased activity of 5-alpha-reductase, which converts testosterone to dihydrotestosterone (DHT), results in excessive DHT production that promotes the development of hirsutism and acne. Primary treatment with weight loss often results in restoration of normal reproductive function.

KEY POINTS 1: AMENORRHEA

1. Amenorrhea with estrogen deficiency can result in osteoporosis and premature cardiovascular disease.
2. Hyperprolactinemia and hypothalamic amenorrhea are the most common causes of acquired amenorrhea with low estrogen and low follicle-stimulating hormone levels.
3. Premature ovarian insufficiency is an autoimmune disease; affected patients are at risk for other autoimmune disorders, such as adrenal and thyroid disease, pernicious anemia, celiac sprue, and rheumatologic disorders.
4. Hyperandrogenic anovulation refers to amenorrhea with hirsutism and acne.
5. Polycystic ovary syndrome is the most common type of hyperandrogenic amenorrhea, associated with risks of infertility, endometrial cancer, the metabolic syndrome, and type 2 diabetes.

BIBLIOGRAPHY

Berga SL: Functional hypothalamic chronic anovulation. In Adashi WY, Rock JA, Rosenwaks Z, editors: *Reproductive Endocrinology, Surgery, and Technology*, Philadelphia, 1996, Lippincott-Raven, pp 1061–1075.

Broer SL, Eijkemans MJ, Sheffer GJ: Anti-mullerian hormone predicts menopause: a long term follow up in normoovulatory, *J Clin Endocrinol Metab* 96:2532–2539, 2011.

Cumming DC: Exercise-associated amenorrhea, low bone density, and estrogen replacement therapy, *Arch Intern Med* 156:2193–2195, 1996.

Legro RS: A 27-year-old woman with a diagnosis of polycystic ovary syndrome, *JAMA* 297:509–519, 2007.

Legro RS, Barnhart HX, Schlaff WD, et al: Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome, *N Engl J Med* 356:551–566, 2007.

Norman RJ, Dewailly D, Legro RS, et al: Polycystic ovary syndrome, *Lancet* 370:685–697, 2007.

Pralong FP, Crowley WF Jr: Gonadotropins: normal physiology. In Wierman ME, editor: *Diseases of the Pituitary: Diagnosis and Treatment*, Totowa, NJ, 1997, Humana Press, pp 203–219.

Rothman MS, Wierman ME: Female hypogonadism: evaluation of the hypothalamic-pituitary-ovarian axis, *Pituitary* 11:163–169, 2008.

Santoro N: Update in hyper- and hypogonadotropic amenorrhea, *J Clin Endocrinol Metab* 96:3281–3288, 2011.

Schlechte JA: Differential diagnosis and management of hyperprolactinemia. In Wierman ME, editor: *Diseases of the Pituitary: Diagnosis and Treatment*, Totowa, NJ, 1997, Humana Press, pp 71–77.

Taylor AE, Adams JM, Mulder JE, et al: A randomized, controlled trial of estradiol replacement therapy in women with hypergonadotropic amenorrhea, *J Clin Endocrinol Metab* 81:3615–3621, 1996.

Warren MP: Anorexia, bulimia, and exercise-induced amenorrhea: medical approach, *Curr Ther Endocrinol Metab* 6: 13–17, 1997.

Welt CK, Hall JE: Gonadotropin deficiency: differential diagnosis and treatment. In Wierman ME, editor: *Diseases of the Pituitary: Diagnosis and Treatment*, Totowa, NJ, 1997, Humana Press, pp 221–246.

Wierman ME: Gonadotropin releasing hormone. In Adashi WY, Rock JA, Rosenwaks Z, editors: *Reproductive Endocrinology, Surgery, and Technology*, Philadelphia, 1996, Lippincott-Raven, pp 665–681.

HIRSUTISM AND VIRILIZATION

Tamis M. Bright

1. Define hirsutism.

Hirsutism is the excessive growth of terminal hair in androgen-dependent areas: upper lip, chin, sideburns, earlobes, tip of the nose, back, chest, areolae, axillae, lower abdomen, pubic triangle, and anterior thighs. Hirsutism is frequently associated with irregular menses and acne. Hirsutism should be distinguished from hypertrichosis, which is a nonandrogen-dependent increase in vellus hair. Hirsutism affects 5% to 10% of females.

2. Define virilization.

Virilization consists of hirsutism, acne, and irregular menses along with signs of masculinization: deepening of the voice, increased muscle mass, temporal balding, clitoromegaly, and increased libido. Virilization results from high circulating levels of androgens, close to or in the male range, and is usually caused by an androgen-secreting tumor.

3. Where are androgens produced?

Twenty-five percent of testosterone comes from the ovaries, 25% from the adrenal glands, and 50% from peripheral conversion of androstenedione, which is produced by both the ovaries and adrenals. Testosterone is converted into dihydrotestosterone (DHT) by the enzyme 5-alpha-reductase, which is present in hair follicles, or to estradiol by the aromatase enzyme present in adipose tissue (Fig. 48-1). DHT binds to androgen receptors and is responsible for the transformation of vellus into terminal hair. Hair follicles also contain the enzymes that convert dehydroepiandrosterone (DHEA), which is produced by the adrenals, and androstenedione into testosterone.

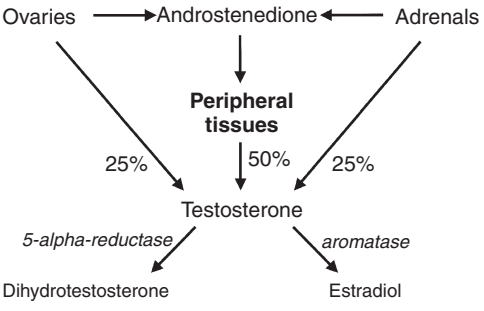

Figure 48-1. Testosterone production and metabolism.

4. What causes hirsutism?

Hirsutism is caused by hyperandrogenism. Androgens transform the fine, downy, minimally pigmented vellus hair in androgen-sensitive areas into coarse, pigmented, terminal hair. An increase in any of the androgenic steroids may cause high levels of DHT in the hair follicle and result in hirsutism.

Low levels of sex hormone–binding globulin (SHBG), which is produced by the liver, may promote hirsutism. Eighty percent of circulating testosterone is bound to SHBG, 19% is bound to albumin, and 1% is free. Decreases in SHBG increase the free fraction of hormone available to androgen-sensitive hair.

Increased activity of 5-alpha-reductase, even with normal circulating androgen levels, also may cause hirsutism by the excessive conversion of testosterone into DHT.

5. List the conditions that result in hirsutism

- Polycystic ovary syndrome (PCOS)
- Congenital adrenal hyperplasia (CAH)
- Idiopathic or familial hirsutism
- Cushing syndrome
- Prolactinoma
- Hypothyroidism
- Acromegaly
- Medications

6. Describe the pathophysiology of PCOS.

The exact cause of PCOS is unknown, but affected patients have been shown to have an accelerated rate of pulsatile gonadotropin-releasing hormone (GnRH) secretion from the hypothalamus. The gonadotropin secretory profile is highly dependent on the rate of GnRH pulsatility. Rapid GnRH pulses stimulate the secretion of luteinizing hormone (LH), but not follicle-stimulating hormone (FSH), from the pituitary gland. The increased LH/FSH secretory ratio results in arrested ovarian follicle development with cyst formation and hypertrophy of theca cells (hyperthecosis), thus leading to constant estrogen and increased androgen production with chronic anovulation.

7. How does PCOS manifest?

PCOS affects 5% to 10% of premenopausal women and is the most common cause of hirsutism. The hirsutism is gradually progressive, usually beginning at puberty, and most patients have irregular menses from the onset of menarche. However, in a study of hirsute patients with regular menses, 50% had polycystic ovaries. PCOS patients also frequently have insulin resistance and hyperinsulinemia. Because insulin decreases SHBG and increases the ovarian androgen response to LH stimulation, the hyperinsulinemia contributes to the elevated free androgen levels in PCOS. Thus, PCOS presents as a spectrum: some patients have minimal findings, whereas others have the entire constellation of hirsutism, acne, obesity, infertility, amenorrhea or oligomenorrhea, male pattern alopecia, acanthosis nigricans, hyperinsulinemia, and hyperlipidemia. The hyperandrogenism-insulin resistance-acanthosis nigricans (HAIR-AN) syndrome is a subtype of PCOS with marked hyperinsulinemia and androgen excess frequently associated with insulin receptor defects.

8. Describe the pathophysiology of the hyperandrogenism in CAH.

CAH results from a deficiency of one of the key enzymes in the cortisol biosynthesis pathway; it often manifests with precocious puberty and childhood hirsutism. Partial or late-onset CAH, resulting from milder deficiencies of the same enzymes, may cause postpubertal hirsutism. Ninety percent of CAH is secondary to 21-hydroxylase deficiency, which causes a defect in the conversion of 17-hydroxyprogesterone (17-OHP) to 11-deoxycortisol and of progesterone to desoxycorticosterone (DOC). The resulting low cortisol production rate leads to hypersecretion of pituitary adrenocorticotropic hormone (ACTH), which stimulates overproduction of 17-OHP and progesterone, as well as adrenal androgens, particularly androstenedione (Fig. 48-2). Hirsutism results from the androgen excess.

9. Do any other causes of CAH result in hirsutism?

Deficiency of 11-beta-hydroxylase decreases the conversion of 11-deoxycortisol to cortisol and of DOC to corticosterone. This stimulates hypersecretion of ACTH, with consequent overproduction of

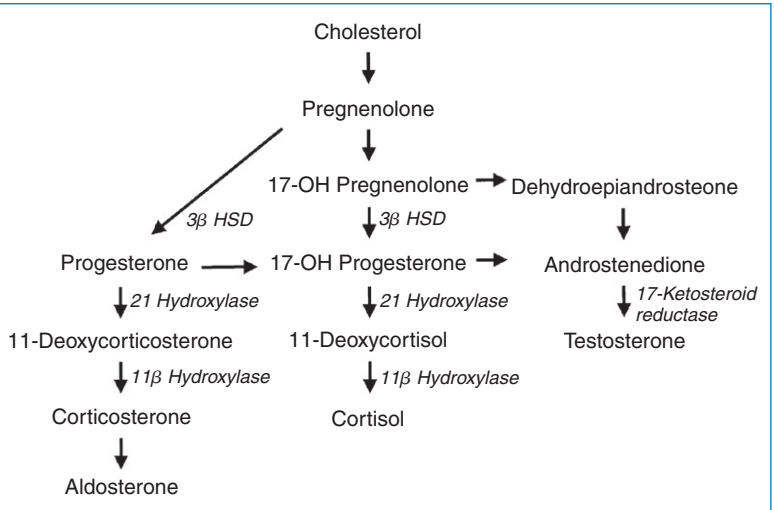

Figure 48-2. Adrenal steroid biosynthesis. *3β HSD,* 3-beta-hydroxysteroid dehydrogenase.

11-deoxycortisol, DOC, and androstenedione. Patients also frequently develop hypertension from the mineralocorticoid DOC. Deficiency of 3-beta-hydroxysteroid dehydrogenase (3β HSD) decreases the conversion of pregnenolone to progesterone and 17-hydroxypregnenolone to 17-OHP. This defect increases pregnenolone, 17-hydroxypregnenolone, and the androgens DHEA, DHEA sulfate (DHEAS), and androstenediol, which promote the development of hirsutism. Deficiency of 17-ketosteroid reductase decreases the conversion of androstenedione to testosterone, DHEA to androstenediol, and estrone to estradiol. Affected patients have elevated basal levels of androstenedione, DHEA, and estrone (see Fig. 48-2).

10. Describe the pathophysiology of idiopathic and familial hirsutism.

Idiopathic hirsutism is believed to be caused by increased cutaneous activity of 5-alpha-reductase or enhanced skin sensitivity to androgens. Familial hirsutism is an ethnic tendency to have a higher density of hair follicles per unit area of skin. Mediterraneans and Hispanics have increased hair density, whereas Asians have lower density. Patients with idiopathic or familial hirsutism usually have the onset of hirsutism shortly after puberty with a slow subsequent progression. They have normal menses and fertility, as well as a normal hormonal profile.

11. How do Cushing syndrome, prolactinomas, hypothyroidism, and acromegaly cause hirsutism?

All causes of Cushing syndrome may result in hypertrichosis because of increased vellus hair on the face, forehead, limbs, and trunk secondary to cortisol hypersecretion. Cushing syndrome resulting from an adrenal tumor also may produce hirsutism and virilization from increased secretion of androgens with cortisol.

Hyperprolactinemia suppresses GnRH activity, which diminishes pulsatile LH secretion from the pituitary gland and results in decreased ovarian estrogen production and amenorrhea. Prolactin also increases the adrenal androgens, DHEA and DHEAS. Hypothyroidism decreases SHBG and thereby leads to an increase in free testosterone. Acromegaly is frequently associated with PCOS, and the hirsutism may result from the PCOS in conjunction with excessive insulin-like growth factor-I (IGF-I), growth hormone, and insulin resistance.

12. Which medications can cause hirsutism?

Danazol, testosterone, glucocorticoids, metyrapone, phenothiazines, anabolic steroids, valproic acid, and oral contraceptive pills (OCPs) containing levonorgestrel, norgestrel, and norethindrone can cause hirsutism. Phenytoin, cyclosporin, diazoxide, minoxidil, glucocorticoids, streptomycin, penicillamine, and psoralens can cause hypertrichosis.

13. What conditions cause virilization?

Ovarian Tumors	Adrenal Disorders
Thecoma	Congenital adrenal hyperplasia
Fibrothecoma	Adenoma
Granulosa and granulosa-theca cell tumors	Carcinoma
Arrhenoblastoma (Sertoli-Leydig cell tumors)	
Hilus cell tumors	
Adrenal rest tumors of the ovary	
Luteoma of pregnancy	

KEY POINTS 1: PATHOGENESIS OF HIRSUTISM AND VIRILIZATION

1. Hirsutism is the excessive growth of terminal hair and is frequently associated with irregular menses.
2. Virilization consists of hirsutism and irregular menses associated with signs of masculinization.
3. Hirsutism and virilization usually result from excess androgens.
4. The common causes of hirsutism are polycystic ovary syndrome, congenital adrenal hyperplasia (CAH), idiopathic or familial hirsutism, and medications.
5. The common causes of virilization are ovarian tumors, adrenal tumors, and CAH.

14. When should a patient be evaluated for hirsutism?

Any patient with moderate to severe hirsutism, rapid development of hirsutism, or coexistence of amenorrhea, irregular menses, infertility, acanthosis, or virilization should be evaluated. A patient with regular menses who shows significant concern about her hirsutism also may warrant a workup.

15. What information is important in the history?

- Age of onset, progression, and extent of hair growth
- Current measures of hair removal and frequency of use
- Age at menarche, regularity of menses, and fertility
- Family history of hirsutism
- Change in libido or change in voice
- Symptoms of Cushing's disease, prolactinoma, acromegaly, or hypothyroidism
- Medications or anabolic steroid use

16. What findings are important on physical examination?

- Distribution and degree of hirsutism
- Increased muscle mass, temporal balding, clitoromegaly, or acne
- Obesity
- Acanthosis nigricans
- Visual field defects

- Moon facies, plethora, buffalo hump, supraclavicular fat pads, striae, or thin skin
- Galactorrhea
- Goiter, loss of lateral eyebrows, periorbital edema, dry skin, or delayed reflexes
- Acromegalic features
- Abdominal or pelvic masses

17. What laboratory tests should be ordered for a patient with hirsutism?

Laboratory testing should be guided by the results of the history and physical examination. Many authors advocate against testing in patients with regular menses and only gradual progression of mild hirsutism. However, serum levels of total and free testosterone, DHEAS, and 17-OHP can be useful tests, depending on the individual patient. Patients with signs or symptoms of hypothyroidism, hyperprolactinemia, acromegaly, or Cushing syndrome also should be evaluated with serum thyroid-stimulating hormone (TSH), prolactin, IGF-I, or 24-hour urine cortisol testing, respectively. Otherwise, these tests need not be obtained for every patient.

18. How are the results of these laboratory tests interpreted?

For a patient without signs of virilization, it is important to differentiate idiopathic hirsutism, PCOS, and CAH because each is treated differently. Total and free testosterone, DHEAS, and 17-OHP help in the differentiation. Idiopathic hirsutism has normal levels on all four tests. PCOS has mildly increased testosterone, normal or slightly increased DHEAS, and normal 17-OHP. CAH has elevated testosterone and DHEAS and mild to marked elevation of 17-OHP. An early morning follicular phase level of 17-OHP greater than 500 ng/dL (normal $\leq$200 ng/dL) is diagnostic.

19. What do you do if a patient has borderline (200–500 ng/dL) elevations of 17-OHP?

A borderline elevated level requires an ACTH stimulation test with assessment of 17-OHP levels at baseline and 60 minutes after stimulation with ACTH. The levels are then plotted on a nomogram to determine normals, heterozygous carriers of the abnormal 21-OH gene, and patients with late-onset 21-OH deficiency. Some patients with late-onset 21-OH deficiency have normal baseline 17-OHP levels; however, the ACTH-stimulated levels are usually diagnostic. Results can be confirmed with a molecular genetic test of CYP21A2.

20. What laboratory tests should be ordered in a patient with virilization?

A patient with virilization should be evaluated to determine whether she has an ovarian tumor, an adrenal tumor, or CAH. As in patients without virilization, tests should include serum total testosterone, DHEAS, and 17-OHP. A markedly increased testosterone level ($>$200 ng/dL) with normal values on the other tests points to an ovarian tumor. High levels of DHEAS ($>$700 ng/mL) with or without high testosterone levels suggest an adrenal tumor. Increased levels of 17-OHP with modest elevations of DHEAS and testosterone are more consistent with CAH. Laboratory values suggesting tumors should be followed with a transvaginal ultrasound scan of the ovaries or computed tomography (CT) of the adrenals or ovaries. If no mass is found, iodocholesterol scanning of the adrenals or venous sampling of the ovaries or adrenals can be performed for localization before surgical removal.

21. How is PCOS treated in a patient desiring pregnancy?

If the patient's primary concern is fertility, clomiphene is the usual drug of choice. If clomiphene fails to induce ovulation, cyclic gonadotropin administration is often useful. Pulsatile GnRH also has been used with some success. In obese patients, weight reduction alone has been shown to increase the spontaneous ovulation rate. If a component of adrenal androgen (DHEAS) hypersecretion appears to be present, low-dose dexamethasone, 0.125 to 0.5 mg, or prednisone, 5 to 7.5 mg, can be added at night. Steroids may improve the ovulation rate, as well as decrease hirsutism. In patients resistant to medical management, surgical destruction of small sections of the ovaries induces ovulation in some patients. Wedge resection of the ovaries has been replaced by laparoscopic ovarian diathermy, in which laser or electrocautery is used to destroy portions of the ovaries.

22. How is PCOS treated in a patient not desiring pregnancy?

If fertility is not the issue, OCPs or cyclic progestins are used to induce regular menses and thereby decrease the risk of endometrial cancer. Preparations containing androgenic progestins, such as norgestrel and norethindrone, should be avoided. Weight reduction should be encouraged. As noted earlier, steroids may be added in patients with an elevated DHEAS level; however, this may increase glucose in an already glucose-intolerant patient. If hirsutism does not improve with these measures, the agents listed in questions 24 and 27 through 30 may be necessary.

23. What can be done about the hyperinsulinemia of PCOS?

Patients with PCOS should be evaluated with a fasting blood glucose or an oral glucose tolerance test and a lipid profile because of the high prevalence of glucose intolerance, diabetes, and hyperlipidemia in this disorder. These problems should be addressed separately because they are not resolved by treating the hyperandrogenism alone. The insulin sensitizers metformin and thiazolidinediones have been used in patients with PCOS with and without increased glucose levels. Metformin, rosiglitazone, and pioglitazone improve insulin resistance, decrease androgens, increase SHBG, improve regularity of menses, and increase fertility. In patients whose condition is not controlled on metformin alone, there is some added benefit in combination with pioglitazone, thus resulting in further increases in SHBG, insulin sensitivity, and improved menstrual regularity. Thiazolidinediones have several side effects, including fluid retention, exacerbation of heart failure, increased osteoporotic fractures, and possible increased risk of cardiovascular events and bladder cancer, and therefore these drugs should be used with caution.

24. What is the treatment for CAH?

Glucocorticoid replacement decreases ACTH secretion and thereby reduces excessive adrenal androgen production. Mineralocorticoid replacement is also required for some causes of CAH. Treatment with the regimens listed in questions 26 through 30 can hasten improvement of the hirsutism.

25. Describe how OCPs are used for the treatment of hirsutism.

OCPs are the most commonly used therapy. They increase serum estrogens and SHBG, which decreases free testosterone levels. Monophasic and triphasic preparations work equally well. Preparations containing the progestins desogestrel, norgestimate, drospirenone, and gestodene are believed to be the best because they are the least androgenic. Potential side effects include weight gain, bloating, nausea, emotional lability, breast pain, and deep venous thrombosis.

26. Describe how antiandrogens are used for the treatment of hirsutism.

Spironolactone is an androgen receptor blocker and inhibits 5-alpha-reductase. Side effects include diuresis, fatigue, and dysfunctional uterine bleeding. Initial doses are 50 to 100 mg twice daily, tapered to 25 to 50 mg/day after an effect has been seen. Flutamide, another androgen receptor blocker, is dosed at 62.5 to 500 mg daily. Side effects include increased liver function tests (LFTs) and rare fatal hepatotoxicity. Finasteride, a 5-alpha-reductase inhibitor, effectively decreases hirsutism. Side effects include headache and depression. Dosage is 2.5 to 7.5 mg/day. The antiandrogens are usually used in combination with OCPs for additive effects and to give adequate birth control because antiandrogens can feminize a male fetus.

27. Describe how GnRH agonists are used for the treatment of hirsutism.

By providing constant rather than pulsatile GnRH levels to the pituitary, GnRH agonists reduce gonadotropin secretion and thereby decrease ovarian production of both estrogen and androgen. Estrogen replacement must be given to avoid hot flashes, vaginal dryness, and bone density loss. Leuprolide (3.75 mg/month intramuscularly), buserelin or nafarelin nasal spray, and goserelin subcutaneous implants effectively reduce hirsutism. Some studies demonstrated an increased effect over OCPs alone, whereas others showed similar effects. The preparations are expensive and thus are usually reserved for severe PCOS unresponsive to other therapies.

KEY POINTS 2: DIAGNOSIS AND TREATMENT OF HIRSUTISM AND VIRILIZATION

1. Appropriate laboratory testing includes at least serum total testosterone, dehydroepiandrosterone sulfate, and 17-hydroxyprogesterone.
2. Treatment of hirsutism is usually with a combination of oral contraceptive pills, spironolactone, eflornithine, and cosmetic measures; however, other antiandrogens and gonadotropin-releasing hormone agonists can be used.
3. Patients with polycystic ovary syndrome may have improvement of symptoms if they are treated with insulin sensitizers.
4. Treatment of virilization is surgical removal of the tumor or steroid treatment for congenital adrenal hyperplasia.

28. What topical agent is approved for the treatment of hirsutism?

Eflornithine HCl 13.9% cream is the newest agent for the treatment of facial hirsutism. Eflornithine HCl irreversibly inhibits ornithine decarboxylase, an enzyme necessary for hair follicle cell division. Inhibition of ornithine decarboxylase results in a decreased rate of hair growth. In clinical trials, 58% of patients had marked improvement or some improvement as compared with 34% of controls after 24 weeks of treatment. The most common side effects are acne, pseudofolliculitis barbae, burning, tingling, erythema, or rash over the applied area. Generally, side effects resolve without treatment and rarely require discontinuation of the medication. The cream is applied to the face twice daily. The patients' hirsutism will return to baseline by 8 weeks following discontinuation of the medication.

29. What cosmetic measures can be used for the treatment of hirsutism?

Bleaching, shaving, plucking, waxing, depilating, and electrolysis are effective measures that can be used alone or in combination with the previously described treatments. They remove terminal hair that is already present while the patient waits for medications to decrease new growth and rate of transformation to terminal hair.

Laser-assisted hair removal is an effective treatment for hirsutism. It is an outpatient procedure that uses ruby, alexandrite, diode, or yttrium aluminum garnet lasers, or intense pulsed light therapy, all of which cause thermal injury to the hair follicle. At least three to six treatments about 2 to 2.5 months apart are required. The techniques result in removal of hair, and a period of 2 to 6 months before the regrowth of hair, which is thinner and lighter. Alexandrite and diode lasers appear to be the most effective. Patients with light skin and dark hair have the best results with the fewest side effects. The side effects include minimal discomfort, local edema and erythema lasting 24 to 48 hours, rare petechiae, and infrequent hyperpigmentation lasting less than 6 months.

30. How do you choose the appropriate therapy for the patient's hirsutism?

Most patients are given a trial of OCPs, with or without spironolactone, and are advised to use cosmetic measures while waiting for the medications to work. The topical cream eflornithine HCl may be used alone or in combination with other measures. Because of their more serious side effects and higher cost, the other medications are reserved for the most severe cases in which OCPs and spironolactone fail. No matter what therapy is chosen, the patient must be made aware that results will not be seen for at least 3 to 6 months. Although many medications and combinations have been used, only topical eflornithine HCl is currently approved by the Food and Drug Administration for treatment of hirsutism. Unfortunately, most patients have a relapse of hirsutism approximately 12 months after discontinuation of medical therapy.

WEBSITES

http://www.dermis.net/dermisroot/en/35888/diagnose.htm: Atlas of Dermatology. Dermatology Information System.

http://www.emedicine.com/med/topic1017.htm: eMedicine. Medscape.

BIBLIOGRAPHY

Blank S, McCartney C, Marshall J: The origins and sequelae of abnormal neuroendocrine function in polycystic ovary syndrome, *Hum Reprod Update* 12:351–361, 2006.

Cosma M, Swiglo B, Flynn D, et al: Clinical review: insulin sensitizers for the treatment of hirsutism: a systematic review and metaanalyses of randomized controlled trials, *J Clin Endocrinol Metab* 93:1135–1142, 2008.

Lapidoth M, Dierickx C, Lanigan S, et al: Best practice options for hair removal in patients with unwanted facial hair using combination therapy with laser: guidelines drawn up by an expert working group, *Dermatology* 221:34–42, 2010.

Martin K, Chang R, Ehrmann D, et al: Evaluation and treatment of hirsutism in premenopausal women: an Endocrine Society clinical practice guideline, *J Clin Endocrinol Metab* 93:1105–1120, 2008.

Moghetti P, Tosi F, Tosti A, et al: Comparison of spironolactone, flutamide, and finasteride efficacy in the treatment of hirsutism: a randomized, double blind, placebo-controlled trial, *J Clin Endocrinol Metab* 85:89–94, 2000.

Practice Committee of the American Society for Reproductive Medicine: The evaluation and treatment of androgen excess, *Fertil Steril* 86:S241–S247, 2006.

Rothman M, Wierman M: How should postmenopausal androgen excess be evaluated? *Clin Endocrinol* 75:160–164, 2011.

Smith S, Piacquadio D, Beger B, et al: Eflornithine cream combined with laser therapy in the management of unwanted facial hair growth in women: a randomized trial, *Dermatol Surg* 32:1237–1243, 2006.

Unluhizarci K, Kaltsas G, Kelestimur F: Nonpolycystic ovary syndrome–related endocrine disorders associated with hirsutism, *Eur J Clin Invest* 42:86–94, 2012.

Wolf J Jr, Shander D, Huber F, et al: Randomized, double-blind clinical evaluation of the efficacy and safety of topical eflornithine HCl 13.9% cream in the treatment of women with facial hair, *Int J Dermatol* 46:94–98, 2007.

MENOPAUSE

Wesley Nuffer

1. Define menopause.

The formal definition of menopause is the permanent cessation of menses, clinically defined as 12 months after a woman's last menstrual period. It marks the end of a woman's normal ovarian function.

2. When does menopause usually occur?

The median age for the last menses is defined at 51.4 years. There is large variability in the exact age at which menopause occurs. A genetic component appears to be involved because women often experience menopause around the same time as their mother or sister, but there are numerous examples of circumstances when this does not hold true. It also appears that women in Asia may experience menopause at an earlier age (42–49 years old).

3. How is menopause diagnosed clinically?

In a woman who is more than 45 years old, 12 months of secondary amenorrhea is sufficient to diagnose menopause. Although a pelvic examination may reflect some atrophy of the vaginal mucosa, this is not always remarkable. Generally, there are elevations in both follicle-stimulating hormone (FSH), which rises significantly (approximately 10- to 20-fold), and luteinizing hormone (LH), which has a more modest rise (approximately 3-fold). It is generally considered that an FSH level higher than 40 IU/L indicates ovarian failure, but these levels are not reliable for diagnosis because in certain circumstances these hormones may be elevated before menopause.

4. What is perimenopause?

Menopause should not be thought of as occurring suddenly, but rather as a transitional process over time. Perimenopause (also called menopause transition) describes the transition toward menopause, in which women's cycles can vary in frequency and severity. Menopause symptoms often begin to appear during this time.

5. Physiologically, what determines the timing of menopause?

The absence of ovarian oocytes signals the cessation of menstruation in women. Oocyte numbers decline throughout a woman's life; they actually peak in number in utero and decline quite rapidly before birth, by which time approximately 80% of oocytes have been lost. Exhaustion of oocytes causes cessation of menses.

6. What is premature ovarian failure?

Ovarian failure is considered premature when it occurs in women who are less than 35 years old. Symptoms are very similar to those experienced by women entering menopause. There can be several causes of this condition, including autoimmune disorders, chromosomal defects, chemotherapy treatment, and some unknown causes. The incidence of this condition is estimated at 0.3% within the United States.

7. What are the symptoms of menopause?

The hallmark symptom of menopause, which often occurs during the perimenopause transition, consists of hot flashes. During these episodes, which last seconds to minutes, the woman experiences a tremendous warming of her body, often with accompanying redness of the skin and sweat production.

Menopausal women often describe this variable temperature control as occurring at night, a condition termed "night sweats." Other symptoms that are less prevalent include the following: insomnia; short-term memory loss or "mental fogginess"; a loss of "youthfulness" to the skin, hair, and nail cells; and skin and vaginal dryness.

8. Will all women experience menopause symptoms?

It is estimated that most women (approximately 85%) will experience some types of vasomotor symptoms with menopause. These can vary greatly in severity; the most severe symptoms usually occur in women who have had their ovaries surgically removed, thereby transitioning to what has been called "instant menopause."

9. Do menopausal symptoms last indefinitely?

Generally, menopausal symptoms are worst during perimenopause or the first few years after menopause. Most women are able to tolerate these symptoms after approximately 3 to 5 years. Some women, however, continue to suffer from hot flashes and other menopause symptoms 10 years or longer after menopause occurs, at almost the same severity as when the symptoms first appeared.

10. What physiologic changes accompany menopause?

Loss of bone calcium, increased rates of coronary artery disease, skin and vaginal atrophy, hot flashes, and alterations in the lipid profile (mainly increased triglycerides and low-density lipoprotein cholesterol, and decreased high-density lipoprotein cholesterol) all occur through and after menopause.

11. What estrogens are present in a woman's body?

Women naturally have three different estrogens present in varying amounts: estrone (E1), estradiol (E2), and estriol (E3). Estradiol is the most potent of the three estrogens, binds equally to both the α- and β-estrogen receptors, and converts freely back and forth with estrone in the body. Some evidence suggests that estrone has a higher carcinogenic risk compared with the other estrogens, possibly because of its higher affinity to the α-estrogen receptor (approximately 5:1 α:β). Estriol is a metabolite of estradiol and estrone and will not convert back to E1 or E2 once formed, but rather is excreted out through the urine. It has a higher selective binding to the β-estrogen receptor (3:1 β:α).

12. What is the predominant circulating estrogen during and after menopause?

Estradiol, or E2, is the most abundant estrogen in a woman's body during reproductive years, and it is produced by the ovaries. During menopause, this production wanes and then stops, and estrone, or E1, becomes the dominant estrogen, converted in adipose tissue from androstenedione, which is secreted from the adrenal glands.

13. There was a major shift in managing women at menopause after the Women's Health Initiative (WHI) trial. Why did this occur?

The WHI trial was a landmark trial from the National Institutes of Health (NIH) that enrolled more than 27,000 women 50 to 79 years old. Those women with no previous hysterectomy received combined conjugated equine estrogen (CEE) plus medroxyprogesterone acetate (MPA) or placebo (16,608 women), and those women who had previously had a hysterectomy received either CEE or placebo (10,739 women). The primary outcomes for this trial were coronary heart disease events. Much of the media attention toward this trial came when the combined arm of CEE and MPA was stopped early in July 2002 after investigators found that the associated health risks outweighed potential benefits of therapy. Data showed an increased risk of invasive breast cancer, along with an increased incidence of coronary heart disease, pulmonary embolism, and stroke. Positive outcomes included a reduction in colon cancer and fewer hip fractures. The estrogen-alone arm of the trial also showed an increased risk of stroke and blood clots without preventing heart disease (Fig. 49-1).

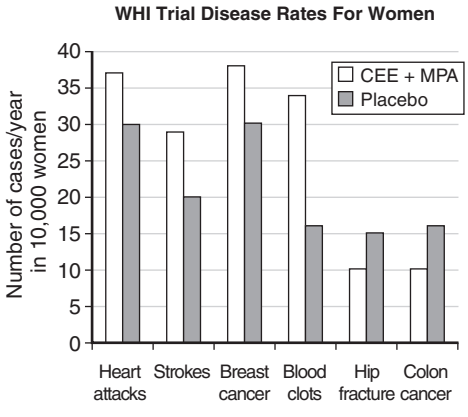

Figure 49-1. Women's Health Initiative trial disease rates for women. CEE, Conjugated equine estrogen; MPA, medroxyprogesterone acetate.

14. What are some of the limitations of the WHI trial data?

One of the largest recognized limitations to these data is the age of women at enrollment; it is widely believed that a woman's greatest benefit derived from hormone replacement therapy (HRT) occurs in the years just following menopause, or in the age range of 50 to 60 years. Enrolling women 50 to 79 years old included a large number of women more than 60 years old, and this may have affected the results shown from the trial. The investigators identified that only one hormone regimen (CEE 0.625 mg/day and MPA 2.5 mg/day) was used in the arm of the trial in which women had an intact uterus, so the rationale of extrapolating these results to state that all hormone products carry the same risk has been questioned.

15. Should women be taking HRT at menopause?

The American Association of Clinical Endocrinologists (AACE) clinical guidelines recommend against long-term HRT and recommend that estrogen therapy not be used for cardiovascular disease prevention. Estrogen is indicated for the prevention of osteoporosis, but the risks of long-term use are thought to outweigh the benefits. Therefore, this indication is generally reserved for women less than 60 years old, and it should be carefully evaluated based on the individual woman's risk and possible use of other treatments, including bisphosphonates. Similarly, the American Congress (formerly College) of Obstetrics and Gynecologists (ACOG) and the North American Menopause Society (NAMS) recommend estrogen and possible progestin supplementation only for symptomatic relief. They further recommend that women should take the lowest dose possible for the shortest amount of time.

The decision regarding whether a woman should be treated for severe hormone symptoms should be an individual choice made in collaboration between the patient and provider. Perceived risks based on the WHI trial and accompanying literature should be presented and weighed against the severity of symptoms and the woman's health-related quality of life. Because the greatest benefits of HRT are seen in women less than 60 years old, it is generally thought that any HRT use should occur between the ages of 50 and 60 years, and attempts should be made to taper the therapy to discontinuation every 3 to 5 years.

16. What is a bio-identical hormone?

The term *bio-identical* was coined to represent hormones that are identical to what the body naturally produces. Although bio-identical hormones are often promoted from compounding pharmacy sources,

many of the prescription hormone products that are approved by the Food and Drug Administration (FDA), such as estradiol and progesterone, are also bio-identical. This term has been used to contrast these hormones from other hormone products, most notably CEE, which originates from the urine of pregnant horses, or MPA, a synthetic progestin compound that binds to the progesterone receptor.

17. Are bio-identical hormones safer for supplementation?

There was a tremendous amount of publicity and promotion for bio-identical hormones following the WHI trial, as women sought other options for controlling severe menopause symptoms. Currently, most of the evidence suggests that all estrogen products are similar in nature and effect, regardless of source. Proponents of bio-identical hormones believe that the physiologic similarity of these molecules yields benefits to the body that are not seen with other estrogen and progestin hormones. Some compounded hormones include estriol, or E3, which is not FDA approved for use in the United States, although it is used in Europe and other countries. Estriol has limited data to support its efficacy, and the FDA took a strong stance in 2008 in response to a petition from Wyeth Ayerst to prohibit the use of estriol, by citing a lack of safety and efficacy with its use. With regard to progesterone, some data support different physiologic activities when compared with MPA, and evidence from observational trials and controlled primate trials suggests a better safety profile than MPA, but large randomized placebo-controlled trials are still lacking to verify this potential benefit.

KEY POINTS 1: MENOPAUSE

1. Menopause is the cessation of menses, and it comprises approximately the last third of a woman's life.
2. Menopausal symptoms are most severe early during perimenopause and menopause, and the hallmark symptom consists of hot flashes.
3. Hormone replacement therapy should be reserved primarily for symptomatic relief, targeting women 50 to 60 years old, and the using lowest doses for the shortest interval of time.
4. The term *bio-identical* refers to any hormone identical to what is found in the body and includes both prescription hormones (i.e., estradiol, progesterone) and compounded products.
5. Hormone therapy should be based on symptom control, not on blood or saliva hormone levels.

18. If a woman is taking HRT, should dosing be based on serum or saliva levels?

According to AACE guidelines, HRT should be based on a woman's symptoms, not on specific drug levels. There is some debate about whether serum or saliva levels are optimal for measuring hormone levels. Saliva test proponents cite the findings that hormones are generally quite lipophilic and are not widely found in the blood, and that saliva levels more closely represent intracellular levels of hormone. Saliva levels, however, are documented to vary substantially depending on the time of day when they are collected, and they have not been established as a reliable indicator of therapeutic response. They are not FDA approved and are generally not considered to correlate with serum hormone levels. It is also often difficult for women to obtain saliva level tests through their medical benefits, and the cost of measuring saliva levels can be significant. There is no clearly established therapeutic range for estrogen or progestin in the body, so current recommendations are to base therapy on the lowest possible dose that will adequately control menopausal symptoms.

19. What is the role of progestin supplementation?

Progestins, most notably MPA, are used in conjunction with estrogen treatment to protect women from developing endometrial cancer. They are given to women who have not received a hysterectomy. There is a suggestion based on smaller studies that supplementing progesterone may yield

additional benefits, even in women who have received a hysterectomy, but it is not routinely recommended for use beyond endometrial protection.

20. Do women need androgen supplementation?

This is a controversial area. The Endocrine Society's consensus statement recommends against a diagnosis of androgen deficiency in women because of a lack of data documenting "normal" androgen levels in women across their life span. Evidence indicates that, in some women, supplementing low levels of testosterone (often starting with 1% testosterone creams) may help treat symptoms of fatigue or low energy and decreased libido. When androgen is supplemented, dosing is often limited by unwanted side effects (oily skin and acne, hirsutism, voice lowering).

21. Are compounded hormones superior to other hormone treatment?

Currently, there is no evidence that compounded hormones outperform other HRTs. Compounded medications depend on a reliable source, so women who seek compounded hormones need to identify a pharmacy that performs its own quality assurance on products, follows proper protocols, and has reliable equipment to provide consistent, accurate products. Some data suggest that compounded progesterone creams may not provide high enough systemic levels to provide adequate protection to the endometrium.

22. Does male menopause exist?

There is literature to suggest that androgen levels decline in men, and indications exist for supplementation in some circumstances. Generally, this is not considered "male menopause," most likely because it does not appear to be a physiologically programmed event.

23. What are some other options for managing menopausal symptoms?

Based on the severity of the woman's symptoms and the specific symptoms she is experiencing, there are numerous other approaches for managing these without HRT. Antidepressant drugs such as fluoxetine, paroxetine, and venlafaxine have documented evidence for helping to manage hot flash symptoms, and clonidine has been used for this indication, particularly at night, although side effects (hypotension and dry mouth) limit clonidine's use. There are herbal products that have some documented success, some of which have weaker phytoestrogen activity, such as soy products and black cohosh. These herbal products typically do not have the potency to control more severe menopausal symptoms, but they may manage mild to moderate symptoms.

24. What are some good menopause and HRT references?

General menopause reference: Endotext.com: *The post-menopausal woman* chapter by Dr. McAvey and Dr. Santoro.

Good review of the literature regarding bio-identical hormones: Cirigliano M: Bioidentical hormone therapy: a review of the evidence. *J Womens Health (Larchmt)* 16:600–631, 2007.

Holtorf K: The bioidentical hormone debate: are bioidentical hormones (estradiol, estriol, and progesterone) safer or more efficacious than commonly used synthetic versions in hormone replacement therapy? *Postgrad Med* 121:73–85, 2009.

KEY POINTS 2: KEY WORDS

1. Hot flashes
2. Bio-identical
3. Progestin
4. Oocyte

TOP SECRETS

1. It appears that women in Asia may experience menopause 5 to 10 years earlier than American and European women.
2. Prescription products with estradiol and progesterone are considered to be bio-identical.
3. Although the Women's Health Initiative has an excellent study design, the trial results may not accurately translate to all women in menopause because of the wide age range of enrollment up through age 79 years.

WEBSITES

1. American Congress of Obstetricians and Gynecologists: www.acog.org.
2. North American Menopause Society: www.menopause.org.
3. American Association of Clinical Endocrinologist Guidelines for Treatment of Menopause: www.aace.com/files/menopause.pdf.

BIBLIOGRAPHY

Anderson GL, Limacher M, Assaf AR, et al: Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial, *JAMA* 291:1701–1712, 2004.
Cirigliano M: Bioidentical hormone therapy: a review of the evidence, *J Womens Health (Larchmt)* 16:600–631, 2007.
Goodwin TM: *Management of common problems in obstetrics and gynecology*, ed 5, Hoboken, NJ, 2010, Wiley-Blackwell.
Grady D: Clinical practice: management of menopausal symptoms, *N Engl J Med* 355:2338–2347, 2006.
Holtorf K: The bioidentical hormone debate: are bioidentical hormones (estradiol, estriol, and progesterone) safer or more efficacious than commonly used synthetic versions in hormone replacement therapy? *Postgrad Med* 121:73–85, 2009.
Nelson HD: Commonly used types of postmenopausal estrogen for treatment of hot flashes: scientific review, *JAMA* 291:1610–1620, 2004.
Nelson HD: Postmenopausal estrogen for treatment of hot flashes: clinical applications, *JAMA* 291:1621–1625, 2004.
Rossouw JE, Anderson GL, Prentice RL, et al: Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial, *JAMA* 288:321–333, 2002.
Weinstein M, O'Connor K, New York Academy of Sciences: *Reproductive aging*. Boston, 2009, Blackwell Publishing on behalf of the New York Academy of Sciences.

USE AND ABUSE OF ANABOLIC–ANDROGENIC STEROIDS AND ANDROGEN PRECURSORS

CHAPTER 50

Amy A. Yau, Ryan M. Decort, Stephanie B. Ng, and Homer J. LeMar, Jr

1. What are anabolic-androgenic steroids (AASs)?

AASs are a group of steroid hormones derived from chemical modification of testosterone. The precursor to testosterone is cholesterol; endogenous synthesis is limited by cholesterol delivery to mitochondria for modification. After synthesis and secretion, testosterone is further converted to strong androgens to include dihydrotestosterone (DHT) via 5α-reductase, and weak androgens to include dehydroepiandrosterone (DHEA) and androstenedione. Testosterone is also converted via aromatase to estradiol, an active metabolite, although not an AAS. The terms *anabolic* and *androgenic* derive from their ability to promote positive nitrogen balance and accretion of lean body mass, as well as masculinization.

2. Where are AASs made?

In men, androgens are made in the Leydig cells of the testes. In women, androgens are made in the corpus luteum of the ovary. The adrenal cortex is the main site of DHEA synthesis. Peripheral conversion of testosterone into DHT occurs in the skin, prostate, and external genitalia and into estradiol by liver and adipose tissue.

3. Summarize the biologic effects of AASs.

Endogenous AASs have diverse effects with three distinct physiologic surges. The most prominent are effects on male sexual differentiation starting during the fetal period at weeks 6 through 8 of gestation, when AASs promote the development of male genitalia. The second surge occurs during the neonatal period, when AASs are involved in the growth of the phallus to normal size, in testicular descent, and in spermatogonial development. The final surge assists with secondary sexual characteristics during puberty, including growth and development of the prostate, seminal vesicles, penis, and scrotum. Pubertal changes in hair growth and sebaceous glands result in the male pattern of hair growth on the chin, pubic area, chest, and axillary regions, as well as acne provocation via increased sebum production. Vocal cords begin to thicken along with enlargement of the larynx, with resulting voice deepening. Data indicating decreased urinary nitrogen levels support AAS effects on protein anabolism that lead to an increase in lean body mass, specifically in the upper girdle, and alterations of fat distribution. Further structural changes occur with increases in bone mineral density and long bone growth, as well as closure of the epiphyses. Neurologic changes include increased libido and spontaneous erections. Other effects include assistance with wound healing, stimulation of liver release of clotting factors and erythropoietin with a secondary increase in hematocrit, and suppression of high-density lipoprotein (HDL) synthesis (Box 50-1).

4. How does testosterone mediate effects via estradiol?

During puberty, when testosterone levels surge to stimulate bone growth, peripheral androgen conversion via aromatase also peaks. Newly synthesized estradiol promotes epiphyseal closure during puberty, thus counteracting the effects of testosterone. In patients with aromatase deficiency or estradiol receptor dysfunction, long bones continue to grow, with resultant osteoporosis secondary to continued and unmonitored growth. This mechanism is different from estrogen's effect on osteoclasts and osteoblasts associated with osteoporosis in postmenopausal women.

BOX 50-1. PHYSIOLOGIC EFFECTS OF ANDROGENS

Fetal Period
Internal and external male genitalia development

Neonatal Period
Phallus size development
Testicular descent
Spermatogonia development

Puberty
Growth and development of prostate and seminal vesicles
Increased size and width of penis
Increased scrotal size
Increased male pattern hair growth
Increased skin thickness
Increased sebaceous gland production, resulting in oily skin and development of acne
Deepening of voice via vocal cord thickening and enlargement of larynx
Increase in lean body mass
Altered fat distribution
Increased bone mineral density
Long bone growth and closure of epiphyses
Increased libido, sexual desire, and spontaneous erections
Fibroblast stimulation promoting wound healing
Liver synthesis of clotting factors and erythropoiesis
Suppression of high-density lipoprotein cholesterol formation

Adult
Maintenance of testosterone tissue effects

5. How do AAS levels change with age?

Total, free, and bioavailable testosterone levels decrease with age. This change contributes to the decrease in muscle mass, increase in fat, decrease in libido, increase in fatigue, and minor decreases in cognitive function seen in elderly persons.

6. How do AASs exert their effects?

Approximately 50% of circulating testosterone is strongly bound to sex hormone–binding globulin (SHBG); 40% is weakly bound to albumin; and 2% is unbound or free. The albumin-bound and unbound forms constitute the "bioavailable" and thus active forms of testosterone. AASs act by binding to specific intracellular androgen receptors located throughout the body; this interaction mediates the androgenic and anabolic effects of androgens. Dihydrotestosterone, being a strong androgen, has very high affinity for androgen receptors. Estradiol, formed by aromatase conversion of testosterone, exerts its effects by binding to estrogen receptors throughout the body.

7. How are androgens metabolized, and why is it necessary to modify testosterone for administration?

Because AASs are rapidly metabolized by the first-pass effect through the gut and liver, oral testosterone supplements are highly ineffective in the absence of modification. Alkylation of testosterone confers resistance to hepatic metabolism and results in AASs that can be administered orally. Esterification of testosterone emulsifies testosterone for intramuscular injection. Addition of carbon chains to the ring structure of testosterone increases fat solubility and extends the duration of action.

8. What are signs and symptoms of low or high androgen levels?

Patients with low androgen levels may complain of fatigue, hypoactive sexual desire, erectile dysfunction, diminished pubic and/or facial hair, and testicular atrophy. Other findings include diminished prostate size, abnormal sperm morphology, absent motility of sperm, and hypoproliferative normochromic anemia. Patients with elevated levels may complain of resistant acne or sudden-onset acne. Women in particular complain of hirsutism and irregular menses.

9. What are the indications for AAS therapy?

AASs are indicated for use in male hypogonadism and constitutional delay of growth and puberty. Use for stimulation of growth is cautioned because it may also concomitantly accelerate epiphyseal closure

and thereby limit ultimate height achievement. Androgens are also used as prophylaxis in hereditary angioneurotic edema and as second-line therapies for osteoporosis and aplastic or hypoplastic anemias. Gynecologic uses include treatment of endometriosis with weak androgens, reduction of postpartum breast engorgement in conjunction with estrogen, and elimination of estrogen-mediated menstrual bleeding for postmenopausal women undergoing hormone replacement. Oncologically, androgens can be used to suppress some breast tumors in premenopausal women.

10. Are there any other potential uses for AASs?

AASs may help elderly men by increasing body weight and muscle mass, preventing bone loss (vertebral but not femoral bone density), and improving the hematocrit; however, AASs are not without side effects. In addition, research has used androgens as male contraceptives, in chronic obstructive pulmonary disease, and in other hypogonadal wasting syndromes such as human immunodeficiency virus (HIV)–related muscle wasting and glucocorticoid muscle and bone wasting. All these uses are still under investigation.

11. What are the uses for androgen antagonists and/or inhibitors?

5α-Reductase inhibitors are used to diminish testosterone conversion to DHT in peripheral tissues, most importantly the prostate gland and hair follicles. They are approved by the Food and Drug Administration (FDA) for treatment of benign prostatic hyperplasia and to combat early male pattern baldness. Androgen antagonists are also used for metastatic prostate cancer and female hirsutism.

12. How common is abuse of AASs?

First noted in the 1950s, AAS abuse was mostly limited to bodybuilders, other muscle building enthusiasts, and various professional athletes. It is now known that AAS abuse is far more widespread. According to the results of a 2003 monitoring study, 60% of high school seniors (male and female) have a history of AAS use, with a dramatic increase in female adolescents over the past few years. The National Institute of Drug Abuse (NIDA) report in 2007 noted use in 2.3% of boys versus 0.6% of girls. The NIDA more recently estimated that more than half a million eighth through tenth grade students are abusing AASs. Another study found that 1,084,000 Americans, or 0.5% of the adult population, have admitted to using AASs.

13. Who is at risk for using illegal AASs?

In the world of competitive athletics, bodybuilders are the biggest offenders with regard to AAS abuse. Because AASs increase the hematocrit through enhanced erythropoietin production, these substances may also be used by athletes participating in endurance-oriented sports. Nonathletes may use AASs solely to improve appearance. Surveys have shown the percentage of students who reported lifetime AAS use has increased from 2.7% to 6.1% since 2000. Most users are men, although up to 2% may be women. Other risk factors include involvement in school sports and the use of other illicit drugs, alcohol, or tobacco.

14. Do AASs truly help athletes?

Both athletes and coaches are likely to answer unequivocally, "Yes." AASs used in conjunction with adequate protein and carbohydrate intake, and proper training, in experienced athletes seem to induce greater and more rapid gains. A study comparing supraphysiologic doses of testosterone enanthate with placebo in eugonadal men found clear increases in muscle size and strength, with or without weight-training exercise. Studies of AASs in athletes have shown an increase in body weight and lean body mass, but no significant decrease in the percentage of body fat. Not only do muscle fibers gain in cross-sectional diameter with anabolic steroid use, but also new muscle fibers are formed. The upper regions of the body are the most susceptible to gains from AAS because of the relatively larger number of androgen receptors in these areas.

15. What doses of AASs are used in attempts to enhance sports performance and appearance?

Doses used for illicit purposes are markedly higher (10-fold or more) than physiologic and therapeutic doses. Furthermore, multiple agents are often used in so-called stacking regimens or arrays in which

multiple steroids at increasing doses are used to derive further effects. The drugs are often taken in 6- to 12-week cycles with variable periods off the drugs, but some athletes may use them as long as 1 year or more. Human chorionic gonadotropin may be used at the end of a cycle to stimulate gonadal function. Little is known about precise doses or stacking regimens; however, some anecdotal information is available.

16. What are the potential adverse effects of AAS use?

Many different side effects have occurred with AAS use and abuse. Abuse is associated with increased rates of morbidity and mortality. Fortunately, most side effects are temporary and reversible with cessation of AASs (Table 50-1). The most common side effects are hepatic dysfunction, including cholestatic jaundice and development of hepatic neoplasms; most worrisome is peliosis hepatis, rupture of which can result in death. Other common side effects include gynecomastia, acne, male pattern baldness, increased aggression, and alterations in the cholesterol profile including an increase in low-density lipoprotein (LDL) and a decrease in HDL. Long-term AAS use is associated with a reduction in the production of natural sex hormones that is usually reversible but may take more than a year to resolve. There is also an increase in cardiovascular disease because of fluid retention, exacerbation of hypertension, increased liver synthesis of clotting factors, development of polycythemia, and vasospasm induction via

TABLE 50-1. POTENTIAL ADVERSE EFFECTS OF ANABOLIC-ANDROGENIC STEROID USE AND ABUSE

SYSTEM	ADVERSE EFFECTS
Liver	Cholestatic hepatitis
	Peliosis hepatis (hemorrhagic liver cysts)
	Liver tumors: benign and malignant (oral agents)
Cardiovascular	Stroke and myocardial infarction incidence increased
	High-density lipoprotein cholesterol reduced and low-density lipoprotein cholesterol increased
	Left ventricular enlargement (cardiac androgen receptors)
	Increased vasomotor tone and vasospasm (effects on vascular nitric oxide)
Reproductive	Testicular atrophy
	Oligospermia or azoospermia
	Priapism
	Gynecomastia or breast tenderness
	Natural sex hormone production diminished
	Prostate disease worsening (benign or local disease)
	Clitoral hypertrophy
	Menstrual irregularity, amenorrhea, and infertility
Hematologic	Platelet count and aggregation increased
	Polycythemia
Psychological	Aggressive behavior
	Psychotic symptoms
	Dependence or withdrawal
	Depression
Skin	Sebum production and acne increased
	Male pattern baldness
	Hirsutism (women)
Other	Fluid retention resulting in peripheral edema and exacerbation of hypertension and/or congestive heart failure
	Deepening of voice
	Stunted growth (for adolescents)
	Epiphyseal closure with decreased final adult height

effects on vascular nitric oxide. Men may be at increased risk for development of prostate problems in previously benign or local disease, impotence, and testicular atrophy resulting in infertility. Women may experience menstrual irregularities such as oligomenorrhea or amenorrhea and virilizing effects such as hirsutism, clitoromegaly, and deepening of the voice. In adolescents, one must be cautious of premature epiphyseal closure leading to a reduction in final adult height and psychological dysfunction resulting from androgen effects on brain development (see Table 50-1).

17. What screening tests are used to detect AASs in athletes?

Urine samples are evaluated via mass spectroscopy and gas chromatography, in which direct confirmation comes from measurement of protein kinase C (PKC). PKC reflects an endogenous synthetic origin and rules in or out a potential physiologic anomaly. An increased ratio of urine testosterone to epitestosterone (>6:1) is also confirmatory of AAS use. Furthermore, urine samples with a high ratio of testosterone to leuteinizing hormone (LH) greater than 30 suggest AAS abuse because LH secretion is suppressed in subjects using testosterone.

18. What are the so-called androgen precursors or prohormones?

These are products or supplements advertised to be metabolized to testosterone or other active metabolites. In 2004, the U.S. Congress passed the Anabolic Steroid Control Act, which banned prohormones indefinitely.

Mixed data since 2000 have shown that acute oral ingestion of greater than or equal to 200 mg daily of androstenedione or androstenediol modestly increases serum testosterone and circulating estrogen concentrations in men and women. However, doses lower than 300 mg taken for up to 12 weeks have shown no effect on body composition or physical performance.

19. Have androgen precursors been shown to be anabolic in men or women?

Yes, the literature suggests that use of supraphamacologic doses can be anabolic in certain situations. However, the situations and mechanisms of action are unclear, and side effects similar to those for AAS occur.

KEY POINTS

1. Biological effects of androgenic anabolic steroids (AAS) include growth and development of the prostate, seminal vesicles, penis and scrotum, beard, pubic, chest, and axillary hair, enlargement of the larynx and thickening of the vocal cords.
2. Indications for AAS include male hypogonadism, constitutional delay of growth and puberty, hereditary angioneurotic edema, osteoporosis, aplastic or hypoplastic anemias, endometriosis, reduction of postpartum breast engorgement in conjunction with estrogen, elimination of estrogen mediated menstrual bleeding in postmenopausal women on hormone replacement, and to suppress some breast tumors in premenopausal women.
3. Common side effects of AAS abuse include fluid retention, testicular atrophy, oligospermia, azoospermia, gynecomastia, cholestatic hepatitis, pelioses hepatis, both benign and malignant hepatic tumors, and reduced high-density lipoprotein and higher low-density lipoprotein cholesterol levels.
4. The illegal use of AASs to enhance sports performance or physical appearance probably represents the single most common use.

BIBLIOGRAPHY

Ayotte C: Detecting the administration of endogenous anabolic androgenic steroids. In Hofmann FB, editor: *Handbook of experimental pharmacology*, Berlin, 2010, Springer, pp 77–98.

Bahrke MS, Yesalis CE: Abuse of anabolic androgenic steroids and related substances in sport and exercise, *Curr Opin Pharmacol* 4:614–620, 2004.

Bhasin S, Jameson JL: Disorders of the testes and male reproductive system. In Longo D, Fauci A, Kaasper D, Hauser S, editors: *Harrison's online featuring the complete contents of Harrison's principles of internal medicine,* ed 18, New York, 2012, McGraw-Hill Medical.

Bonci L: Nutrition, pharmacology, and psychology in sports. In DeLee J, Drez D, Miller M, editors: *DeLee and Drez's orthopaedic sports medicine: principles and practice,* ed 3, Philadelphia, 2009, Saunders, pp 399–461.

Chrousos GP: The gonadal hormones and inhibitors. In Katzung B, Masters S, Trevor A, editors: *Basic and clinical pharmacology,* ed 12, New York, 2012, McGraw-Hill Medical.

Kalus AA, Chien AJ, Olerud JE: Diabetes mellitus and other endocrine diseases. In Wolff K, Goldsmith L, Katz S, et al, editors: *Fitzpatrick's dermatology in general medicine,* ed 7, New York, 2008, McGraw-Hill Medical.

Kuhn CM: Anabolic steroids, *Recent Prog Horm Res* 57:411–434, 2002.

Leder BZ, Leblanc KM, Longcope C, et al: Effects of oral androstenedione administration on serum testosterone and estradiol levels in postmenopausal women, *J Clin Endocrinol Metab* 87:5449–5454, 2002.

Matsumoto AM, Bremner WJ: Testicular disorders. In Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, editors: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders, pp 688–777.

Morales A: Androgen deficiency in the aging male. In Wein AJ, Kavoussi LR, Novick AC, Partin AW, editors: *Campbell-Walsh urology,* ed 10, Philadelphia, 2012, Saunders, pp 810–822.

National Institute on Drug Abuse: Steroids (anabolic-androgenic): drug facts. http://www.drugabuse.gov/publications/drugfacts/steroids-anabolic-androgenic.

Nelson JB: Hormone therapy for prostate cancer. In Wein AJ, Kavoussi LR, Novick AC, Partin AW, editors: *Campbell-Walsh urology,* ed 10, Philadelphia, 2012, Saunders, pp 2934–2953.

Parr MK, Laudenbach-Leschowsky U, Höfer N, et al: Anabolic and androgenic activity of 19-norandrostenedione after oral and subcutaneous administration: analysis of side effects and metabolism, *Toxicol Lett* 188:137–141, 2009.

Snyder PJ: Androgens. In Brunton L, Chabner B, Knollman B, editors: *Goodman and Gilman's pharmacological basis of therapeutics,* ed 12, New York, 2011, McGraw-Hill.

Tenover JL: Sexuality, sexual function, androgen therapy, and the aging male. In Halter J, Ouslander J, Tinetti M, Studenski S, editors: *Hazzard's geriatric medicine and gerontology,* ed 6, New York, 2009, McGraw-Hill Medical.

U.S. Congress: 108th U.S. Congress. Anabolic Steroid Control Act of 2004.

Weil PA: The diversity of the endocrine system. In Murray R, Bender D, Botham KM, Kennelly PJ, editors: *Harper's illustrated biochemistry,* ed 29, New York, 2012, McGraw-Hill Medical.

Ziegenfuss TN, Berardi JM, Lowery LM, Antonio J: Effects of prohormone supplementation in humans: a review, *Can J Appl Physiol* 27:628–645, 2002.

MULTIPLE ENDOCRINE NEOPLASIA

Arnold A. Asp

1. What are the multiple endocrine neoplasia (MEN) syndromes?

There are three well-characterized, inherited pluriglandular disorders in which several endocrine glands simultaneously undergo neoplastic transformation and become hyperfunctional. All these disorders are genetically transmitted in an autosomal dominant fashion. These disorders are MEN-1, MEN-2A, and MEN-2B.

2. Define MEN-1.

MEN-1 consists of hyperplasia or neoplastic transformation of the parathyroid glands, pancreatic islets, and pituitary.

3. Define MEN-2A.

MEN-2A consists of hyperplasia or neoplastic transformation of the thyroid parafollicular cells (medullary thyroid carcinoma [MTC]), parathyroid glands, and adrenal medulla (pheochromocytoma).

4. Define MEN-2B.

MEN-2B consists of hyperplasia or neoplastic transformation of the thyroid parafollicular cells (MTC) and adrenal medulla (pheochromocytoma) with concomitant development of mucosal neuromas.

5. How can so many various endocrine organs be affected in these syndromes?

The cells that comprise many endocrine organs are able to decarboxylate various amino acids and convert the molecules to amines or peptides that act as hormones or neurotransmitters. These cells have been classified as amine precursor uptake and decarboxylation (APUD) cells and are considered to be embryologically of neuroectodermal origin. APUD cells contain markers of their common neuroendocrine origin, including neuron-specific enolase and chromogranin A. Neoplastic transformation of APUD cells long after organogenesis is complete appears to result from a germline mutation (loss of a tumor suppressor gene in MEN-1 or mutation of a protooncogene to an oncogene in MEN-2A and MEN-2B) in a gene that is expressed only in neuroectodermal cells. When neuroectodermal cells later migrate to specific developing organs, the genetic mutation similarly is distributed to those organs. This explains the common mutations manifested in this class of neuroendocrine tumors (NETs).

6. What is Wermer syndrome?

This is the eponym for the MEN-1 syndrome. Wermer first recognized the association of parathyroid hyperplasia, multicentric pituitary tumors, and pancreatic islet-cell tumors in several kindreds and described the syndrome in 1954. Although neoplastic transformation occurs most commonly in the parathyroid glands, pituitary, and pancreas, hyperplastic adrenal cortical and nodular thyroid disorders have been described. Carcinoid tumors, especially involving the foregut (thymus, lung, stomach, and duodenum), are uncommon but also have been reported in MEN-1 syndrome.

7. How common is Wermer syndrome?

Wermer syndrome is the most common form of MEN. Its prevalence is estimated to vary between 2 and 20 per 100,000 population. The syndrome is characterized by a high degree of penetrance; expression increases with age.

8. Is hyperparathyroidism in MEN-1 similar to sporadic primary hyperparathyroidism?

No. Hyperparathyroidism associated with MEN-1 results from hyperplasia of all four glands, whereas sporadic primary hyperparathyroidism is usually characterized by adenomatous change in a single gland. Hyperparathyroidism is the most common and earliest manifestation of MEN-1, and it occurs in 80% to 95% of cases. It has been described in patients as young as 17 years and develops in nearly all patients with MEN-1 by age 40 years.

9. What causes the hyperplasia of parathyroid glands affected by MEN-1?

Hyperplasia of parathyroid glands affected by MEN-1 results from expansion of multiple cell clones, whereas sporadic parathyroid adenomas result from activation of a single cell clone. A mitogenic factor, similar to basic fibroblast growth factor (bFGF), has been found in MEN-1. The factor may originate from the pituitary and specifically stimulate angiogenesis of parathyroid cells. Complications of MEN-1 hyperparathyroidism are similar to those of sporadic hyperparathyroidism; they include nephrolithiasis, osteoporosis, mental status changes, and muscular weakness.

10. Summarize the therapy for hyperplastic parathyroid glands.

Therapy of both sporadic adenomas and MEN-1–associated hyperplastic glands depends on surgical resection. In sporadic primary hyperparathyroidism, removal of the solitary adenoma is curative in 95% of cases. In MEN-1–associated hyperplasia, at least 3.5 hyperplastic glands must be resected to restore normocalcemia. Only 75% of patients are normocalcemic postoperatively; 10% to 25% of patients are rendered hypoparathyroid. Unfortunately, the parathyroid remnants in the patient with MEN-1 have a great propensity to regenerate; 50% of patients become hypercalcemic again within 10 years of surgery. This recurrence rate dictates that surgery be delayed until complications of hypercalcemia are imminent or gastrin levels are elevated, as discussed later. Recurrence may be treated surgically or with cinacalcet, which acts at the calcium-sensing receptor, to reduce parathyroid hormone (PTH) secretion.

11. How common is neoplastic transformation of pancreatic islet cells in MEN-1?

Neoplastic transformation of the pancreatic islet cells is the second most common manifestation of MEN-1, and it occurs in approximately 66% to 80% of cases. These pancreatic NETs are commonly referred to as PNETs.

12. What types of pancreatic tumors are found in MEN-1 syndrome?

PNETs in MEN-1 syndrome are usually multicentric and are often capable of elaborating several peptides and biogenic amines. They are, by convention, classified on the basis of the clinical syndrome produced by the predominant secretory product. This group of tumors characteristically progresses from hyperplasia to malignancy with metastases, thus making curative resection unlikely. PNETs may arise from normal islet cells (eutopic) or cells that are not normal constituents of the adult pancreas (ectopic).

13. What is the most common type of functional pancreatic tumor in MEN-1?

Gastrinomas are the most common functional PNETs in MEN-1 syndrome (47%–78% of cases). They are ectopic tumors; G cells are normally present in the fetal pancreas only. Gastrinomas also may occur independently of MEN-1 (only 15%–48% of all patients with a gastrinoma are later found to have MEN-1). Gastrinomas associated with MEN-1 are multiple and often extrapancreatic, occurring in the duodenal wall and retroperitoneal lymphatics.

14. Describe the symptoms of gastrinomas associated with MEN-1.

Excessive gastrin secretion by these tumors causes prolific production of gastric acid with resultant duodenal and jejunal ulcers and diarrhea. Basal acid output exceeds 15 mmol/hour, and basal fasting serum gastrin levels usually exceed 300 pg/mL.

15. What other conditions may cause hypergastrinemia?

Hypergastrinemia also may result from any condition that stimulates normal gastrin secretion (hypercalcemia) or that interferes with normal gastric acid production and feedback to the G cells (achlorhydria, gastric outlet obstruction, retained antrum with a Billroth II procedure, vagotomy, and the use of histamine-2 [H_2] blockers and proton pump inhibitors). Hyperparathyroidism (see questions 8 and 9) can therefore falsely elevate serum gastrin levels.

16. How are gastrinomas distinguished from other causes of hypergastrinemia?

A secretin stimulation test may aid in the differentiation of gastrinomas from other hypergastrinemic states; serum gastrin levels in patients with gastrinomas increase by at least 200 pg/mL. More information about gastrinomas is included in Chapter 53.

17. What is the second most common type of functional pancreatic tumor in MEN-1?

Insulinomas are the second most common PNET in the MEN-1 syndrome (12%–36% of islet-cell tumors) and the most common eutopic type. Persistent or disordered insulin secretion causes severe hypoglycemia; inappropriately elevated concentrations of insulin, proinsulin, and C-peptide are present in the serum. Insulinomas associated with MEN-1 syndrome are more frequently multicentric and malignant than are the sporadic tumors. Approximately 1% to 5% of all patients with an insulinoma are eventually discovered to have MEN-1. An excellent discussion of the diagnosis and therapy of insulinomas is found in Chapter 53.

18. What other pancreatic tumors may be seen in MEN-1?

Pancreatic tumors less frequently associated with MEN-1 include glucagonomas, somatostatinomas, and vasoactive intestinal polypeptide–secreting tumors (VIPomas). Associated syndromes and therapy are also described in Chapter 53.

19. How are the most common pancreatic tumors of MEN-1 treated?

Multicentric gastrinomas are rarely cured surgically (10%–15% of cases). Fortunately, symptoms of hypergastrinemia can be pharmacologically controlled with administration of an H_2 blocker, proton pump inhibitor, or octreotide. Because metastases to the liver become increasingly common when gastrinomas exceed 2 cm in diameter, most surgeons reserve excision for tumors smaller than 2 cm. Gastrinomas express surface receptors for somatostatin, thus potentiating the use of somatostatin-receptor scintigraphy in combination with annual magnetic resonance imaging (MRI) and computed tomography (CT) surveillance to monitor tumor progression.

20. Summarize the approach to treatment of hypoglycemia associated with insulinomas.

Insulinomas, unlike gastrinomas, produce devastating hypoglycemia, which is difficult to counteract medically. Without effective long-term pharmacotherapy, surgical resection of the tumor is required in most patients. Fortunately, when the largest tumor is excised, many of the patient's symptoms are ameliorated. Localization is accomplished preoperatively with endoscopic ultrasonography, MRI or CT, or comparison of insulin levels in the right hepatic vein following selective infusion of the intrapancreatic arteries with calcium gluconate. Intraoperative ultrasonography may also assist precise localization at the time of surgery.

21. Which pituitary tumors are associated with MEN-1?

Pituitary tumors occur in 50% to 71% of patients with MEN-1. These tumors may result either from neoplastic transformation of anterior pituitary cells with clonal expansion to a tumor or from excessive stimulation of the pituitary by ectopically produced hypothalamic releasing factors elaborated by carcinoids or pancreatic islet cells.

22. What pituitary tumors are most commonly associated with MEN-1?

Prolactinomas, the most common pituitary tumors associated with MEN-1, constitute 60% of the total. The symptoms of hyperprolactinemia (galactorrhea and amenorrhea in women; impotence in men) are the third most common manifestation of MEN-1. The tumors are typically multicentric and large but respond to dopamine agonists, such as bromocriptine. In earlier series, many pituitary tumors described as chromophobe adenomas were, in reality, prolactinomas that contained sparse, poorly staining secretory granules. These tumors are also discussed in Chapter 20.

23. What is the second most common pituitary tumor in MEN-1?

The second most commonly encountered pituitary tumor type is the growth hormone–producing tumor, which is reported in 10% to 25% of patients. Overproduction of growth hormone results in gigantism in children and acromegaly in adults. The tumors are often multicentric and may result from secretion of growth hormone–releasing hormone by pancreatic or carcinoid tumors. Diagnosis and therapy are described in Chapter 21.

24. What other pituitary tumors may be seen in MEN-1?

Corticotropin (ACTH)-producing tumors that cause Cushing syndrome may be associated with MEN-1. Such tumors result from neoplastic transformation of the pituitary or elaboration of corticotropin-releasing hormone by pancreatic or carcinoid tumors. Diagnosis and therapy are described in Chapter 23.

25. What causes MEN-1?

The gene predisposing to the development of MEN-1 (MEN-1 susceptibility gene) is located on the long arm of chromosome 11 (11q13) and encodes a protein known as menin, which functionally acts as a tumor suppressor. To date 1133 germline mutations have been discovered, thus rendering genetic screening extremely challenging. The cellular function of menin is complex; menin regulates transcription and genome stability. The proband inherits an allele predisposing to MEN-1 from the affected parent, whereas a normal allele is passed down from the unaffected parent. The gene for this tumor suppressor is unusually susceptible to mutation. If a somatic mutation later inactivates the normal allele, suppressor function is lost, thereby permitting hyperplasia of the gland to occur.

26. How is MEN1 diagnosed, and how should a kindred be screened after the proband is identified?

The three means of diagnosing MEN-1 are as follows:

Clinical: Two or more MEN-1–associated tumors

Familial: Patient with one MEN-1–associated tumor and a first-degree relative with MEN-1

Genetic: An asymptomatic carrier of MEN-1 mutation (no biochemical manifestations)

Carriers of the genetic defect must first be clinically identified, the extent of their organ involvement determined, and their family screened for additional carriers of one of the MEN-1 mutations. As mentioned earlier, multiple mutations in the gene coding for menin have been described in patients with MEN-1 and may be used to identify carriers of the disorder. Although mutational analysis was previously restricted to research laboratories, clinical testing for mutations in the MEN-1 gene is now available to detect disease within affected kindreds.

27. At what age should screening begin?

Asymptomatic carriers of the MEN-1 mutation should be screened for biochemical and anatomic evidence of tumors. Manifestations of MEN-1 syndrome have been reported as early as 5 years of age; therefore, for patients at risk, endocrine screening should be considered at that time. Nearly all people at risk develop the disorder by the age of 40 years; screening may be unnecessary in family members older than 50 years who are proved to be disease free.

28. Summarize the tests used for screening of MEN-1 individuals.

In known mutant gene carriers, annual testing for calcium, PTH, prolactin, insulin-like growth factor-I (IGF-I), chromogranin A, fasting gastrin, fasting glucose, and insulin levels is recommended. MRI of the pituitary and CT of the abdomen is recommended every 12 to 36 months.

KEY POINTS 1: MULTIPLE ENDOCRINE NEOPLASIA TYPE 1

1. Multiple endocrine neoplasia type 1 (MEN-1) consists of neoplastic transformation in at least two of these three glands: parathyroids, pancreas, and pituitary.
2. MEN-1 results from a mutation inactivating the menin tumor suppressor on chromosome 11. Routine clinical testing for the mutation is currently available.
3. Therapy for MEN-1 includes surgical resection of hyperplastic parathyroid tissue and pituitary adenomas; surgical cure for the associated pancreatic tumors is not usually possible.

29. What is Sipple syndrome?

This is the eponym for MEN-2A. In 1961, Sipple recognized and described a patient who died of an intracerebral aneurysm and was found at autopsy to have MTC, pheochromocytomas, and hyperparathyroidism. This disorder is inherited in an autosomal dominant fashion and exhibits a high degree of penetrance and variable expressivity. It is less common than MEN-1 syndrome.

30. Is the form of MTC associated with MEN-2A similar to the sporadic form of MTC?

No. MTC results from malignant transformation of the parafollicular cells (or C cells) that normally elaborate calcitonin and are scattered throughout the thyroid gland. MTC accounts for 2% to 10% of all thyroid malignant tumors. The sporadic form of MTC, as described in Chapter 37, is more common (75% of all MTC), occurs in a solitary form (<20% multicentric), and metastasizes to local lymphatics, lung, bone, and liver early in the course of disease (metastasis may occur with primary tumors <1 cm in diameter). Sporadic MTC occurs more commonly in an older population (peak age, 40–60 years) and is usually located in the upper two thirds of the gland.

31. Summarize the essential characteristics of MTC associated with MEN-2A.

MTC associated with MEN-2A is multicentric (90% at the time of diagnosis), occurs at a younger age than sporadic MTC (as young as 2 years), and generally has a better prognosis than the sporadic form. MTC occurs in nearly 95% of all cases of MEN-2A and is usually the first tumor to appear.

32. How common is diarrhea in MTC associated with MEN-2A?

Calcitonin or other peptides elaborated by the tumor may cause secretory diarrhea that is present in 4% to 7% of patients at the time of diagnosis but develops in 25% to 30% during the course of the disease.

33. How is MEN-2A–associated MTC treated?

Parafollicular cells in patients with MEN-2A characteristically progress through a state of C-cell hyperplasia to nodular hyperplasia to malignant degeneration over a variable period. It is imperative that patients at risk be diagnosed while still in the C-cell hyperplasia stage; total thyroidectomy precludes malignant degeneration and metastases.

34. How is C-cell hyperplasia detected?

Detection of C-cell hyperplasia is facilitated by the pentagastrin stimulation test. MTC also expresses peptides and hormones not commonly elaborated by parafollicular cells, including somatostatin, thyrotropin-releasing hormone, vasoactive intestinal peptide, proopiomelanocortin, carcinoembryonic antigen, and neurotensin.

35. What is the second most common neoplasm associated with MEN-2A?

Pheochromocytomas occur in 50% to 70% of cases of MEN-2A and are bilateral in up to 84% of patients. Compared with the sporadic form, pheochromocytomas associated with MEN-2A secrete greater amounts of epinephrine. Hypertension is therefore less common, and urinary excretion of catecholamines may become supranormal later in the course of the disease.

36. Summarize the treatment of pheochromocytomas associated with MEN-2A.

Surgical resection is indicated, but controversy surrounds the need for prophylactic resection of contralateral uninvolved adrenals, 50% of which develop pheochromocytomas within 10 years of the original surgical procedure. The diagnosis and management of pheochromocytomas are discussed in Chapter 28.

37. Is hyperparathyroidism associated with MEN-2A similar to that found in MEN-1?

Yes, but it is encountered much less commonly, involving only 40% of cases.

38. What is the genetic basis for the MEN-2A syndrome?

MEN-2A is caused by an activating mutation of the RET protooncogene located on chromosome 10q11.2. The gene codes for a receptor tyrosine kinase that phosphorylates and activates enzymes critical to cellular development. The ligand that normally activates the tyrosine kinase is glial cell–derived neurotropic factor (GDNF). When GDNF binds, two receptors bind together (homodimerization), and phosphorylation of enzymes occurs downstream. Mutation of the RET protooncogene to an oncogene results in constitutive activation of the enzyme, thus causing unregulated phosphorylation of other critical enzymes. Inheritance of one RET oncogene from one affected parent is sufficient to cause MEN-2A syndrome in children. Five distinct mutations involving exons 10 and 11 have been described in 98% of 203 kindreds with the disorder.

39. How should a kindred be screened after the proband with MEN-2A is identified?

As explained in question 26, screening initially entails the differentiation of gene carriers from uninvolved family members and the subsequent delineation of organ involvement in the affected members. Direct DNA sequencing of the RET oncogene causing MEN-2A is clinically available. With appropriate repeat analysis of positive and negative test results, the assay offers near 100% accuracy in identification of affected individuals. Genetic analysis of the kindred should be performed to identify the specific RET oncogene mutation; characterization of the familial oncogene precludes the need for repetitive biochemical screening of noncarriers in subsequent generations.

40. How is MEN-2A treated?

Because C-cell hyperplasia has been described in gene carriers as young as 2 years, total thyroidectomy is suggested in affected individuals before age 5 years. An alternative to preemptive thyroidectomy is to perform annual pentagastrin stimulation tests and withhold surgery until a positive result is obtained. Because MEN-2A–associated pheochromocytoma may produce large amounts of epinephrine that do not cause hypertension, annual timed urine collections for catecholamines should be obtained in all gene carriers. Serum levels of calcium should be assessed every 2 years. After the presence of the syndrome has been established, screening for adrenal and parathyroid involvement should continue through life.

41. What comprises the MEN-2B syndrome?

MEN-2B syndrome is the association of MTC and pheochromocytoma with multiple mucosal neuromas in an affected individual or kindred. Hyperparathyroidism is not associated with MEN-2B. This syndrome is less common than the MEN-2A and is more commonly sporadic than familial, but if inherited, it is transmitted in an autosomal dominant fashion.

42. What findings raise the suspicion of MEN-2B syndrome?

The occurrence of multiple mucosal neuromas on the distal tongue, lips, and eyelids and along the gastrointestinal tract should always raise the possibility of MEN-2B. Other manifestations of MEN-2B include a marfanoid habitus (without ectopia lentis or aortic aneurysms), hypertrophic corneal nerves, and slipped femoral epiphysis.

43. How should MEN-2B be treated?

The MTC associated with this syndrome is more aggressive than other forms; metastatic lesions have been described in infancy. Because of the propensity toward early metastasis, many clinicians advocate that children with the syndrome should undergo total thyroidectomy as soon as surgery can be tolerated. Pheochromocytomas occur in nearly half of all patients and follow a clinical course similar to those in the MEN-2A syndrome.

44. What is the overall mortality rate associated with MEN-2B?

Overall mortality in MEN-2B is more severe; the average age of death for patients with MEN-2A is 60 years, whereas in patients with MEN-2B, the average age of death is 30 years.

45. Summarize the screening recommendations for MEN-2B.

Screening of family members with pentagastrin stimulation for MTC should begin at birth and continue through life if thyroidectomy is deferred. Screening for pheochromocytoma should begin at 5 years and continue for life.

46. What causes MEN-2B?

More than 95% of the kindreds with MEN-2B have been found to carry a mutation of the RET proto-oncogene at codon 918 (exon 16). This oncogene codes for a methionine-to-threonine substitution and results in activation of the innermost tyrosine kinase moiety of the same receptor associated with MEN-2A.

47. Have the clinical presentations and prognoses of the MEN syndromes changed since the time of their original descriptions?

Yes. When the MEN syndromes were initially described, most patients presented with involvement of all the aforementioned organ systems because diagnostic capabilities were limited. At present, early diagnosis of the proband and aggressive screening of the kindred may permit detection of hyperplasia and prompt prophylactic surgery or medical therapy that limits morbidity and mortality.

KEY POINTS 2: MULTIPLE ENDOCRINE NEOPLASIA TYPES 2A AND 2B

1. Multiple endocrine neoplasia type 2A (MEN-2A) consists of neoplastic transformation of parathyroids, thyroid parafollicular C cells, and adrenal medulla.
2. MEN-2B consists of neoplastic transformation of thyroid parafollicular C cells, and adrenal medulla, with mucosal neuromas.
3. Genetic testing for the RET mutation causing MEN-2 syndromes is now clinically available.

BIBLIOGRAPHY

Brandi ML, Gagel RF, Angeli A, et al: Guidelines for diagnosis and therapy of MEN type 1 and type 2, *J Clin Endocrinol Metab* 86:5658–5671, 2001.

Cadiot G, Laurent-Piug P, Thuille B, et al: Is the multiple endocrine neoplasia type 1 gene a suppressor for fundic argyrophil tumors in Zollinger-Ellison syndrome? *Gastroenterology* 105:579–582, 1993.

Chandrasekharappa SCV, Guru SC, Manickam P, et al: Positional cloning of the gene for multiple endocrine neoplasia type 1, *Science* 276:404–407, 1997.

Eng C, Clayton D, Schuffenecker I, et al: The relationship between specific RET proto-oncogene mutations and disease phenotype in multiple endocrine neoplasia type 2, *JAMA* 276:1575–1579, 1996.

Eng C: The RET proto-oncogene in multiple endocrine neoplasia type 2 and Hirschsprung's disease, *N Engl J Med* 335:943–951, 1996.

Gicquel C, Bertherat J, Le Bouc Y, et al: The pathogenesis of adrenocortical incidentalomas and genetic syndromes associated with adrenocortical neoplasms, *Endocrinol Metab Clin North Am* 29:1–13, 2000.

Grauer A, Raue F, Gagel RF: Changing concepts in the management of hereditary and sporadic medullary thyroid carcinoma, *Endocrinol Metab Clin North Am* 19:613–635, 1990.
Hu MI, Gagel RF: Multiple endocrine neoplasia type 2, *Translat Endocrinol Metab* 2:45–76, 2012.
Joseph S, Wang YZ, Boudreau JP, et al: Neuroendocrine tumors: current recommendations for diagnosis and surgical management, *Endocrinol Metab Clin North Am* 40:205–231, 2011.
Kopp P: Applications of molecular biology and genetics in endocrinology, *Endocr Pract* 13:534–541, 2007.
Lemos MC, Thakker RV: Multiple endocrine neoplasia type 1 (MEN1): analysis of 1336 mutations reported in the first decade following identification of the gene, *Hum Mutat* 29:22–32, 2008.
Phay JE, Moley JF, Lairmore TL: Multiple endocrine neoplasias, *Semin Surg Oncol* 18:324–332, 2000.
Santoro M, Carlomagno F, Romano A, et al: Activation of RET as a dominant transforming gene by germline mutations of MEN-IIA and MEN-IIB, *Science* 267:381–383, 1995.
Thakker RV, Newey PJ, Walls GV, et al: Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN 1), *J Clin Endocrinol Metab* 97:2990–3011, 2012.
Thakker RV: Multiple endocrine neoplasia type 1. *Translat Endocrinol Metabol* 2:13–44, 2012.
Tham E, Grandell U, Lindgren E, et al: Clinical testing for mutations in the MEN-I gene in Sweden: a report of 200 unrelated cases, *J Clin Endocrinol Metab* 92:3389–3395, 2007.
Vinik AI, Gonzales MR: New and emerging syndromes due to neuroendocrine tumors, *Endocrinol Metab Clin North Am* 40:19–63, 2011.

AUTOIMMUNE POLYENDOCRINOPATHY SYNDROMES

CHAPTER 52

Arnold A. Asp

1. Define the autoimmune polyendocrinopathy syndromes (APSs). How many clinical forms are there?

The APSs are disorders in which two or more endocrine glands are simultaneously hypofunctional or hyperfunctional as the result of autoimmune dysfunction. It is theorized that a defect in the T-suppressor cell subset inadvertently permits activation of the cellular and humoral arms of the immune system. The nature of this dysfunction is unknown. The two widely recognized clinical forms are appropriately designated APS type 1 and APS type 2. The common clinical link between the syndromes is adrenal insufficiency.

2. Is evidence of nonendocrine autoimmune dysfunction associated with APSs?

Yes. Connective tissue diseases and hematologic and gastrointestinal autoimmune disorders are commonly associated with the APSs.

3. What constitutes APS type 1?

APS type 1 is a pediatric disorder manifested by the presence of a combination of two of the following three disorders: hypoparathyroidism, adrenal insufficiency, and chronic mucocutaneous candidiasis. Usually, hypoparathyroidism and candidiasis manifest by age 5 years. Adrenal insufficiency occurs by age 12 years, and all manifestations are present by age 15 years. Some affected individuals develop only one manifestation. Other endocrine conditions may also occur; the largest series of patients had the following endocrine manifestations:

- Hypoparathyroidism: 89%
- Adrenal insufficiency: 60%
- Gonadal failure: 45%
- Thyroid disease: 12%
- Diabetes mellitus type 1: 1% to 4%

4. Are nonendocrine manifestations associated with APS type 1?

Yes. Chronic mucocutaneous candidiasis occurs in 75% of patients, celiac disease in 25%, alopecia in 20%, pernicious anemia in 16%, and chronic autoimmune hepatitis in 9%. Dystrophy of the dental enamel, vitiligo, keratopathy, and hypoplasia of the teeth and nails also may occur, thus prompting the alternative designation for APS type 1: autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED).

5. Explain the etiology of APS type 1.

Mutations of the autoimmune regulator (AIRE) gene on chromosome 21 cause APS type 1, which is inherited in an autosomal recessive pattern. There appears to be no human leukocyte antigen (HLA) association. The cause of the candidiasis is not known, although delayed hypersensitivity is defective in affected patients. Antibodies to adrenal enzymes (21-hydroxylase, an enzyme in the biosynthetic pathway for aldosterone and cortisol) and to poorly characterized parathyroid antigens have been described by some groups.

6. What therapy can be offered?

Annual screening of levels of serum calcium, cosyntropin-stimulated cortisol, and liver-associated enzymes is performed in affected sibships until age 15 years. Adrenal insufficiency and hypoparathyroidism are treated with glucocorticoids and with oral calcium and vitamin D supplementation, respectively. Mucocutaneous candidiasis is treated with fluconazole. Use of prophylactic immunosuppressives, such as cyclosporine, is not recommended.

7. What disorders are associated with APS type 2?

APS type 2 occurs in adulthood and consists of autoimmune adrenal insufficiency with autoimmune thyroid disease and/or diabetes mellitus type 1. The age of onset tends to be between 20 and 30 years; one half of the cases are sporadic, and one half are familial. Endocrine organ involvement is as follows:

- Adrenal insufficiency: 100%
- Autoimmune thyroid disease: 70%
- Diabetes mellitus type 1: 50%
- Gonadal failure: 5% to 50%

Very rarely, geriatric hypoparathyroidism may occur in elderly patients with APS type 2.

8. What is the most common presenting disorder in APS type 2?

Adrenal insufficiency is the presenting disorder in 50% of cases, whereas adrenal insufficiency with diabetes mellitus or thyroid disease is present at the time of diagnosis in 20% of cases. In the remaining 30%, adrenal insufficiency occurs after other endocrine dysfunction. Between 69% and 90% of patients have circulating antibodies to 21-hydroxylase.

9. What thyroid disorders are associated with APS type 2?

Thyroid disorders associated with APS type 2 include Graves' disease (50%) and Hashimoto's disease or atrophic thyroiditis (50%). As expected, thyroid-stimulating immunoglobulins (TSIs) are present in cases of hyperthyroidism, whereas antibodies to thyroid peroxidase or thyroglobulin are present in cases of hypothyroidism.

10. Summarize the significance of cytoplasmic islet-cell antibodies (ICAs) in APS type 2.

Cytoplasmic ICAs are present in patients with APS type 2 and diabetes mellitus; however, the significance of these antibodies is questionable. Patients with APS type 2 who have ICAs but not diabetes may have no compromise of beta-cell function and subsequently develop diabetes at a rate of 2% per year, whereas ICA-positive first-degree relatives of non-APS, type 1 diabetic individuals develop diabetes at a rate of 8% per year.

11. How common is gonadal failure in APS type 2?

Gonadal failure is more common in women than in men and is associated with antibodies to gonadal tissue.

12. Are nonendocrine abnormalities described in APS type 2?

Yes. In about 5% of cases, other autoimmune disorders are found, including vitiligo, pernicious anemia, alopecia, myasthenia gravis, celiac disease, Sjögren's syndrome, and rheumatoid arthritis.

13. How should kindreds with suspected APS type 2 be screened?

Because APS type 2 appears in multiple generations and because 20 years may lapse between the development of various endocrine organ failures, affected patients should be screened by assessing levels of serum glucose, thyrotropin (TSH), and vitamin B_{12} every 3 to 5 years. Symptoms of adrenal insufficiency should be investigated by assessing levels of cosyntropin-stimulated cortisol. First-degree relatives of the proband should be educated about the syndrome and advised to undergo screening every 3 to 5 years. Antibodies to thyroid peroxidase or thyroglobulin are so common in the general population as to preclude their use as a screening test.

14. Explain the etiology of APS type 2.

The genetic basis of APS type 2 is uncertain, although it appears to be associated with an HLA-DR3 phenotype that may be permissive for the development of autoimmunity. Organ-specific antibodies may cause organ dysfunction; for example, TSIs may cause Graves' disease, and antiacetylcholine receptor antibodies may cause myasthenia gravis. Or, like antithyroglobulin antibodies, they may be epiphenomena of disease. The only consistent abnormality noted in affected patients is decreased function of T-suppressor cells.

15. What is POEMS syndrome?

POEMS syndrome is a disorder of unknown origin, unrelated to either APS type 1 or APS type 2, that appears to have an immunologic basis. The acronym highlights the cardinal features of the syndrome: polyneuropathy, organomegaly, endocrinopathy, monoclonal component, and skin changes. All the symptoms are considered to be secondary to overproduction of proinflammatory and other cytokines (most commonly vascular endothelial growth factor [VEGF]). This condition may represent plasma cell dyscrasia (monoclonal gammopathies of undetermined significance; plasmacytoma, osteosclerotic, osteolytic, or mixed myeloma).

KEY POINTS 1: AUTOIMMUNE POLYENDOCRINOPATHY SYNDROMES

1. Autoimmune polyendocrinopathy syndrome (APS) type 1 is a pediatric syndrome marked by hypoparathyroidism, adrenal insufficiency, and mucocutaneous candidiasis.
2. APS type 1 is inherited in an autosomal recessive manner, is not human leukocyte antigen (HLA) associated, and is clinically apparent by 15 years of age.
3. APS type 2 consists of adrenal insufficiency, thyroid dysfunction, and diabetes mellitus type 1.
4. APS type 2–associated organ failure progresses over many years during adulthood and affects multiple generations. It is associated with HLA-DR3.
5. Both APS type 1 and APS type 2 manifest as nonendocrine organ dysfunction, primarily gastrointestinal and dermatologic diseases.

16. What eponym is associated with POEMS syndrome?

Another name for the disorder is Crow-Fukase syndrome.

17. How does POEMS syndrome usually manifest?

Most patients with POEMS syndrome are men 45 to 55 years old. The most common presentation is that of distal, symmetric peripheral sensorimotor neuropathy. There is usually loss of pinprick and vibratory sense and decreased deep tendon reflexes, predominantly in the lower extremities. The neuropathy is slowly progressive. Findings of electromyograms and nerve biopsies are most consistent with both demyelination and axonal degeneration. Autonomic neuropathy has not been observed. Papilledema is present in 40% to 80% of cases. Nerve damage may result from myelin cross-reactivity with monoclonal immunoglobulin A (IgA) or IgG M proteins produced by plasmacytomas in sclerotic bone lesions, but evidence of intraneural immunoglobulin deposition has not been found in all series.

18. How does the organomegaly manifest?

Hepatomegaly (uncommon in multiple myeloma), splenomegaly, or both can be noted in approximately two thirds of patients with POEMS syndrome. The hepatomegaly may be associated with fibrosis and liver dysfunction.

19. Which endocrine systems are involved?

Primary hypogonadism is the most common endocrine manifestation, followed by primary hypothyroidism. Diabetes mellitus type 2 is less commonly encountered; rarely, adrenal insufficiency is reported. Antibodies to the thyroid or adrenal glands have not been consistently detected.

20. What skin changes have been encountered?

Skin changes include sclerosis, hypertrichosis, hyperpigmentation, and hyperhidrosis.

21. How is POEMS syndrome treated?

Treatment of POEMS syndrome is based on elimination of plasmacytomas and osteosclerotic lesions with radiation or chemotherapy, which, if successful, results in amelioration of the polyneuropathy and reduction in organomegaly. Endocrine deficiencies are treated with replacement hormones.

BIBLIOGRAPHY

Ahonen P, Myllarniemi S, Sipila I, et al: Clinical variation of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) in a series of 68 patients, *N Engl J Med* 322:1829–1836, 1990.

Chatila TA. Regulatory T cells: key players in tolerance and autoimmunity, *Endocrinol Metab Clin North Am* 38:265–272, 2009.

Dittmar M, Kahaly GJ: Polyglandular autoimmune syndromes: immunogenetics and long-term follow-up, *J Clin Endocrinol Metab* 88:2983–2992, 2003.

Eisenbarth GS: Autoimmune polyendocrine syndromes, *Adv Exp Med Biol* 55:2204–2218, 2004.

Gandhi GY, Basu R, Dispenzieri A, et al: Endocrinopathy in POEMS syndrome: the Mayo Clinic experience, *Mayo Clin Proc* 82:836–842, 2007.

Gavalas NG, Kemp EH, Krohn KJ, et al: The calcium-sensing receptor is a target of autoantibodies in patients with autoimmune polyendocrine syndrome type 1, *J Clin Endocrinol Metab* 92:2107–2114, 2007.

Gianani R, Eisenbarth GS: Autoimmunity to gastrointestinal endocrine cells in autoimmune polyendocrine syndrome type 1 [editorial], *J Clin Endocrinol Metab* 88:1442–1444, 2003.

Husebye ES, Bratland E, Bredholt G, et al: The substrate-binding domain of 21-hydroxylase, the main autoantigen in autoimmune Addison's disease, is an immunodominant T-cell epitope, *Endocrinology* 147:2411–2416, 2006.

Mhyre AG, Halonen M, Eskelin P, et al: Autoimmune polyendocrine syndrome, *Clin Endocrinol* 45:211–217, 2001.

Owen CJ, Cheetham TD: Diagnosis and management of polyendocrinopathy syndromes, *Endocrinol Metab Clin North Am* 38:419–436, 2009.

Perheentupa J: Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy, *J Clin Endocrinol Metab* 91: 2843–2850, 2006.

Shikama N, Nusspaumer G, Hollander GA: Clearing the AIRE: on the pathological basis of the autoimmune polyendocrinopathy syndrome type-1, *Endocrinol Metabol Clin North Am* 38:273–288, 2009.

Soubrier M, Sauron C, Souweine B, et al: Growth factors and proinflammatory cytokines in the renal involvement of POEMS syndrome, *Am J Kidney Dis* 34:633–638, 1999.

PANCREATIC ENDOCRINE TUMORS

Michael T. McDermott

CHAPTER 53

1. What are the pancreatic endocrine tumors?

Tumors that arise from the islet cells of the pancreas are generally named for the hormones they secrete. These include tumors that secrete insulin (insulinomas), gastrin (gastrinomas), vasoactive intestinal polypeptide (VIPomas), glucagon (glucagonomas), somatostatin (somatostatinomas), pancreatic polypeptide (PPomas), corticotropin-releasing factor (CRFomas), adrenocorticotropic hormone (ACTHomas), and growth hormone–releasing factor (GRFomas) (Fig. 53-1).

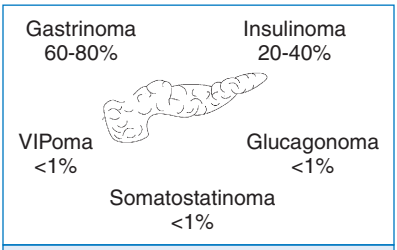

Figure 53-1. Pancreatic islet-cell tumors.

2. Are pancreatic endocrine tumors usually benign or malignant?

Insulinomas are usually benign (80%–90%); other pancreatic endocrine tumors are frequently malignant (50%–80%).

3. Are pancreatic endocrine tumors associated with other endocrine disorders?

Multiple endocrine neoplasia type 1 (MEN-1) syndrome accounts for up to 10% of pancreatic endocrine tumors. This inherited disorder consists of pituitary tumors, pancreatic endocrine tumors, and hyperparathyroidism. Hyperparathyroidism usually precedes the pituitary and pancreatic tumors by years. The condition is caused by an inherited mutation in the menin gene.

4. What are insulinomas?

Insulinomas are discrete insulin-producing tumors within the pancreas. They belong to a larger group of hyperinsulinemic pancreatic beta-cell disorders that include insulinomas, islet-cell hyperplasia, and nesidioblastosis (neoproliferation of beta cells along the pancreatic ducts).

5. What is Whipple's triad?

- Hypoglycemia
- Symptoms during hypoglycemia
- Relief of symptoms with correction of hypoglycemia

6. What glucose levels are considered to be hypoglycemia?

Glucose levels lower than 55 mg/dL are commonly considered to be hypoglycemic, but the best criteria for hypoglycemia continue to be controversial.

7. What are the symptoms of hypoglycemia?

Hypoglycemic symptoms are classified by their type and timing in relation to meals. Neuroglycopenic symptoms (confusion, slurred speech, blurred vision, seizures, coma) result from inadequate glucose delivery to the brain. Adrenergic symptoms (tremors, sweating, palpitations, nausea) result from catecholamine discharges. Symptoms that occur within 5 hours after a meal are termed *postprandial;* those occurring more than 5 hours after meals are considered *fasting*. Neuroglycopenic symptoms are characteristic of insulinomas, but adrenergic symptoms may also occur. Insulinomas most commonly cause fasting hypoglycemia (73%), although both fasting and postprandial hypoglycemia (21%) and pure postprandial hypoglycemia (6%) may be seen.

8. What evaluation should be done to test for an insulinoma?

Blood samples can be obtained during an episode of witnessed hypoglycemia, or the conditions that provoke the hypoglycemia must be replicated. This is most commonly done with a prolonged fast (supervised 72-hour fast or outpatient 12- to 18-hour fast). For this procedure, patients are allowed to drink calorie-free, caffeine-free beverages only. Blood is drawn every 6 hours until the glucose is less than 60 mg/dL, and then every 1 to 2 hours. Sufficient blood is obtained for measurement of glucose, insulin, C-peptide, proinsulin, and beta-hydroxybutyrate; glucose is measured immediately on all samples, and the other tests are run only on samples for which the glucose is lower than 55 mg/dL. Insulin antibodies are ordered on one sample, and a urine screen is sent for sulfonylureas and meglitinides. The test is stopped when the patient has typical symptoms, when the glucose level is less than 45 mg/dL (or <55 mg/dL if Whipple's triad was previously demonstrated) or at the end of 72 hours. At the end of the test, glucagon 1 mg is given intravenously, and glucose is measured 10, 20, and 30 minutes later.

9. What are the diagnostic criteria for an insulinoma?

Hypoglycemia with endogenous hyperinsulinemia must be demonstrated to diagnose an insulinoma. Diagnostic criteria are shown in Table 53-1.

10. How can an insulinoma be localized?

Computed tomography (CT) or magnetic resonance imaging (MRI) is usually the first localization procedure; reported sensitivities of these techniques vary from 15% to 90%. Endoscopic ultrasound of the pancreas has higher sensitivity (56%–93%) and can detect tumors as small as 2 to 3 mm. Intraarterial pancreatic calcium infusions with measurement of insulin changes in the right hepatic vein yield similar or superior results. Intraoperative ultrasound is highly accurate and useful for finding small tumors that could not be localized preoperatively.

TABLE 53-1. DIAGNOSTIC CRITERIA FOR INSULINOMA: DEMONSTRATION OF HYPOGLYCEMIA WITH ENDOGENOUS HYPERINSULINEMIA

TEST	THRESHOLD	SENSITIVITY	SPECIFICITY*
Glucose	<55 mg/dL		
Insulin	≥3 μU/mL	93%	95%
C-Peptide	≥0.6 ng/mL	100%	60%
Proinsulin	≥5 pmol/L	100%	68%
Beta-hydroxybutyrate	≤2.7 mmol/L	100%	100%
Glucose rise after glucagon	≥25 mg/dL	91%	95%
Insulin antibodies	Negative		
Sulfonylurea screen	Negative		
Meglitinide screen	Negative		

Adapted from Cryer PE, Axelrod L, Grossman AB, et al: Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 94:709–728, 2009; and KA Placzkowski, A Vella, GB Thompson, et al: Secular trends in the presentation and management of functioning insulinoma at the Mayo Clinic, 1987–2007. *J Clin Endocrinol Metab* 94:1069–1073, 2009.

*Compared with normal controls who developed glucose <60 mg/dL during a 72-hour fast.

11. What is the treatment for an insulinoma?

Surgery is the treatment of choice. When surgery is not desired or feasible, symptom relief can often be achieved with dietary management (multiple small meals per day) and medical therapy to inhibit insulin secretion with diazoxide, somatostatin analogs (octreotide, lanreotide), or calcium channel blockers. Malignant insulinomas can show partial responses to cytotoxic chemotherapy (streptozotocin with doxorubicin or 5-fluorouracil). Other considerations may include everolimus, an inhibitor of mammalian target of rapamycin (mTOR), sunitinib and other inhibitors of vascular endothelial growth factor receptor (VEGF-R), and radiolabeled somatostatin analog therapy.

12. What are the clinical manifestations of gastrinomas?

Gastrinomas secrete excessive gastrin, which stimulates prolific gastric acid secretion. Patients develop severe peptic ulcer disease, often associated with secretory diarrhea. This disorder is also known as the Zollinger-Ellison syndrome.

13. Do gastrinomas always arise from pancreatic islet cells?

Gastrinomas may arise from the pancreatic islets, but they also can occur in the duodenum and stomach.

14. How is the diagnosis of gastrinoma made?

Gastrinoma is diagnosed by demonstrating a fasting serum gastrin level greater than 1000 pg/mL associated with high gastric acidity ($pH \leq 4.0$). For moderately elevated serum gastrin levels of 110 to 1000 pg/mL, a secretin test should be conducted. A gastrin increment of 200 pg/mL or higher 15 minutes after intravenous secretin administration is also diagnostic of this condition. Serum chromogranin A, a nonspecific marker of neuroendocrine tumors, is also significantly elevated in gastrinomas. Patients should discontinue proton pump inhibitor therapy for 1 week before testing for gastrinoma.

15. What is the best way to localize a gastrinoma?

Localization of the tumor may be pursued with various techniques, including CT scan, MRI, endoscopic ultrasonography, octreotide scanning, transhepatic portal venous sampling, and selective arterial secretin infusions with right hepatic vein gastrin measurements.

16. How are gastrinomas managed?

Most benign and some malignant gastrinomas can be cured by surgery. Otherwise, attention should be directed toward reducing gastric acid overproduction. Proton pump inhibitors, in high doses, are the medications of choice for this purpose. Somatostatin analogs (octreotide, Octreotide LAR, lanreotide) are also effective agents. High-dose histamine-2 blockers may be useful but are rarely adequate by themselves. Patients with refractory cases may require total gastrectomy and vagotomy for symptom relief.

17. How do you treat malignant gastrinomas?

Gastrinomas are usually malignant, and therefore antitumor therapy is often necessary. Because liver metastases are common, hepatically directed therapies such as partial resection, hepatic artery embolization, and liver transplantation may be considered. Streptozotocin-doxorubicin combination therapy is the most commonly used cytotoxic regimen for malignant pancreatic endocrine tumors. Everolimus, an inhibitor of mTOR, sunitinib and other inhibitors of VEGF-R, and radiolabeled somatostatin analog therapy are other potential approaches that have shown modest success.

18. What are the characteristics of glucagonomas?

Glucagon antagonizes the effects of insulin in the liver by stimulating glycogenolysis and gluconeogenesis. Glucagonomas secrete excessive glucagon and thereby cause diabetes mellitus, weight loss, anemia, and a characteristic skin rash, necrolytic migratory erythema. Affected patients also have thromboembolic diathesis. The diagnosis depends on finding an elevated level of serum glucagon ($>$500 pg/mL). Techniques similar to those used for gastrinomas are useful for localizing these tumors.

19. How are glucagonomas treated?

Treatment options include surgery for localized disease, somatostatin analogs (octreotide, Octreotide LAR, lanreotide) to reduce glucagon secretion, hepatically directed therapies, and chemotherapy regimens similar to those used for gastrinomas. Long-term anticoagulation to reduce the risk of thromboembolic events should also be considered. Finally, zinc supplements and intermittent amino acid infusions may help to reduce the skin rash and to improve the patient's overall sense of well-being.

20. What are the characteristics of somatostatinomas?

Among its multiple systemic effects, somatostatin inhibits secretion of insulin and pancreatic enzymes, production of gastric acid, and gallbladder contraction. Somatostatinomas secrete excess somatostatin and cause diabetes mellitus, weight loss, steatorrhea, hypochlorhydria, and cholelithiasis. The diagnosis is made by finding a significantly elevated serum somatostatin level.

KEY POINTS 1: PANCREATIC ENDOCRINE TUMORS

1. Insulinomas most often cause fasting hypoglycemia with neuroglycopenic symptoms but sometimes cause mainly postprandial symptoms.
2. Suspected insulinomas are investigated by measuring serum glucose, insulin, C-peptide, proinsulin, beta-hydroxybutyrate, and a sulfonylurea screen during a symptomatic episode or a supervised fast.
3. Insulinomas are treated by surgical resection, when possible, or with multiple frequent feedings or medications, such as diazoxide, somatostatin analogs, or calcium channel blockers.
4. Gastrinomas (Zollinger-Ellison syndrome) cause aggressive peptic ulcer disease, which is sometimes associated with secretory diarrhea.
5. Gastrinomas are diagnosed by finding a markedly elevated serum gastrin level or a prominent increase in gastrin after intravenous secretin administration in a patient with significant gastric acidity.
6. Gastrinomas are treated by surgical resection, if possible, or by reduction of gastric acid production by high-dose proton pump inhibitors, somatostatin analogs, or gastrectomy, if necessary.

21. What is the treatment for somatostatinoma?

Surgery is the treatment of choice. When surgery is not possible, the same treatment options as discussed earlier for gastrinomas should be considered.

22. What are the characteristics of VIPomas?

VIPomas cause watery diarrhea, hypokalemia, and achlorhydria (WDHA syndrome). The diagnosis is made by finding a significantly elevated serum VIP level. This is also known as the Verner-Morrison syndrome or pancreatic cholera.

23. How are VIPomas treated?

Surgery is the treatment of choice. Somatostatin analogs effectively reduce diarrhea in most patients. Radiation therapy and chemotherapy also may effectively decrease diarrhea and tumor size.

24. Briefly discuss the remaining pancreatic endocrine tumors.

The remaining pancreatic endocrine tumors are rare. CRFomas and ACTHomas lead to the development of Cushing's syndrome, and GRFomas cause acromegaly. PPomas are initially asymptomatic but may eventually enlarge to produce mass effects without a recognizable hormone hypersecretion syndrome. Localization procedures and treatments are similar to those described earlier for other pancreatic endocrine tumors.

BIBLIOGRAPHY

Arnold R, Simon B, Wied M: Treatment of neuroendocrine GEP tumors with somatostatin analogues: review, *Digestion* 62(Suppl S1):84–91, 2000.

Baudin E: Gastroenteropancreatic endocrine tumors: clinical characterization before therapy, *Nat Clin Pract Endocrinol Metab* 3:228–238, 2007.

Boukhman MP, Karam JM, Shaver J, et al: Localization of insulinomas, *Arch Surg* 134:818–822 (discussion 822–823), 1999.

Bousquet C, Lasfargues C, Chalabi M, et al: Current scientific rationale for use of somatostatin analogs and mTOR inhibitors in neuroendocrine tumor therapy, *J Clin Endocrinol Metab* 97:727–737, 2012.

Cryer PE, Axelrod L, Grossman AB, et al: Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline, *J Clin Endocrinol Metab* 94:709–728, 2009.

Guettier J-M, Kam A, Chang R, et al: Localization of insulinomas to regions of the pancreas by intraarterial calcium stimulation: the NIH experience, *J Clin Endocrinol Metab* 94:1074–1080, 2009.

Jaffe BM: Current issues in the management of Zollinger-Ellison syndrome, *Surgery* 111:241–243, 1992.

Kar P, Price P, Sawers S, et al: Insulinomas may present with normoglycemia after prolonged fasting but glucose-stimulated hypoglycemia, *J Clin Endocrinol Metab* 91:4733–4736, 2006.

Kauhanen S, Sappanen M, Minn H, et al: Fluorine-18-L-dihydroxyphenylalanine (F18DOPA) positron emission tomography as a tool to localize an insulinoma or B-cell hyperplasia in adult patients, *J Clin Endocrinol Metab* 92:1237–1244, 2007.

Krejs GJ, Orci L, Conlon M, et al: Somatostatinoma syndrome: biochemical, morphologic and clinical features, *N Engl J Med* 301:283–292, 1979.

Leichter SB: Clinical and metabolic aspects of glucagonoma, *Medicine* 59:100–113, 1980.

Placzkowski KA, Vella A, Thompson GB, et al: Secular trends in the presentation and management of functioning insulinoma at the Mayo Clinic, 1987–2007, *J Clin Endocrinol Metab* 94:1069–1073, 2009.

Raymond E, Dahan L, Raoul J-L: Sunitinib for the treatment of pancreatic neuroendocrine tumors, *N Engl J Med* 364: 501–513, 2011.

Ricke J, Klose K: Imaging procedures in neuroendocrine tumors, *Digestion* 62(Suppl S1):39–44, 2000.

Service FJ: Classification of hypoglycemic disorders, *Endocrinol Metab Clin North Am* 28:501–517, 1999.

Service FJ: Recurrent hyperinsulinemic hypoglycemia caused by an insulin-secreting insulinoma, *Nat Clin Pract Endocrinol Metab* 2:467–470, 2006.

van Schaik E, van Vliet EI, Feelders RA, et al: Improved control of severe hypoglycemia in patients with malignant insulinomas by peptide receptor radionuclide therapy, *J Clin Endocrinol Metab* 96:3381–3389, 2011.

Wermers RA, Fatourechi V, Krols LK: Clinical spectrum of hyperglucagonemia associated with malignant neuroendocrine tumors, *Mayo Clin Proc* 71:1030–1038, 1996.

Yao JC, Shah MH, Ito T, et al: Everolimus for advanced pancreatic neuroendocrine tumors, *N Engl J Med* 364:514–523, 2011.

CHAPTER 54

CARCINOID SYNDROME

Michael T. McDermott

1. What are carcinoid tumors? How are they classified?

Carcinoid tumors are neoplasms that arise from enterochromaffin cells. They are classified according to their site of origin as foregut (bronchus, stomach, duodenum, bile ducts, pancreas), midgut (jejunum, ileum, appendix, ascending colon), or hindgut (transverse and descending colon, rectum) carcinoids. They also develop in the ovaries, testes, prostate, kidney, breast, thymus, or skin. Approximately 55% of carcinoid tumors occur in the gastrointestinal (GI) tract, and 30% are found in the bronchopulmonary system. Of those tumors in the GI tract, the location frequencies are as follows: small intestine (45%, most commonly the ileum), rectum (20%), appendix (16%), colon (11%), and stomach (7%).

2. Define carcinoid syndrome.

Carcinoid syndrome is a humorally mediated disorder consisting of cutaneous flushing (90%), diarrhea (75%), bronchospasm (20%), endocardial fibrosis (33%), right-sided heart valvular lesions, and occasionally pleural, peritoneal, or retroperitoneal fibrosis.

3. What are the biochemical mediators of carcinoid syndrome?

Carcinoid tumors produce a variety of humoral mediators, including serotonin, chromogranin A, neuron-specific enolase (NSE), histamine, prostaglandins, bradykinin, tachykinins, neurotensin, motilin, and substance P. Diarrhea and fibrous tissue formation may be caused by serotonin, whereas flushing and wheezing are likely the result of histamine, prostaglandins, or kinins (Fig. 54-1). The formation and metabolism of serotonin are shown in Figure 54-2.

4. Why does pellagra often accompany carcinoid syndrome?

Pellagra is caused by niacin deficiency that results when a carcinoid tumor diverts large amounts of tryptophan from niacin synthesis to produce serotonin (see Fig. 54-2).

5. Why do intestinal carcinoid tumors so infrequently cause carcinoid syndrome?

Carcinoid syndrome occurs when humoral mediators enter the systemic circulation in large quantities. Solitary intestinal carcinoids secrete mediators into the portal circulation, where they are almost totally

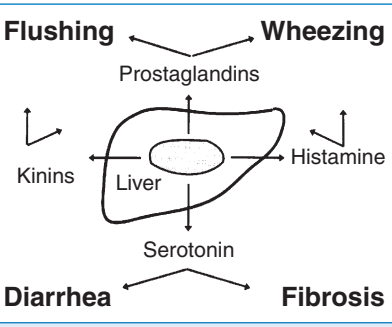

Figure 54-1. Carcinoid syndrome.

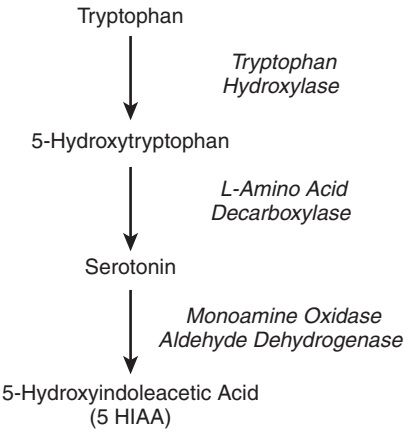

Figure 54-2. Serotonin metabolism.

metabolized by the liver and never reach the systemic circulation. Carcinoid syndrome does not usually occur with these tumors unless the patient has hepatic metastases that impair mediator metabolism or that secrete mediators directly into the hepatic vein. Extraintestinal carcinoids, however, may cause carcinoid syndrome in the absence of metastases because they secrete mediators into venous systems that do not first pass through the liver.

6. Do carcinoid tumors cause any other humoral syndromes?

Carcinoids may also secrete corticotropin-releasing factor (CRF) or corticotropin (adrenocorticotropin [ACTH]), thus causing Cushing's syndrome, or growth hormone–releasing factor (GRF), thus causing acromegaly. These syndromes have been reported mainly with bronchial and pancreatic carcinoid tumors.

KEY POINTS 1: CARCINOID SYNDROME

1. Carcinoid syndrome results from tumor production of humoral mediators that cause flushing, diarrhea, bronchospasm, and fibrous tissue formation.
2. Most patients with carcinoid syndrome have extensive liver metastases that either impair the metabolic clearance of mediators secreted by the primary tumor or secrete the mediators directly into the hepatic vein.
3. Carcinoid syndrome is diagnosed by demonstrating markedly increased urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA) or elevated levels of serum chromogranin A or whole blood serotonin.
4. The treatment for carcinoid syndrome is surgery, when possible, or palliation of symptoms by giving medications that reduce secretion of the humoral mediators or antagonize their effects.
5. A carcinoid crisis can be precipitated when a patient with a carcinoid tumor is given an adrenergic or sympathomimetic medication or a monoamine oxidase (MAO) inhibitor.
6. A carcinoid crisis is best treated with intravenous octreotide and hydrocortisone and avoidance of adrenergic and sympathomimetic agents.

7. How is the diagnosis of carcinoid syndrome usually made?

The diagnosis is made by finding markedly elevated urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA), a breakdown product of serotonin (see Fig. 54-2). Normal urinary 5-HIAA excretion is less than 8 mg/24 hours. Malabsorption syndromes, ingestion of tryptophan-rich foods, and use of certain medications can elevate urinary 5-HIAA, but the value usually remains lower than 30 mg/24 hours (Table 54-1). Carcinoid syndrome is most often associated with urinary 5-HIAA excretion greater than 100 mg/24 hours, although mild or no elevation may be seen in some patients.

8. How is carcinoid syndrome diagnosed if urinary 5-HIAA is normal?

Foregut carcinoid tumors often lack the enzyme L-amino acid decarboxylase and therefore do not make serotonin or 5-HIAA (see Fig. 54-2). Chromogranin A, a sensitive but nonspecific marker of neuroendocrine tumors, is a good alternative test. Mild elevations may occur in many conditions (Table 54-2), but values greater than 31 U/L have 75% sensitivity and 84% specificity for diagnosing carcinoid syndrome. Whole blood serotonin and NSE, when available, may also be helpful in equivocal cases.

9. What procedures are best to localize the source of carcinoid syndrome?

Abdominal computed tomography (CT) scan and octreotide scintigraphy (OctreoScan) are currently the most accurate options. When these scans are negative or not feasible, positron emission tomography (PET) with fluorine-18 [^{18}F]-fluorodeoxyglucose (FDG-PET) is often helpful. Other specific functional PET imaging agents, such as 6-[18-F]-fluorodopa and carbon-11 [^{11}C]-5- hydroxytryptophan, are in development but are not yet available.

10. What is the treatment for carcinoid syndrome?

Surgery can be curative when carcinoid syndrome results from a carcinoid tumor that has not metastasized. However, approximately 90% of patients with carcinoid syndrome have extensive metastases at the time of diagnosis. The usual goals of therapy are therefore is to provide palliation and to prolong survival.

TABLE 54–1. NONCARCINOID CAUSES OF ABNORMAL 5-HYDROXYINDOLEACETIC ACID EXCRETION

Diseases: malabsorption disorders
Food (tryptophan rich): bananas, pineapples, kiwi, plums, avocados, eggplant, pecans, walnuts, hickory nuts
Medications that increase 5-HIAA: acetaminophen, ephedrine, guaifenesin, mephenesin, methocarbamol, phenacetin, caffeine, nicotine, methamphetamine, phenobarbital, acetanilid, reserpine, phentolamine, phenmetrazine, coumaric acid, melphalan, fluorouracil
Medications that decrease 5-HIAA: aspirin, ethanol, heparin, imipramine, levodopa, methyldopa, monoamine oxidase inhibitors, phenothiazines, isoniazid, corticotropin, gentisic acid, methenamine, streptozotocin

5-HIAA, 5-Hydroxyindoleacetic acid.

TABLE 54–2. CAUSES OF ELEVATED SERUM CHROMOGRANIN A

Neuroendocrine disorders: carcinoid tumors, pheochromocytoma, islet cell tumors, medullary carcinoma of the thyroid, neurofibromatosis
Other conditions: prostate cancer, hyperthyroidism, renal failure, heart failure, hypertension, atrophic gastritis
Medications: proton pump inhibitors

11. How does one control carcinoid syndrome symptoms?

The most troublesome symptoms patients with carcinoid syndrome experience are intense flushing and frequent diarrhea. Somatostatin analogs (octreotide, lanreotide) are often highly effective in controlling carcinoid symptoms. Other antiflushing and antidiarrheal strategies can be added if symptom control is inadequate. Table 54-3 lists various medication options for relief of refractory symptoms. Hepatic resection can be very effective in patients with focal liver metastases. Other options include hepatic artery embolization, chemoembolization, 90-Y microsphere radioembolization, radiolabeled somatostatin analog therapy, and alpha-interferon.

12. What chemotherapy regimens are most effective in carcinoid tumors?

Cytotoxic chemotherapy has produced disappointing results in patients with carcinoid syndrome. Etoposide and cisplatin combination therapy is the most commonly used regimen for poorly differentiated carcinoid tumors. Everolimus, an antagonist of mammalian target of rapamycin (mTOR), and vascular endothelial growth factor receptor (VEGF-R) antagonists, such as Vatalanib, Sunitinib, Sorafenib, and bevacizumab, are also under investigation. Other agents that have been used with limited success include streptozotocin, 5-fluorouracil, lomustine, doxorubicin, and dacarbazine.

13. What is a carcinoid crisis?

Carcinoid crisis is a life-threatening episode of hypotension, flushing, and bronchospasm that is triggered most often by tumor manipulation or anesthesia and less commonly by chemotherapy, hepatic artery embolization, or radionuclide therapy. It can also be provoked by the administration of adrenergic agents, such as epinephrine and sympathomimetic amines, or monoamine oxidase (MAO) inhibitors in patients with underlying carcinoid tumors.

TABLE 54-3. MEDICATIONS FOR RELIEF OF SYMPTOMS RELATED TO CARCINOID SYNDROME

Medications to Control Carcinoid Flushing	
Octreotide (Sandostatin)	50-150 μg two or three times/day subcutaneously
Octreotide, long-acting (Sandostatin LAR)	10-30 mg every mo intragluteally
Lanreotide (Somatuline)	60-120 mg every mo subcutaneously
Phentolamine (Regitine)	25-50 mg one to three times/day
Phenoxybenzamine (Dibenzyline)	30 mg/day
Cyproheptadine (Periactin)	2-4 mg three or four times/day
Methysergide (Sansert)	2 mg three times/day
Prochlorperazine (Compazine)	5-10 mg every 4-6 hr
Chlorpromazine (Thorazine)	10-25 mg every 4-6 hr
Clonidine (Catapres)	0.1-0.2 mg two times/day
Methyldopa (Aldomet)	250 mg three times/day
Cimetidine (Tagamet), plus:	300 mg three times/day
Diphenhydramine (Benadryl)	50 mg four times/day
Glucocorticoids	
Medications to Control Carcinoid Diarrhea	
Standard antidiarrheal measures, plus:	
Octreotide (Sandostatin)	50-150 μg two or three times/day subcutaneously
Octreotide, long-acting (Sandostatin LAR)	10-30 mg every mo intragluteally
Lanreotide (Somatuline)	60-120 mg every mo subcutaneously
Clonidine (Catapres)	0.1-0.2 mg two times/day
Cyproheptadine (Periactin)	2-4 mg three or four times/day
Methysergide (Sansert)	2 mg three times/day
Ondansetron (Zofran)	8 mg three times/day

TABLE 54-4. MANAGEMENT OF CARCINOID CRISIS

MEDICATION	DOSE REGIMEN
Octreotide (Sandostatin)	50 μg IV over 1 min, then 50 mg IV over 15 min
Hydrocortisone (Solu-Cortef)	100 mg IV over 15 min
Methotrimeprazine (Levoprome)	2.5-5.0 mg slow IV push
Methoxamine (Vasoxyl)	3-5 mg slow IV push, followed by an infusion
Phentolamine (Regitine)	5 mg slow IV push
Ondansetron (Zofran)	20 mg IV over 15 min
Glucagon	0.5-1.5 mg slow IV push

From Warner RRP: Gut neuroendocrine tumors. In Bardin CW, editor: *Current therapy in endocrinology and metabolism,* ed 6, St. Louis, 1997, Mosby, pp 606–614.
IV, Intravenous.

14. How can a carcinoid crisis be prevented?

Epinephrine, sympathomimetic amines, and MAO inhibitors should be avoided in patients with carcinoid syndrome. When these patients undergo surgery or hepatic artery embolization for their tumor or metastases, they should be pretreated with octreotide (Sandostatin), 300 to 500 μg subcutaneously or intravenously, 30 to 60 minutes before the procedure. Anesthesiologists should be specifically notified that the patient has carcinoid syndrome.

15. Can a carcinoid crisis be predicted?

Patients with carcinoid tumors who have not developed carcinoid syndrome can be tested for their potential to have a carcinoid crisis. This is most commonly accomplished with an epinephrine provocation test; patients are given progressive intravenous (IV) boluses of epinephrine every 5 minutes, starting with a dose of 1 μg and increasing, if necessary, to 10 μg, while heart rate and blood pressure are monitored every 60 seconds. A positive response consists of flushing or a blood pressure drop of 20 mm Hg systolic or 10 mm Hg diastolic 45 to 120 minutes after an injection. All patients undergoing this test must have venous catheters and be monitored carefully throughout the test; IV phentolamine (Regitine) 5-mg and methoxamine (Vasoxyl) 3-mg preparations must also be available to reverse a crisis should it occur.

16. Describe the management of a carcinoid crisis.

Effective treatment for carcinoid crisis consists of IV administration of octreotide and glucocorticoids. If this does not abort the episode, additional options include methotrimeprazine (an antiserotonin agent), methoxamine (a direct vasoconstrictor), phentolamine (an alpha-adrenergic blocker), ondansetron (a serotonin receptor antagonist), and glucagon. It is critical to avoid the use of adrenergic and sympathomimetic agents in patients with suspected carcinoid crisis because these drugs can significantly worsen the condition. Effective medication dose regimens for this condition are listed in Table 54-4.

BIBLIOGRAPHY

Baudin E: Gastroenteropancreatic endocrine tumors: clinical characterization before therapy, *Nat Clin Pract Endocrinol Metab* 3:228–238, 2007.
Campana D, Nori F, Piscitelli L, et al: Chromogranin A: is it a useful marker of neuroendocrine tumors? *J Clin Oncol* 25:1967–1963, 2007.
Eriksson B, Kloppel G, Krenning E, et al: Consensus guidelines for the management of patients with digestive neuroendocrine tumors: well differentiated jejunal-ileal tumor/carcinoma, *Neuroendocrinology* 87:8–19, 2008.
Feldman JM: The carcinoid syndrome, *Endocrinologist* 3:129–135, 1993.
Galanis E, Kvols LK, Rubin J: Carcinoid syndrome, *J Clin Oncol* 16:796–798, 1998.

Koopmans KP, Neels OC, Kema IP, et al: Improved staging of patients with carcinoid and islet cell tumors with ^{18}F-dihydroxy-phenyl-alanine and ^{11}C-5-hydroxy-tryptophan positron emission tomography, *J Clin Oncol* 26:1489–1495, 2008.

Maggard MA, O'Connell JB, Ko CY: Updated population-based review of carcinoid tumors, *Ann Surg* 240:117–122, 2004.

Modlin IM, Lye KD, Kidd M: A 5-decade analysis of 13,715 carcinoid tumors, *Cancer* 97:934–959, 2003.

Moldin IM, Oberg K, Chung CD, et al: Gastroenteropancreatic neuroendocrine tumors, *Lancet Oncol* 9:61–72, 2008.

O'Toole D, Ducreaux M, Bommelaer G, et al: Treatment of carcinoid syndrome: a prospective crossover evaluation of lanreotide versus octreotide in terms of efficacy, patient acceptability, and tolerance, *Cancer* 88:770–776, 2000.

Plockinger U, Wiedenmann B: Management of metastatic endocrine tumors, *Best Pract Res Clin Gastroenterol* 19:553–576, 2005.

Soga J, Yakuwa Y, Osaka M: Carcinoid syndrome: a statistical evaluation of 748 reported cases, *J Exp Clin Cancer Res* 18:133–141, 1999.

Stuart K, Levy DE, Anderson T, et al: Phase II study of interferon gamma in malignant carcinoid tumors (E9292): a trial of the Eastern Oncology Group, *Invest New Drugs* 22:75–81, 2004.

CHAPTER 55

CUTANEOUS MANIFESTATIONS OF DIABETES MELLITUS AND THYROID DISEASE

Gary Goldenberg and James E. Fitzpatrick

1. How often do patients with diabetes mellitus demonstrate an associated skin disorder?

Most published studies report that 30% to 50% of patients with diabetes mellitus ultimately develop a skin disorder attributable to their primary disease. However, if one includes subtle findings such as nail changes, vascular changes, and alteration of the cutaneous connective tissue, the incidence approaches 100%. Skin disorders most often manifest in patients with known diabetes mellitus, but cutaneous manifestations also may be an early sign of undiagnosed diabetes.

KEY POINTS 1: CUTANEOUS MANIFESTATIONS

1. Patients with diabetes mellitus demonstrate cutaneous findings attributable to diabetes in almost 100% of cases.
2. The most common cause of acanthosis nigricans is diabetes associated with insulin resistance and obesity.
3. Necrobiosis lipoidica is a granulomatous dermatitis that is typically associated with diabetes mellitus in almost two thirds of cases.
4. Pretibial myxedema is most commonly associated with Graves' disease.
5. Generalized myxedema is the most characteristic cutaneous sign of hypothyroidism.

2. Are any skin disorders pathognomonic of diabetes mellitus?

Yes. Bullous diabeticorum (bullous eruption of diabetes, diabetic bullae) is specific for diabetes mellitus, but it is uncommon. Bullous diabeticorum most often occurs in patients with severe diabetes, particularly those with associated peripheral neuropathy. In general, all other reported skin findings may be found to some extent in normal individuals. However, some cutaneous conditions (e.g., necrobiosis lipoidica diabeticorum) demonstrate strong associations with diabetes.

3. What is bullous diabeticorum?

Bullous diabeticorum is a blistering disorder that primarily occurs on the distal extremities of diabetic patients. Lesions typically appear as spontaneous tense blisters that are asymptomatic, except for a burning sensation. The exact mechanism is not understood, but most patients have peripheral neuropathy, retinopathy, or nephropathy.

4. What are the skin disorders most likely to be encountered in diabetic patients?

The most common skin disorders are finger pebbles, nail bed telangiectasia, red face (rubeosis), skin tags (acrochordons), diabetic dermopathy, yellow skin, yellow nails, and pedal petechial purpura (Table 55-1). Less common cutaneous disorders that are closely associated with diabetes mellitus include necrobiosis lipoidica diabeticorum, bullous eruption of diabetes, acanthosis nigricans, and scleredema adultorum.

TABLE 55-1. COMMON CUTANEOUS FINDINGS IN DIABETES MELLITUS

CUTANEOUS FINDING	INCIDENCE IN CONTROLS (%)	INCIDENCE IN DIABETIC PATIENTS (%)
Finger pebbles	21	75
Nail bed telangiectasia	12	65
Rubeosis (red face)	18	59
Skin tags	3	55
Diabetic dermopathy	Uncommon	54
Yellow skin	24	51
Yellow nails	Uncommon	50
Erythrasma	Uncommon	47
Diabetic thick skin	Uncommon	30

5. What are finger pebbles?

Finger pebbles (Huntley's papules) are multiple, grouped minute papules that tend to affect the extensor surfaces of the fingers, particularly near the knuckles. They are asymptomatic and may be extremely subtle in appearance. Histologically, finger pebbles are the result of increased collagen in the dermal papillae. The pathogenesis is not understood.

6. What is acanthosis nigricans?

Acanthosis nigricans is a skin condition caused by papillomatous (wartlike) hyperplasia of the skin. It is associated with various conditions, including diabetes mellitus, obesity, acromegaly, Cushing's syndrome, certain medications, and underlying malignant diseases. Acanthosis nigricans associated with insulin-dependent diabetes has been linked to insulin resistance by three mechanisms: type A (receptor defect), type B (antireceptor antibodies), and type C (postreceptor defect). It is proposed that, in insulin-resistant states, hyperinsulinemia competes for the insulin-like growth factor receptors on keratinocytes and thus stimulates epidermal growth. In the case of hypercortisolism, as seen in Cushing's disease, there is induced insulin resistance, which is believed to induce epidermal growth.

7. What does acanthosis nigricans look like?

It is most noticeable in axillary, inframammary, and neck creases, where it appears as hyperpigmented velvety skin that has the appearance of being "dirty" (Fig. 55-1). The tops of the knuckles may also have small papules that resemble finger pebbles, except that they are more pronounced (Fig. 55-2).

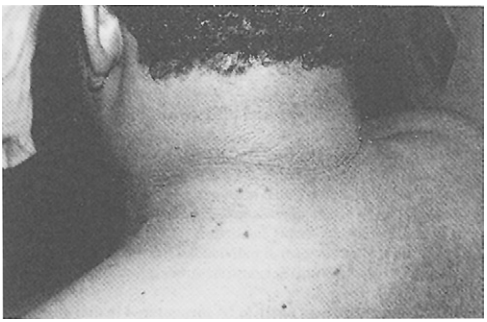

Figure 55-1. Acanthosis nigricans. Characteristic velvety hyperpigmentation of flexural areas is evident.

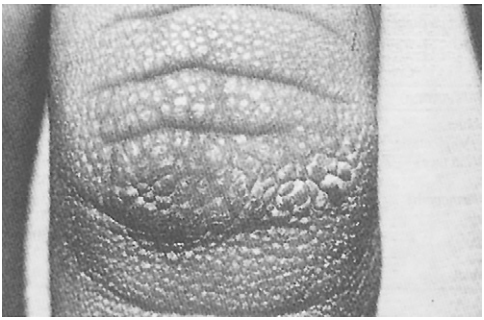

Figure 55-2. Acanthosis nigricans. Typical papillomatous lesions occur over the knuckles.

8. What is diabetic dermopathy?

Diabetic dermopathy (shin spots or pretibial pigmented patches) is a common affliction of diabetic patients that initially manifests as erythematous to brown to brownish-red macules that typically measure 0.5 to 1.5 cm, with variable scale on the pretibial surface (Fig. 55-3). The lesions are typically asymptomatic but are occasionally pruritic or are associated with a burning sensation. Patients with diabetic dermopathy are more likely to have retinopathy, nephropathy, and neuropathy. The lesions heal with varying degrees of atrophy and hyperpigmentation over 1 to 2 years. The pathogenesis is unknown, but skin biopsies from the lesions demonstrate diabetic microangiopathy characterized by a proliferation of endothelial cells and thickening of the basement membranes of arterioles, capillaries, and venules associated with deposition of hemosiderin. Although many physicians attribute these lesions to trauma, this view is not supported by an unusual study in which patients with diabetes mellitus failed to develop lesions after they were struck on the pretibial surface with a hard rubber hammer. Diabetic dermopathy has no known effective treatment.

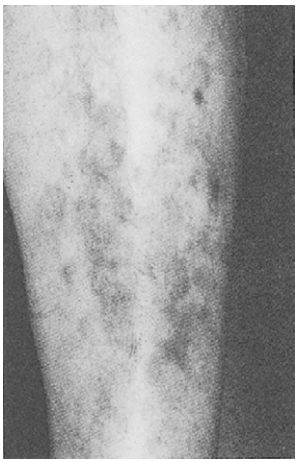

Figure 55-3. Diabetic dermopathy. Characteristic brown macules are present over pretibial areas.

9. What is necrobiosis lipoidica diabeticorum?

Necrobiosis lipoidica diabeticorum is a disease that most commonly occurs on the pretibial areas, although it may occur at other sites. It is more common in women. Early lesions manifest as nondiagnostic erythematous papules or plaques that evolve into annular lesions characterized by a yellowish or yellowish-brown color, dilated blood vessels, and central epidermal atrophy. Developed lesions are characteristic and usually can be diagnosed by clinical appearance. Less commonly, ulcers may develop. Biopsies are usually diagnostic and demonstrate palisaded granulomas that surround large zones of necrotic and sclerotic collagen. Additional findings include dilated vascular spaces, plasma cells, and increased dermal fat. The pathogenesis is not known, but proposed causes include immune complex vasculitis and a platelet aggregation defect.

10. What is the relationship of necrobiosis lipoidica diabeticorum with diabetes mellitus?

In a major study of patients with necrobiosis lipoidica diabeticorum, 62% had diabetes. Approximately one half of the nondiabetic patients had abnormal glucose tolerance tests, and almost one half of the nondiabetic patients gave a family history of diabetes. However, necrobiosis lipoidica diabeticorum is present in only 0.3% of patients with diabetes. The term *necrobiosis lipoidica* is used for patients who have the disorder without associated diabetes. Because of the strong association between these conditions, patients who present with necrobiosis lipoidica should be screened for diabetes; patients who test negative should be reevaluated periodically.

11. How should necrobiosis lipoidica diabeticorum be treated?

Necrobiosis lipoidica occasionally may resolve without treatment. It does not seem to respond to treatment of diabetes in new cases or to tighter control of established diabetes. Early lesions may respond to treatment with potent topical or intralesional corticosteroids. More severe cases may respond to oral treatment with stanozolol, niacinamide, pentoxifylline, mycophenolate mofetil, cyclosporine, or photodynamic therapy. Severe cases with recalcitrant ulcers may require surgical grafting.

12. Are skin infections more common in diabetic patients than in control populations?

Yes, but skin infections are probably not as common as most medical personnel believe. Studies show that an increased incidence of skin infections strongly correlates with elevated levels of mean plasma glucose.

13. What are the most common bacterial skin infections associated with diabetes mellitus?

The most common serious skin infections associated with diabetes mellitus are related to diabetic foot and amputation ulcers. One autopsy study revealed that 2.4% of all diabetic patients had infectious skin ulcerations of the extremities compared with 0.5% of a control population. Even though there are no well-controlled studies, it is believed that staphylococcal skin infections, including furunculosis and staphylococcal wound infections, are more common and serious in diabetic patients. Erythrasma, a benign superficial bacterial infection caused by *Corynebacterium minutissimum,* was present in 47% of adult diabetic patients in one study. Clinically, erythrasma manifests as tan to reddish-brown lesions with slight scale in intertriginous areas such as the groin. Because the organisms produce porphyrins, the diagnosis can be made by demonstrating a spectacular coral red fluorescence with Wood's lamp.

14. What is the most common fungal mucocutaneous infection associated with diabetes mellitus?

The most common mucocutaneous fungal infection associated with diabetes is candidiasis, usually caused by *Candida albicans*. Women are particularly prone to vulvovaginitis. One study demonstrated that two thirds of all diabetic patients have positive cultures for *Candida albicans*. In women with signs and symptoms of vulvitis, the incidence of positive cultures approaches 99%. Similarly, positive cultures are extremely common in diabetic men and women who complain of anal pruritus. Other mucocutaneous forms of candidiasis include thrush, perlèche (angular cheilitis), intertrigo, erosio

interdigitalis blastomycetica chronica (Fig. 55-4), paronychia (infection of the soft tissue around the nail plate), and onychomycosis (infection of the nail). The mechanism appears to be related to increased levels of glucose that serve as a substrate for *Candida* species to proliferate. Patients with recurrent cutaneous candidiasis of any form should be screened for diabetes.

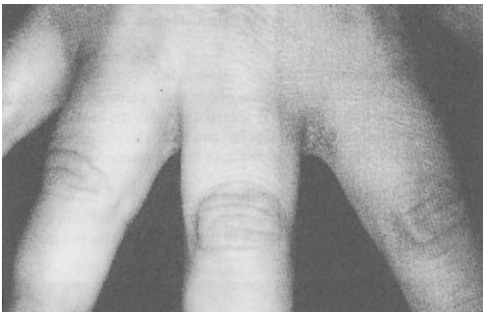

Figure 55-4. Erosio interdigitalis blastomycetic chronica. *Candida* infection is present in the interdigital spaces in a diabetic patient. This is a very long name for a very small infection.

15. Why are diabetic patients in ketoacidosis especially prone to mucormycosis?

Some Zygomycetes, including *Mucor, Mortierella, Rhizopus,* and *Absidia* species, are thermotolerant, prefer an acid pH, grow rapidly in the presence of high levels of glucose, and are among the few fungi that use ketones as a growth substrate. Thus, diabetic patients with ketoacidosis provide an ideal environment for the proliferation of these fungi and are especially prone to develop rhinocerebral mucormycosis. Fortunately, these fulminant and often fatal fungal infections are rare.

16. Are any skin complications associated with the treatment of diabetes mellitus?

Yes. Adverse reactions to injected insulin are relatively common. The reported incidence varies from 10% to 56%, depending on the study. In general, these complications may be divided into three categories: reactions resulting from faulty injections (e.g., intradermal injection), idiosyncratic reactions, and allergic reactions. Several types of allergic reactions have been described, including localized and generalized urticaria, Arthus reactions, and localized delayed hypersensitivity. Oral hypoglycemic agents occasionally may produce adverse cutaneous reactions, including photosensitivity, urticaria, erythema multiforme, and erythema nodosum. Chlorpropamide in particular may produce a flushing reaction when it is consumed with alcohol.

17. What is scleredema adultorum?

Scleredema adultorum is a woody induration that most commonly manifests on the posterior neck, upper back, and shoulders. Less commonly, it may be more extensive and involve the face, abdomen, and extremities. It is most commonly associated with insulin-dependent diabetes and is less commonly associated with monoclonal gammopathies and streptococcal infections. Biopsies demonstrate increased dermal collagen and hyaluronic acid (dermal mucin). The pathogenesis is not understood. When associated with insulin-dependent diabetes, scleredema adultorum is chronic and recalcitrant to therapy.

18. What are the most important cutaneous manifestations of the hypothyroid state?

Generalized myxedema is the most characteristic cutaneous sign of hypothyroidism. Other skin findings include xerosis (dry skin), follicular hyperkeratosis (Fig. 55-5), diffuse hair loss (especially the

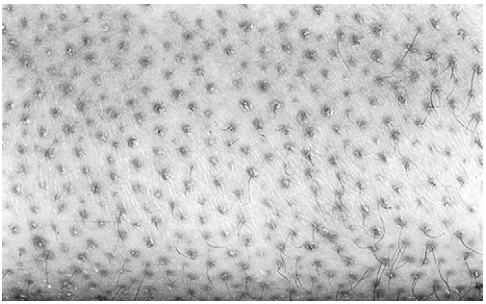

Figure 55-5. Hypothyroidism. Marked follicular hyperkeratosis quickly disappeared with thyroid replacement.

outer one third of the eyebrows), dry and brittle nails, yellowish discoloration of the skin, and thyroid acropachy (thickening of the distal fingers). These skin changes are all reversible with appropriate thyroid replacement.

19. Why do hypothyroid patients often have yellow skin?

The yellow color results from the accumulation of carotene (carotenoderma) in the top layer of the epidermis (stratum corneum). Carotene is excreted by both the sweat and the sebaceous glands and tends to concentrate on the palms, soles, and face. The increased levels of carotene are probably secondary to impaired hepatic conversion of beta-carotene to vitamin A.

20. What are the clinical findings in generalized myxedema?

Generalized myxedema is characterized by pale, waxy, edematous skin that does not demonstrate pitting. These changes are most noticeable in the periorbital area but may also be observed in the distal extremities, lips, and tongue (Fig. 55-6).

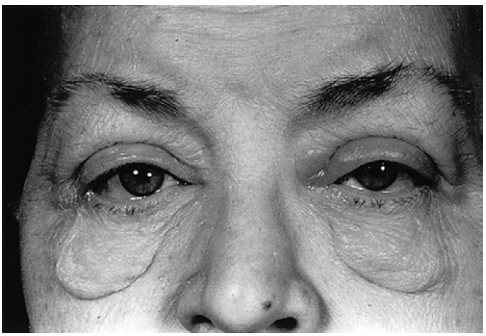

Figure 55-6. Generalized myxedema. Pale, waxy skin of the upper eyelids is associated with marked pendulous edema of lower eyelids. These changes quickly disappeared with thyroid replacement.

21. What is the pathogenesis of generalized myxedema?

The skin demonstrates an increased accumulation of dermal acid mucopolysaccharides, of which hyaluronic acid (ground substance) is the most important. Studies also have demonstrated that an increased transcapillary escape of serum albumin into the dermis adds to the edematous appearance. Neither of these changes is permanent; both are reversible with replacement therapy.

22. What is the difference between generalized myxedema and pretibial myxedema?

Generalized myxedema is associated with only the hypothyroid state, whereas pretibial myxedema is characteristically associated with Graves' disease. Patients with pretibial myxedema may be hypothyroid, hyperthyroid, or euthyroid when the skin disorder appears. The pathogenesis has not been proved, but it has been demonstrated that serum from patients with pretibial myxedema will stimulate the production of acid mucopolysaccharides of fibroblasts. Fibroblasts from the pretibial area are more sensitive to stimulation than are fibroblasts from other areas; this accounts for the tendency for these lesions to occur in pretibial areas. The nature of this circulating factor is unknown, but stimulatory thyroid-stimulating hormone (TSH) receptor autoantibodies are thought to be the most likely candidate. Investigators have also postulated that activated T cells induce both fibroblast proliferation and the production of acid mucopolysaccharides.

23. What are the clinical manifestations of pretibial myxedema?

Pretibial myxedema occurs in approximately 3% to 5% of patients with Graves' disease. Most patients have associated exophthalmos. Thyroid acropachy is also present in 1% of patients with Graves' disease (Fig. 55-7). Clinically, pretibial myxedema is characterized by edematous, indurated plaques over the pretibial areas, although other sites of the body also may be involved. The plaques are usually sharply demarcated, but diffuse variants are also reported. The overlying skin surface is usually normal, although it may be studded with smaller papules. The color varies from skin colored to brownish red (Fig. 55-8). Overlying hypertrichosis may be present on rare occasions. Histologically, pretibial myxedema demonstrates massive accumulation of dermal hyaluronic acid.

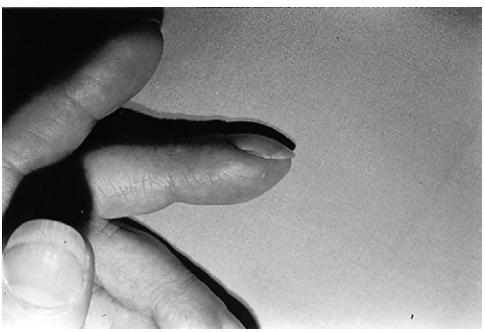

Figure 55-7. Thyroid acropachy. This patient with Graves' disease demonstrated swelling of soft tissue and increased curvature of the nail plate.

24. How is pretibial myxedema treated?

Studies comparing different treatment modalities have not been performed. Because the condition is not harmful to patients and because it may resolve spontaneously, treatment is not always indicated. Many cases respond to potent topical corticosteroids under occlusion or intralesional corticosteroids. More extensive cases may be treated with oral systemic corticosteroids or rituximab in combination with plasmapheresis. Treatment of the thyroid disease does not affect the cutaneous findings.

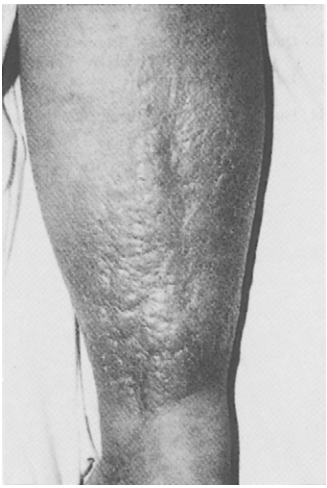

Figure 55-8. Pretibial myxedema. Indurated brownish-red plaque of the pretibial area is noted.

25. What are the skin manifestations of hyperthyroidism?

Studies have shown that as many as 97% of all patients with hyperthyroidism develop skin manifestations. Common cutaneous findings include cutaneous erythema, evanescent flushing, excoriations, smooth skin, hyperpigmentation, moist skin (from increased sweating), pretibial myxedema, pruritus (itching), and warm skin. Nails are often brittle and may separate from the underlying bed (onycholysis). The hair also may be thinner than normal.

26. What effect does obesity have on skin function and physiology?

Obesity effects skin function and physiology in many ways. The skin barrier function is altered in obese individuals, who show a significantly increased transepidermal water loss. The elevation of androgens, insulin, growth hormone, and insulin-like growth factor seen in obese patients is related to an increase in sebaceous gland function and sebum production, thus exacerbating diseases such as acne vulgaris. The activity of apocrine and eccrine sweat glands is also increased in obese patients. Lymphatic flow is impeded in obese individuals, and this leads to accumulation of protein-rich lymphatic fluid in the subcutaneous tissue that, in turn, leads to lymphedema. In animal studies, obesity is associated with altered collagen structure and function and with impaired wound healing.

27. What are some of the cutaneous manifestations of obesity?

Obese patients have myriad cutaneous manifestations, including changes related to insulin resistance, as well as infectious, mechanical, and inflammatory conditions. These include acanthosis nigricans (discussed earlier), acrochordons (skin tags), keratosis pilaris, striae distensae, and hidradenitis suppurativa.

28. Does obesity aggravate any skin diseases?

Yes. Obesity aggravates multiple skin diseases, including intertrigo, hidradenitis suppurativa, cellulite, psoriasis, and chronic venous insufficiency. Bacterial skin infections are also aggravated by obesity. These range from superficial infections, such as folliculitis, to deep infections, such as cellulitis and necrotizing fasciitis.

TOP SECRETS

1. Bullous diabeticorum is the only cutaneous finding that is pathognomonic of diabetes mellitus.
2. Acanthosis nigricans is associated with several endocrinopathies including diabetes mellitus (most common), acromegaly, and Cushing's syndrome, in addition to several genetic disorders, medications, and malignant diseases.
3. Mucormycosis is more common in diabetic patients with ketoacidosis because the fungi are thermotolerant, grow well in an acid pH, grow rapidly in the presence of high glucose, and are among the few types of fungi that can use ketones as a food substrate.
4. Loss of the lateral one third of the eyebrows is a classic cutaneous finding associated with hypothyroidism.
5. Hypothyroid patients have yellowish skin because of carotenodermia, which results from the accumulation of carotene in the top layer of the epidermis.

BIBLIOGRAPHY

Anderson CK, Miller OF: Triad of exophthalmos, pretibial myxedema, and acropachy in a patient with Graves' disease, *J Am Acad Dermatol* 48:970–972, 2003.

Bello YM, Phillips TJ: Necrobiosis lipoidica: indolent plaques may signal diabetes, *Postgrad Med* 109:93–94, 2001.

Ferringer T, Miller F: Cutaneous manifestations of diabetes mellitus, *Dermatol Clin* 20:483–492, 2002.

Hollister DS, Brodell RT: Finger "pebbles": a dermatologic sign of diabetes mellitus, *Postgrad Med* 107:209–210, 2000.

Levy L, Zeichner JA: Dermatologic manifestations of diabetes, *J Diabetes* 4:68–76, 2012.

Lipsky BA, Berendt AR: Principles and practice of antibiotic therapy of diabetic foot infections, *Diabetes Metab Res Rev* 16:(Suppl 1), S42–S46, 2000.

Niepomniszcze H, Amad RH: Skin disorders and thyroid diseases, *J Endocrinol Invest* 24:628–638, 2001.

Pirotta SS, Johnson JD, Young G, et al: Bullosis diabeticorum, *J Am Podiatr Assoc* 85:169–171, 1995.

Rammaert B, Lanternier F, Poirée S, et al: Diabetes and mucormycosis: a complex interplay, *Diabetes Metab* 38:193–204, 2012.

Shemer A, Bergman R, Linn S, et al: Diabetic dermopathy and internal complications in diabetes mellitus, *Int J Dermatol* 37:113–115, 1998.

Stoddard ML, Blevins KS, Lee ET, et al: Association of acanthosis nigricans with hyperinsulinemia compared with other selected risk factors for type 2 diabetes in Cherokee Indians: the Cherokee Diabetes Study, *Diabetes Care* 25:1009–1014, 2002.

Yosipovitch G, DeVore A, Dawn A: Obesity and the skin: skin physiology and skin manifestations of obesity, *J Am Acad Dermatol* 56:901–916, 2007.

AGING AND ENDOCRINOLOGY

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1. What effect does aging have on body weight?

Aging is associated with important changes in body composition that may be influenced by the endocrine milieu and can have important endocrine and metabolic consequences (Table 56-1). In cross-sectional studies, body weight increases until about age 55 years and then declines. This may be the result of a "die-off" effect in the heaviest patients during middle age. Prospective studies suggest that weight actually declines after age 65 to 70 years. This reduction in body weight, whether intentional or unintentional, appears to be associated with an increase in mortality, morbidity, and disability. Indeed, there is a well-described obesity paradox in older patients, so that the weight with the lowest overall mortality is shifted upward. The explanation for this is not clear, but it is possible that any sustained weight loss may, in fact, be unintentional, given that intentional weight loss is difficult to maintain. Weight loss in the presence of illness or disease that raises cytokine levels may predispose to a disproportionate loss of weight as lean mass (muscle mass), thereby exacerbating age-related "sarcopenia" and leading to a catabolic state. It is also possible that the apparent obesity paradox of aging results from the heterogeneity of obesity in older patients; obesity beginning in young or middle age is associated with untoward consequences, and obesity beginning in older age is less dangerous. Interventions in these two potentially heterogeneous groups may also be expected to produce different effects, but this has not been studied.

2. What changes in lean body mass occur with aging?

There is an inevitable loss of lean body mass, mostly skeletal muscle, with aging. The aging-associated loss of muscle has been termed *sarcopenia* and has been blamed for much, but not all, of the age-related decline in muscle strength and power (dynopenia). In cross-sectional studies, a 20% to 30% loss of lean mass has been detected between ages 30 and 80 years. The decline in strength is even greater, with longitudinal studies finding up to a 60% loss from age 30 to 80 years. Furthermore, the loss of strength and power is not as linear as the loss of muscle mass and seems to accelerate at older ages. A 25% decline in strength has been detected between 70 and 75 years of age. Power (work per unit time) may decline at double the rate of strength. These changes in lean mass, muscle mass, strength, and power have complex but important functional consequences for older people. Of greatest clinical importance are the relationships among muscle mass, strength or power, and functional ability. These relationships are complex and probably nonlinear, and in general they have been difficult to demonstrate clearly. An example is the consistent association of testosterone supplementation with increases in lean mass but inconsistent associations with improvements in strength or function.

A more recent concept, *sarcopenic obesity,* considers the degree of adiposity relative to lean mass. Currently, because consensus is lacking on how sarcopenic obesity should be defined, the prevalence

TABLE 56-1. BODY COMPOSITION CHANGES WITH AGING

	CHANGE
Fat mass	↑
Lean mass	↓
Muscle mass	↓
Bone mass	↓

and clinical relevance have not been established. One contributing factor in sarcopenic obesity could be weight cycling, with loss of lean and fat mass followed by regain of fat mass only. This may be more likely in older patients who are less anabolic and generally less active. The loss of lean mass with aging can have a profound effect on resting metabolic rate and thus can predispose to further accretion of fat mass if caloric intake is not reduced.

3. What changes in bone mass and density occur with aging?

Prospective data indicate that peak bone mass occurs during the late teen years in women and about a decade later in men. Because of the intimate structural and functional link between muscle and bone, the occurrence of peak bone mass likely corresponds to peak skeletal muscle development. It is generally thought that bone mass is maintained, or decreases slowly ($<$ 0.2% per year), at least through age 40 years in women and age 50 years in men. Intuitively, a decline in physical activity during middle age may be expected to induce an even faster rate of bone loss. However, the increase in body weight that typically also occurs during middle age may counter this to a large extent, by increasing mechanical loading forces acting on the skeleton during weight-bearing activity. The inevitable loss of bone mass in old age increases the risk of osteoporosis in elderly men and augments the risk of osteoporosis in postmenopausal women. In elderly women and men, the decrease in bone mineral at the hip appears to be accelerated ($\sim$1% per year) relative to the changes at the spine, which may *increase* in advanced age. Vertebral compression fractures and the development of extravertebral osteophytes lead to an increase in bone mineral density (BMD) that does not reflect increased vertebral bone strength. The utility of spine BMD for the diagnosis of osteoporosis in elderly persons is therefore compromised.

4. Does menopause have an independent effect on bone mass?

There is an accelerated decline in BMD around the time of menopause in women. What remains somewhat controversial is whether the menopause-induced increase in bone resorption diminishes after a few years or persists into old age. In this regard, observational studies of women 65 years old and older indicate that the rate of bone loss continues to increase with age, particularly in the hip region. This finding is corroborated by observations that serum markers of bone turnover increase at menopause and remain elevated into old age.

5. Can weight-bearing exercise prevent the menopause-related loss of bone mineral in women?

It is unlikely that even vigorous weight-bearing exercise can completely mitigate the deleterious effects of estrogen deficiency on BMD. Older female athletes who are not taking hormone replacement therapy have lower BMD than do premenopausal athletes. Moreover, young female athletes with menstrual cycle dysfunction can have BMD levels in the osteopenic range (1.0–2.5 SD below the average peak BMD) and even the osteoporotic range ($>$ 2.5 SD below the average peak BMD), despite participation in sports that involve high levels of mechanical loading (e.g., gymnastics, distance running).

6. Do sex hormones influence the skeletal response to exercise?

Although the direct effects of estrogens on bone metabolism are well known, growing evidence indicates that the responses of bone cells to mechanical stress involve activation of estrogen receptor alpha. The effects of age-related sex hormone deficiency on receptor density and/or function in bone remain unknown. In animal models, the effects of mechanical stress in the presence of estrogens (in females) or androgens (in males) on the bone proliferative response have been found to be either additive or synergistic (i.e., more than additive). There is also evidence for additive or synergistic effects of exercise and estrogens on BMD in postmenopausal women. More recent studies of laboratory animals suggest that estrogen receptor alpha may facilitate the effects of mechanical loading on bone, whereas estrogen receptor beta may inhibit such effects.

7. What criteria are used to determine who should be treated for low bone density?

Dual-energy x-ray absorptiometry (DXA) scans are the best means of following changes in bone density in the elderly population. T-scores higher than -1.0 indicate normal bone density, whereas T-scores

lower than −1.0 but higher than −2.5 indicate osteopenia, and T-scores lower than −2.5 indicate osteoporosis. Pharmacotherapy for low bone density is not only reserved for those with osteoporosis. The World Health Organization (WHO) developed the FRAX score, which gives an individual's 10-year probability of fracture and can identify those patients with osteopenia who would benefit from treatment. The recommendation in the United States is to consider treatment if the 10-year probability of a major osteoporosis-related fracture is at least 20% or at least 3% for a hip fracture. Additionally, anyone with a fragility fracture regardless of BMD should be considered for treatment. A FRAX score may be calculated without DXA.

8. What pharmacologic agents are available for use in elderly patients with low bone density?

Following the supplementation of calcium and vitamin D, bisphosphonates are the first-line drug class for the improvement of bone density and fracture prevention. Their antiresorptive properties have been shown to be efficacious in improving BMD and preventing fractures at all major sites. There have been reports of rare side effects such as osteonecrosis of the jaw, as well as concerns about an association between long-term use (> 3–5 years) of bisphosphonates and atypical fractures of the thigh, known as subtrochanteric and diaphyseal femur fractures. Recommendations are to consider periodic reevaluation of the need for continued bisphosphonate therapy, particularly in patients who have been treated for more than 5 years, and always to ask about symptoms such as new thigh or groin pain.

Denosumab is an antiresorptive osteoporosis drug, approved by the Food and Drug Administration (FDA) in 2010, that is a human monoclonal antibody functioning as a RANK ligand (RANKL) inhibitor. This drug has the net effect of preventing the maturation of osteoclasts, decreasing bone resorption with increased BMD in women and men, and reducing the risk of fracture (better fracture data in women). Use of this agent could be considered in patients who have been unresponsive to or are intolerant of other available osteoporosis therapies and in patients with renal insufficiency. No dose adjustment is necessary in patients with renal impairment, although they may be at more risk for hypocalcemia, particularly if they are not receiving adequate calcium and vitamin D. Additionally, because RANKL functions within the immune system, long-term monitoring is needed to assess increased risk for serious infections and neoplasms.

The only FDA-approved anabolic drug is teriparatide, which is recombinant human parathyroid hormone (PTH[1–34]). It improves BMD and prevents fractures. This drug is administered via daily subcutaneous injection, an important consideration in elderly patients who may not have the functional capacity or appropriate assistance to do so.

9. Does fat mass increase and/or become redistributed with aging?

There is an increase in total adiposity and shift toward more abdominal fat distribution with advancing age. The increase in central adiposity begins in young men who gain excess fat, but this does not appear to occur in women until around the time of the menopausal transition. Although the loss of lean mass was once thought to be the primary determinant of physical disability in old age, more recent studies indicate that increased adiposity is an independent, and perhaps stronger, predictor of disability in older individuals. The increase in abdominal visceral adiposity (along with the decline in physical activity) plays an important role in the age-associated increase in insulin resistance and probably contributes to the high incidence and prevalence of type 2 diabetes mellitus and metabolic syndrome in old age.

10. Does the menopause trigger an increase in abdominal obesity in women?

Cross-sectional comparisons of women across the age spectrum suggest that waist size increases more rapidly in women aged 50 years and older than in younger women. Prospective studies indicate that increases in waist circumference are related to both chronologic and ovarian age, with the most rapid increases in waist girth occurring in perimenopausal women. Premenopausal women treated with gonadotropin-releasing hormone agonists to suppress sex hormones gain 1 to 2 kg of fat mass in 4 to 6 months, with a disproportionate increase in central body regions. Several randomized, controlled

trials provided evidence that postmenopausal women who took hormone therapy gained less weight and had less increase in waist size than did placebo-treated women. The effects seemed to be slightly larger with unopposed estrogens. It has not yet been determined whether estrogens specifically prevent or attenuate intraabdominal fat accumulation.

11. What are the results of prospective studies of voluntary weight loss (through lifestyle or weight loss surgery) in elderly persons?

Obesity in older adults is a mounting public health concern, given its increasing incidence and its association with loss of functional independence and frailty. Hypocaloric diets have been effective in reducing total and visceral fat and improving glucose tolerance, insulin sensitivity, blood pressure, and pulmonary function. Obese elderly adults are capable of participating and adhering to rigorous interventions such as diet, exercise, or diet plus exercise. Such studies have found that diet alone and exercise alone both reduce frailty, but the combination of diet and exercise generates the greatest objective functional and subjective benefits.

Intentional weight loss typically results in a loss of lean mass (muscle and bone), which may exacerbate sarcopenia and the risk of osteoporosis. This could have adverse effects in elderly adults who are already at risk for osteoporosis. The addition of exercise training to diet in older obese adults prevented the weight-loss-induced increase in bone turnover and attenuated, but did not prevent, the decline in BMD.

Some prospective observational studies have suggested that weight loss in older adults may be associated with increased mortality, despite a decrease in comorbidities such as cardiovascular disease and type 2 diabetes. In randomized controlled weight loss interventions, weight loss did not increase mortality in older adults over 8 to 12 years of follow-up. In fact, secondary analyses from one trial suggested that intentional weight loss may reduce mortality risk in this population. Additional trials of intentional weight loss in older adults are needed to confirm whether it does, indeed, reduce mortality risk and whether the risk-to-benefit profile is similar in older adults who became obese earlier versus later in life.

Weight loss surgery is effective at reducing medical comorbidities in elderly persons. The sparse available data do not suggest increased mortality. In fact, mortality rate may be decreased compared with matched obese cohorts.

12. Why is vitamin D status important in older adults?

Vitamin D supplementation has been found to reduce the incidence of osteoporotic fractures in elderly persons. This may occur via increased bone mineralization and/or improved muscle function and reduction in falls. Vitamin D deficiency is defined as a 25-hydroxyvitamin D (25-OHD) level of less than 20 ng/mL (50 nmol/L). It has been estimated that more than 40% of community-dwelling older women and men in the United States are vitamin D deficient, and the prevalence is even higher in nursing home residents. There are multiple causes of vitamin D deficiency in older adults, including the following: decreased skin synthesis; decreased sun exposure; decreased intake; impaired absorption, transport, or liver hydroxylation of oral vitamin D; medications altering vitamin D metabolism; chronic illnesses associated with malabsorption; and liver and kidney disease.

BMD is adversely affected when serum 25-OHD is less than 30 ng/mL. Vitamin D_3 supplementation of 700 to 800 IU/day or 100,000 IU every 4 months has been found to raise serum 25-OHD to more than 30 ng/mL and reduce the incidence of fractures. There is currently no evidence for antifracture efficacy of vitamin D_2 supplementation.

Vitamin D deficiency also causes muscle weakness. Proximal muscle strength is linearly related with serum 25-OHD when levels are less than 30 ng/mL. Vitamin D supplementation has been associated with a 22% reduction in falls. Nursing home residents randomized to receive 800 IU/day of vitamin D_2 plus calcium had a 72% reduction in falls.

In addition to its important role in muscle and bone metabolism, vitamin D deficiency is postulated to influence immune function, cancer risk, PTH and renin production, and insulin secretion. Epidemiologic studies demonstrate higher mortality in patients with insufficient or deficient levels of 25-OHD.

13. What are the recommendations for vitamin D supplementation in older adults?

The recommendations for vitamin D supplementation in older adults differs among professional societies. However, it is agreed that daily supplementation is best achieved with vitamin D3. In 2010, the National Osteoporosis Foundation (NOF) recommended that older adults should have a serum 25-OHD level of 30 ng/mL (75 nmol/L) to reduce risk for falls and fractures. Supplementation doses up to 800 to 1000 IU/day were recommended because of the lack of evidence for the efficacy of higher doses.

In 2012, the United States Preventive Services Task Force (USPSTF) reported that supplementation of 400 IU/day vitamin D in combination with 1000 mg/day calcium does not reduce fracture risk in noninstitutionalized, community-dwelling, asymptomatic adults without a previous history of fractures. It was further noted that evidence regarding the effectiveness of higher doses of vitamin D and calcium on incident fracture is lacking.

The current Institute of Medicine recommendations for vitamin D supplementation are set at 600 IU/day for men and women aged 51 to 70 years and 800 IU/day for older individuals.

14. What interventions have been associated with increased longevity, and have they been shown to work in humans?

Studies of yeast, worms, flies, rodents, and mammals have demonstrated that caloric restriction (CR; 30%–40% reduction in daily energy intake) increases mean (i.e., average life expectancy) and maximal life span. Generating a negative energy balance in rodents through increased energy expenditure (exercise) results in similar improvements in mean life span as CR, but it does not increase maximal life span. Long-term studies of CR in humans and other primates are under way, but short-term studies suggest that CR produces physiologic, metabolic, and hormonal effects that parallel many of the positive effects found in other species.

It is estimated that one fourth to one third of the differences in life expectancy in humans may be explained by genetic factors, but currently no definitive biomarkers or genes are associated with longevity in humans. Large-scale collaborations, such as the pan-European Genetics of Healthy Aging consortium and the United States Longevity Consortium, are studying different populations to address this issue.

15. What happens to testosterone and estradiol levels with aging in men?

Total testosterone (TT) concentrations decline with age (Table 56-2). Additionally sex hormone–binding globulin (SHBG) levels increase with age, which results in an even greater relative reduction in calculated bioavailable testosterone and free testosterone (FT) with age (declines of −14.5% for TT versus −27% FT per decade of aging).

Total plasma estradiol levels in adult men do not change significantly with age, but bioavailable and free estradiol levels decrease because of the increase in SHBG with aging (estradiol binds to SHBG with half the affinity of testosterone). In absolute terms, serum estrogen levels of elderly men are somewhat higher than those of postmenopausal women (average of 33 pg/mL versus 21 pg/mL).

16. What is the cause of decreases in male testosterone levels with aging?

In addition to an age-related decline, changes in health and lifestyle factors, such as weight gain, illness, polypharmacy, glucocorticoid use, and widowhood, can reduce TT. For instance, the decline

TABLE 56-2. HORMONE CHANGES WITH AGING

	WOMEN	MEN
Estradiol	↓	↓
Testosterone	↓	↓
Growth hormone	↓	↓
Insulin-like growth factor-I (IGF-I)	↓	↓
Dehydroepiandrosterone/sulfate (DHEA/S)	↓	↓
Thyroid-stimulating hormone (TSH)	↑	↑
Cortisol	↑	↑

in TT associated with becoming obese (−12%) is comparable to that associated with 10 years of aging among subjects whose obesity status is stable (−13%). Low endogenous testosterone levels are predictive of future development of metabolic syndrome, as well as cardiovascular, respiratory, and all-cause mortality and cognitive dysfunction. It is not known whether raising testosterone levels by supplementation translates into decreased mortality.

17. What is the prevalence of hypogonadism in older men?

The prevalence of male hypogonadism is not known because of the lack of consensus on the definition of hypogonadism with aging. The development of a consensus definition is complicated by several factors: (1) whether there should be an age-specific testosterone reference range or whether hypogonadism should be defined in relation to young male testosterone levels; (2) whether the definition should be based on TT (SHBG bound + albumin bound + free), bioavailable testosterone (albumin bound + free), or FT levels; (3) concern regarding the reliability and variability of immunoassays versus mass spectroscopy; (4) the finding that formulas for calculating bioavailable testosterone and FT may not be valid in some or all older populations; and (5) whether hypogonadism should be defined in relation to a low serum testosterone concentration alone, a low concentration plus symptoms, or symptoms alone. When defined as TT less than 300 ng/dL *and* FT less than 5 ng/dL, almost 50% of men with hypogonadism who were more than 50 years old were asymptomatic, and 65% of men with symptoms had normal testosterone levels. The prevalence of symptomatic androgen deficiency is estimated to be at least 5% in men aged 50 to 70 years and 18% in older men.

18. Are there benefits of testosterone supplementation for older men with low normal testosterone levels?

Of the few randomized controlled trials conducted in healthy older men, most found an increase or maintenance of fat-free mass (bone and muscle) and a decrease in fat mass (including abdominal visceral) in response to testosterone. Whether such physiologic effects translate into strength or functional improvements remains equivocal. Anemia from androgen insufficiency improves with testosterone therapy. Improvements in sexual function and sense of well-being have also been inconsistent.

The lack of consistent findings among trials of testosterone supplementation is likely related to variability in study cohorts (e.g., baseline testosterone levels, symptoms, body composition, comorbidities, physical function), the type of testosterone supplementation therapy (e.g., oral, transdermal, intramuscular, dose, and average testosterone concentration achieved), and the duration of intervention (e.g., months versus years).

19. Is there evidence of adverse effects of testosterone supplementation?

In 2010, researchers from the Testosterone in Older Men with Mobility Limitations (TOM) trial published their data on adverse events associated with testosterone administration, which led to early termination of the study. The original purpose of the study was to determine the effects of testosterone administration on lower extremity strength and physical function in older men with significant mobility limitations and low serum levels of either TT or FT. The participants were men at least 65 years old with limitations in mobility and a high prevalence of chronic disease (diabetes, hypertension, obesity). During the 6-month intervention phase, those men who were randomized to testosterone gel therapy with a goal of attaining a TT level greater than 500 ng/dL unexpectedly had a higher prevalence of cardiovascular, respiratory, and dermatologic adverse events, even after adjustment for baseline risk factors. The increased frequency of cardiovascular events led to trial termination. However, this has not been confirmed in other studies or in meta-analyses of testosterone intervention studies. In addition, a more recently completed study demonstrated a reduction in cardiovascular adverse events in a testosterone-supplemented versus a placebo-treated group of generally healthy men with low normal TT levels at baseline.

Additional adverse effects include worsening of benign prostatic hypertrophy and polycythemia, likely dose related and worsened in the setting of sleep apnea. There is consistent lack of evidence of increased prostate cancer risk in studies of men receiving testosterone therapy.

20. What are the recommendations for testosterone replacement therapy in older men with androgen deficiency?

The most recent guidelines from the Endocrine Society in 2010 recommend screening for androgen deficiency in older men who have consistent signs and symptoms of low androgen levels. These guidelines recommend the use of a high-quality assay measuring the TT level in the morning and confirming a low result with a repeat TT level and/or free or bioavailable testosterone level. Even if low testosterone levels are confirmed, only men with clinically significant and symptomatic androgen deficiency should be considered for treatment. If therapy is initiated, the clinician should ensure that the patient understands the uncertainty of the risks and benefits of testosterone therapy. The choice of supplementation is left up to the discretion of the clinician and patient preference. Although the Endocrine Society advises a target TT level in the midnormal range when prescribing testosterone therapy, many clinicians aim for TT levels in the low normal range to avoid potential cardiovascular or respiratory side effects, despite a lack of evidence supporting this practice.

At this time, testosterone replacement should continue to be reserved for the minority of men with frankly low serum testosterone levels and clear clinical symptoms of hypogonadism who do not have an existing clear contraindication for androgen therapy (prostate cancer, severe obstructive uropathy, liver disease, polycythemia, untreated or poorly controlled obstructive sleep apnea, and poorly controlled heart failure).

21. Should estrogen therapy be given to postmenopausal women?

This has been an area of controversy since the completion of the Women's Health Initiative (WHI) trials. Similar to debates about testosterone replacement, controversy exists regarding who should be treated (age, years menopausal, symptomatic), by what formulation (conjugated estrogens versus estradiol, progesterone versus medroxyprogesterone acetate (MPA), continuous versus intermittent progestins), at what dose (fixed versus target serum estradiol level), by what route (oral, transdermal, transvaginal), and for what length of time. The WHI trials generated important results, but they raised equally important questions. Oral conjugated estrogens with or without MPA may not have the same effects (good or bad) as transdermal estradiol with or without progestins. The WHI trials appear to support the "timing hypothesis," that cardiovascular benefits may occur when therapy is initiated near the time of menopause. However, initiating hormone treatment after 10 or more years of estrogen deficiency may increase the risk of cardiovascular events.

The loss of estrogen with menopause appears to be linked to deleterious changes in body composition, including increased central fat accumulation and decreased BMD, which translates long term into increased risk for cardiovascular disease and fractures. Additionally, the loss of estrogen is associated with hot flashes, decreased sleep quality, vaginal dryness, and worsening of mood disturbances, the sum of which equals a decreased quality of life for many women.

Currently, estrogen therapy is indicated for relief of menopausal symptoms that are not relieved by other methods, with the lowest dose used for the shortest time possible. Transdermal estradiol appears to be associated with fewer thromboembolic events than oral estrogens. Because continuous conjugated estrogens plus MPA were associated with an increased incidence of invasive breast cancer in the WHI (whereas conjugated estrogens alone were not), intermittent progesterone may be a better alternative for endometrial protection.

22. How does dehydroepiandrosterone (DHEA) concentration change with aging?

Dehydroepiandrosterone (DHEA) and its sulfate (DHEAS), collectively referred to as DHEA/S, are the most abundant steroid hormones in humans, with approximately 95% coming from the adrenal glands. DHEAS is one of the best biologic markers of human aging. Peak serum DHEAS levels are reached early in the third decade and then decline steadily. By age 60 to 70 years, circulating levels are only about 20% of peak levels. The decrease in DHEA/S with aging does not represent a general decline in adrenal function because similar changes in other adrenal hormones do not occur.

23. What are the biologic effects of DHEA/S?

Despite the abundance of DHEA/S and the distinctive age-related changes, little is known about the biologic effects of DHEA/S in humans. The actions of DHEA/S in humans are thought to be mediated primarily through conversion to sex hormones, and thus it may function as a large storage pool of prehormone. DHEA is the precursor for 30% to 50% of androgens in older men and for more than 70% of androgens in older women, and it is a major source of estrogens in men and postmenopausal women. The decline in DHEA/S with aging may contribute to physiologic changes that occur as a result of sex hormone deficiency (e.g., the loss of bone and muscle mass). Other proposed biologic effects include increased insulin-like growth factor-I (IGF-I), antiglucocorticoid effects, and antiinflammatory effects via peroxisome proliferator-activated receptor-alpha (PPARα) agonism.

24. What are the hormonal effects of DHEA supplementation?

In the United States, DHEA is considered a dietary supplement and therefore is not an FDA-regulated drug. Hence, over-the-counter products vary greatly in the amounts of bioactive hormone they contain (if any) and may have quite different pharmacokinetic profiles. Even batch-to-batch variability within a brand can be great. Despite being labeled a "dietary supplement," DHEA has measurable effects on concentrations of hormones. In older adults, DHEA, 50 mg of bioactive hormone per day, results in the following: 300% to 600% increases in plasma DHEAS concentration in men and women; a 100% increase in plasma testosterone in women, with nonsignificant changes in men; a 70% to 300% rise in plasma estradiol in women and a 30% to 200% increase in men; and increases in IGF-I of 25% to 30% in women and 5% to 10% in men. However, the physiologic effects of DHEA supplementation in humans appears quite variable.

25. Summarize the controlled studies of DHEA administration to older adults.

In randomized, placebo-controlled trials of 1 to 2 years, DHEA replacement alone in older adults did not result in significant changes in fat or muscle mass or metabolic improvements. Studies of DHEA plus an exercise stimulus (endurance, resistance, or both) have shown mixed effects. In postmenopausal women, 12 weeks of DHEA was not more effective than placebo at potentiating effects of endurance and resistance exercise on body composition, glucose, and lipid metabolism. In contrast, 16 weeks of DHEA improved muscle volume and strength tests compared with placebo when combined with high-intensity resistance exercise in older women and men.

Studies of DHEA on BMD have shown trends for increases in indices at the hip, but improvements at other sites appear to be more study and sex specific. None of the studies has been powered to demonstrate antifracture efficacy. The increases in BMD in response to short-term DHEA replacement therapy have generally been small (1%–2%). However, one study that looked at 1- to 2-year therapy with DHEA on BMD investigated whether restoration of DHEA levels to those of young adults would be protective in maintaining or improving BMD in elderly people. The addition of vitamin D and calcium supplementation to DHEA translated to a 4% improvement in BMD in women, comparable to the effect of bisphosphonate treatment. This effect was not observed in men.

DHEA replacement trials have not shown significant adverse events (e.g., increases in prostate-specific antigen), but much larger trials would be needed to establish safety and efficacy.

26. Describe the changes in the growth hormone (GH)/IGF-I axis with aging.

Aging is associated with a significant decline in the GH area under the curve (AUC), as well as the number and amplitude of nighttime GH peaks. These changes in GH secretion are associated with a steady decline in IGF-I after age 30 years. By age 65 years, most individuals have an IGF-I concentration that is near or below the lower limit of normal for healthy young individuals. The observed decline in the GH/IGF-I axis appears to occur above the level of the pituitary because long-term treatment with GH-releasing hormone (GHRH) and/or other GH secretagogues (GHS) mitigates much of the decline. The cause of the fall-off in axis activity is not clear but could be explained by age-related changes in GHRH, somatostatin, or ghrelin tone. Ghrelin appears to be the natural ligand for the GHS receptor. Although a close physiologic relationship exists between GH secretion and slow-wave sleep, it is unclear whether the altered GH/IGF-I axis is the consequence or cause of profound aging-related changes in sleep architecture.

27. Is the decline in the GH/IGF-I axis related to age-related changes in body composition and function?

Many of the body composition changes that occur with aging seem consistent with a GH/IGF-I–deficient state. Indeed, GH-deficient adults have many of the same physiologic abnormalities as older individuals, including the following:

- Reduced lean body and muscle mass
- Reduced strength and aerobic capacity
- Excess total, central, and intraabdominal fat
- High incidence of metabolic syndrome
- Reduced bone mass and density
- Reduced or absent slow-wave sleep
- High incidence of mood disturbance (depression)

28. Is GH replacement recommended for healthy elderly persons?

Although GH therapy in younger GH-deficient patients improves body composition, bone density, and cholesterol levels and may decrease death, the efficacy and safety of therapy for otherwise "healthy" elderly persons are controversial. A systematic review of clinical trials of GH in healthy elderly persons concluded that therapy does increase IGF-I concentrations, although women may require higher doses of GH for longer periods than men to achieve physiologic replacement levels. Despite higher doses per kilogram of body weight, women do not consistently demonstrate the increase in lean body mass or decrease in fat mass that occurs in men. Further, translation into clinically significant changes in strength, function, bone density, and improved metabolic parameters has been difficult to demonstrate in either sex. GH treatment is associated with several important adverse events, such as a significant additional incidence compared with placebo of soft tissue edema (42%), arthralgias (16%), carpal tunnel syndrome (15%), gynecomastia (6%), new impaired fasting glucose or impaired glucose tolerance (4%), and new-onset of diabetes (4%).

The scant clinical experience of GH treatment for healthy elderly persons suggests that, although GH may minimally improve body composition, it does not improve other clinically relevant outcomes such as strength or function, and it is associated with high rates of adverse events. Furthermore, invertebrate and rodent models suggest that lower GH axis activity may be protective for longevity. On the basis of available evidence, GH cannot be recommended for use among healthy elderly persons. Large randomized controlled trials would be needed to determine the safety and efficacy of GH combined with an exercise intervention, combined with other sex hormones, effects in nonhealthy frail populations, and other replacement strategies such as GHRH.

29. Does GHRH supplementation affect GH secretion, sleep, and cognition?

Elderly persons often experience lack of sleep and feeling tired during the day. The cause may be the almost total loss of slow-wave sleep (stages 3 and 4). The periods of slow-wave sleep in younger individuals coincide exactly with the nighttime peaks of GH secretion. Indeed, animal and some human data suggest that appropriately timed GHRH supplementation may restart pulsatile GH secretion and stimulate slow-wave sleep. Limited evidence also suggests that long-term GHRH supplementation may improve cognitive function, specifically psychomotor and perceptual processing speed, as well as fluid memory.

30. What happens to the hypothalamic-pituitary-adrenal (HPA) axis with aging?

As is the case for most hormones, distinguishing between the independent effects of age-related and body composition–related changes in the HPA axis is challenging. For example, morning cortisol levels tend to be lower and stress-induced HPA axis responsiveness tends to be greater in older as compared with younger adults, but such findings are also associated with central obesity (commonly found with aging; see earlier). However, several characteristics appear to be unique to aging. First, there is evidence for a phase advance characterized by an earlier morning cortisol peak. Second, the evening cortisol nadir appears to be higher in older persons, with a resulting compression of the diurnal amplitude. Third, glucocorticoid-mediated negative feedback is decreased. In total, mean

24-hour serum cortisol concentrations are 20% to 50% higher in both older women and men, likely reflecting the sum of alterations in glucocorticoid clearance, HPA axis responsiveness to stress, and central glucocorticoid-mediated negative feedback.

Whether an increase in the exposure to systemic and/or local/tissue (via 11-beta-hydroxysteroid dehydrogenase-1) glucocorticoids in elderly persons contributes to such age-related changes as central obesity, insulin resistance, decreased lean body mass, increased risk of fractures, decreased sleep quality, and poor memory (all common symptoms of cortisol excess) is an area of ongoing investigation.

31. What do thyroid function profiles look like in older adults?

Interpreting data from thyroid function studies in elderly subjects is difficult because evaluation is often complicated by increased prevalence of chronic disease and medication use. Nevertheless, serum thyroid-stimulating hormone (TSH) concentrations and distributions appear to increase with age, independent of the presence of antithyroid antibodies. This has been hypothesized to result from a decline in thyroid function or a recalibration of baseline TSH.

Serum reverse triiodothyronine (rT_3) concentrations appear to increase with age and the presence of disease. The presence of higher rT_3 was associated with a lower physical function status. Although serum free thyroxine (fT_4) levels tend to remain stable, older individuals with increased fT_4 levels were observed to have a lower physical function status and an increase in overall 4-year mortality. Total T_3 levels were inversely related with physical performance and lean body mass. These trends in thyroid hormone levels may indicate that it is beneficial to have lower activity of the thyroid hormone axis in old age.

Recognition of age-specific reference ranges would have important implications for defining subclinical hypothyroidism in elderly persons and treatment targets for thyroid hormone replacement.

32. What thyroid conditions are more prevalent with aging?

Thyroid nodules increase with age, with an estimated prevalence of 37% to 57%. The risk of malignancy in a nodule also increases with age. The rate of carcinoma in a follicular nodule is increased in adults more than 60 years old and is higher in men than in women.

The most frequent cause of hyperthyroidism in older adults is toxic multinodular goiter, rather than Graves' disease. Presenting symptoms of hyperthyroidism may be more atypical, with apathetic symptoms more common compared with younger patients.

Hypothyroidism increases significantly with age as a result of multiple conditions, including autoimmune thyroid dysfunction, use of medications, and nonthyroidal illness, which can lead to low serum thyroid hormone concentrations. The incidence of myxedema coma is also higher in older adults.

Subclinical hypothyroidism increases with age, but the actual incidence depends on the definition of upper limits of normal for TSH. For instance, in the United States, 15% of disease-free people who are more than 80 years old have TSH levels higher than 4.5 mIU/L, but if the definition were to change to TSH greater than 2.5 mIU/L, the incidence would be as high as 40%.

33. Should subclinical hypothyroidism be treated in elderly persons?

Subclinical hyperthyroidism is a predictor of mortality in elderly patients. Although subclinical hypothyroidism in individuals less than 65 years of age is associated with increased ischemic heart disease and cardiovascular mortality, this risk was not found in older adults. Further guidance on treatment of elderly persons with subclinical hypothyroidism should be generated by randomized controlled trials.

This leaves the question of what TSH concentration should be targeted in patients with frank hypothyroidism, given that epidemiologic studies have not revealed clinical concerns in patients with a TSH lower than 10 mIU/mL. The goal should be to avoid subclinical and frank hyperthyroidism, and a TSH concentration up to 10 mIU/mL is a reasonable target in elderly patients.

34. What factors should be taken into account when determining glycemic management of type 2 diabetes in older patients?

Among U.S. residents 65 years old and older, 10.9 million, or 26.9%, were known to have diabetes in 2010. When managing diabetes in elderly patients, treatment decisions should take into account the

duration of diabetes and existent comorbidities such as heart disease or renal insufficiency, as well as polypharmacy and cost. A glycemic target of less than 8.0% may be more prudent in managing diabetes in patients with long duration of diabetes, established cardiovascular disease, limited life expectancy, and particular susceptibility to severe hypoglycemia. Large multicenter studies that aimed for intense glycemic control of hemoglobin A_{1C} (Hb A_{1C}) of less than 6.0% to 6.5% in older individuals showed no significant reduction in their primary combined cardiovascular end points but reported significantly more episodes of hypoglycemia in those patients with intensive blood glucose management. Thus, the risks of intensive control likely outweigh the benefits in an elderly population as a whole. Given the increasing complexity of glucose management in type 2 diabetes as new medications and drug classes are developed, a patient-centered treatment plan is necessary in reconciling glycemic management and optimal patient outcomes.

35. What medications should be considered for the treatment of diabetes in older adults?

Special care is required in prescribing and monitoring drug therapy for older patients with diabetes. Metformin has traditionally been considered contraindicated at a creatinine value of 1.5 mg/dL or higher in men and 1.4 mg/dL or higher in women or in either gender when the estimated GFR (eGFR) is less than 60 mL/minute. It is important to assess the eGFR, which also takes age and body weight into consideration, because serum creatinine alone is often not an adequate reflection of GFR in older patients. Because of the age-related decline in renal function, the use of metformin is often discouraged in patients who are more than 80 years of age. However, more recent publications have noted that lactic acidosis is rare in patients with an eGFR of at least 30 mL/minute. Therefore, cautious use of metformin with close monitoring of renal function is a reasonable option in patients with an eGFR of 45 to 60 mL/minute, and lower dose metformin may be considered, again with close monitoring, in patients with an eGFR of 30 to 45 mL/minute. Pioglitazone should not be used in patients with congestive heart failure (New York Heart Association class III and IV); there is also an increased risk of peripheral fractures in elderly postmenopausal women using this medication. Furthermore, a possible increased risk of bladder cancer in patients taking pioglitazone is a concern. Insulin secretagogues, such as sulfonylureas, can cause hypoglycemia, and elderly patients may be particularly predisposed. Dipeptidyl peptidase-4 (DPP-4) inhibitors have an advantage of being able to be used in patients with renal impairment and are associated with less hypoglycemia. Insulin therapy requires good visual and motor skills and cognitive ability of the patient or a caregiver, and it can cause hypoglycemia. Hypoglycemia in older patients may be particularly difficult to identify and may be incorrectly diagnosed as irreversible cognitive impairment. Diabetes treatment can be improved in patients with visual impairments through the use of such devices as glucometers with large, easier-to-read screens, audio glucometers, magnifying glasses to help see syringes, or preloaded insulin pens.

TAKE HOME MESSAGE: NO MAGIC HORMONAL FOUNTAIN OF YOUTH

1. Physical activity and long-term CR have the best evidence for ameliorating aging-related increases in adiposity, reductions in lean body mass, and cardiovascular risk factors.
2. Estrogen therapy is controversial other than for treatment of severe postmenopausal symptoms, but it may have cardiovascular benefits if therapy is initiated early (near menopause).
3. Testosterone therapy for older hypogonadal men is associated with consistent improvements in body composition (decreased fat and increased fat-free mass), but instituting therapy requires close monitoring especially with regard to cardiovascular status and prostate cancer screening. Consistent evidence for improvement in strength or function is not available.

Continued

TAKE HOME MESSAGE: NO MAGIC HORMONAL FOUNTAIN OF YOUTH—cont'd

4. DHEA replacement therapy increases levels of estradiol, testosterone (women only), IGF-I, and BMD, but it does not appear to be associated with clear improvements in metabolism or body composition in older humans.
5. GH supplementation appears to be more effective at increasing lean body mass in older men than in older women. These changes have not been demonstrated to translate into functional improvements, and treatment is associated with high rates of adverse events.

KEY POINTS 1: HORMONES AND AGING

1. Weight loss in obese elderly persons is associated with improvements in cardiovascular risk factors, but exercise may be needed to attenuate loss of muscle and bone mass during weight loss and to mitigate against frailty.
2. Adequate calcium and vitamin D are essential for fall and fracture prevention and may improve pain from osteoarthritis.
3. Most hormonal axes are associated with a gradual decline over time, beginning at about age 30 years, with the exception of the relatively rapid decline in estrogen associated with the female menopause.
4. Serum total testosterone decreases with time in men, but numerous other independent health, lifestyle, and secular trends can accelerate the decline.
5. Age-specific reference ranges for thyroid-stimulating hormone may be appropriate and have important implications in defining subclinical hypothyroidism in older adults.
6. Clinicians caring for older adults with diabetes must take into consideration the clinical and functional heterogeneity of their patients when setting and prioritizing an individual's treatment goals and drug regimen. Occult hypoglycemia may be much more common in older patients, especially those treated with insulin, and the consequences of this on central nervous system and cardiovascular function must be carefully considered.

BIBLIOGRAPHY

Araujo AB, Esche GR, Kupelian V, et al: Prevalence of symptomatic androgen deficiency in men, *J Clin Endocrinol Metab* 92:4241–4247, 2007.

Atzmon G, Barzilai N, Hollowell JG, et al: Extreme longevity is associated with increased serum thyrotropin, *J Clin Endocrinol Metab* 94:1251–1254, 2009.

Basaria S, Coviello AD, Travison TG, et al: Adverse events associated with testosterone administration, *N Engl J Med* 363:109–122, 2010.

Dawson-Hughes B, Mithal A, Bonjour JP, et al: IOF position statement: vitamin D recommendations for older adults, *Osteoporos Int* 21:1151–1154, 2010.

Ekstrom N, Scholer L, Svensson AM: Effectiveness and safety of metformin in 51,675 patients with type 2 diabetes and different levels of renal function: a cohort study from the Swedish National Diabetes Register, *BMJ Open* 2:e001076, 2012.

Gozansky WS, Van Pelt RE, Jankowski CM, et al: Protection of bone mass by estrogens and raloxifene during exercise-induced weight loss, *J Clin Endocrinol Metab* 90:52–59, 2005.

Holick MF: Vitamin D deficiency, *N Engl J Med* 357:266–281, 2007.

Inzucchi SE, Bergenstal RM, Buse JB, et al: Management of hyperglycemia in type 2 diabetes: a patient-centered approach, *Diabetes Care* 35:1364–1379, 2012.

Jankowski CM, Gozansky WS, Schwartz RS, et al: Effects of dehydroepiandrosterone replacement therapy on bone mineral density in older adults: a randomized, controlled trial, *J Clin Endocrinol Metab* 91:2986–2993, 2006.

Kaufman JM, Vermeulen A: The decline of androgen levels in elderly men and its clinical and therapeutic implications, *Endocr Rev* 26:833–876, 2005.
Kennedy BK, Steffen KK, Kaeberlein M: Ruminations on dietary restriction and aging, *Cell Mol Life Sci* 64:1323–1328, 2007.
Laron Z: Do deficiencies in growth hormone and insulin-like growth factor-1 (IGF-1) shorten or prolong longevity? *Mech Ageing Dev* 126:305–307, 2005.
Lipska KJ, Bailey CJ, Inzucchi S: Use of metformin in the setting of mild-to-moderate renal insufficiency, *Diabetes Care* 34:1431–1437, 2011.
Liu H, Bravata DM, Olkin I, et al: Systematic review: the safety and efficacy of growth hormone in the healthy elderly, *Ann Intern Med* 146:104–115, 2007.
Miner MM, Seftel AD: Testosterone and aging: what have we learned since the Institute of Medicine report and what lies ahead? *Int J Clin Pract* 61:622–632, 2007.
Sherlock M, Toogood AA: Aging and the growth hormone/insulin like growth factor-I axis, *Pituitary* 10:189–203, 2007.
Sowers M, Zheng H, Tomey K, et al: Changes in body composition in women over six years at midlife: ovarian and chronological aging, *J Clin Endocrinol Metab* 92:895–901, 2007.
Surks MI, Hollowell JG: Age-specific distribution of serum thyrotropin and antithyroid antibodies in the U.S. population: implications for the prevalence of subclinical hypothyroidism, *J Clin Endocrinol Metab* 92:4575–4582, 2007.
Travison TG, Araujo AB, Kupelian V, et al: The relative contributions of aging, health, and lifestyle factors to serum testosterone decline in men, *J Clin Endocrinol Metab* 92:549–555, 2007.
Van den Beld, AW, Visser TJ, Feelders RA, et al: Thyroid hormone concentrations, disease, physical function, and mortality in elderly men, *J Clin Endocrinol Metab* 90:6403–6409, 2005.
Vanderschueren D, Venken K, Ophoff J, et al: Sex steroids and the periosteum: reconsidering the roles of androgens and estrogens in periosteal expansion, *J Clin Endocrinol Metab* 91:378–382, 2006.
Villareal DT, Banks M, Sinacore DR, et al: Effect of weight loss and exercise on frailty in obese older adults, *Arch Intern Med* 166:860–866, 2006.
Villareal DT, Chode S, Parimi N, et al: Weight loss, exercise, or both and physical function in obese older adults, *N Engl J Med* 364:1218–1229, 2011.
Villareal DT, Holloszy JO: DHEA enhances effects of weight training on muscle mass and strength in elderly women and men, *Am J Physiol Endocrinol Metab* 291:E1003–E1008, 2006.
Villareal DT, Miller BV, III, Banks M, et al: Effect of lifestyle intervention on metabolic coronary heart disease risk factors in obese older adults, *Am J Clin Nutr* 84:1317–1323, 2006.
Weiss EP, Shah K, Fontana L, et al: Dehydroepiandrosterone replacement therapy in older adults: 1- and 2-y effects on bone, *Am J Clin Nutr* 89:1459–1467, 2009.
Wierman ME, Kohrt WM: Vascular and metabolic effects of sex steroids: new insights into clinical trials, *Reprod Sci* 14:300–314, 2007.

CHAPTER 57

ENDOCRINE SURGERY

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THYROID

1. Using the Bethesda System, list the possible results of fine-needle aspiration (FNA) of thyroid nodules, and describe the appropriate surgical intervention.

- *Nondiagnostic:* Repeat FNA with ultrasound guidance. Thyroid lobectomy is performed if FNA results are still nondiagnostic.
- *Benign:* Risk of cancer is less than 5%. Clinical follow-up is safe.
- *Atypia of undetermined significance (ACUS) or follicular lesion of undetermined significance (FLUS):* Risk of cancer is 5% to 15%. Options include repeat FNA with or without molecular testing or surgery.
- *Follicular neoplasm:* Risk of cancer is 15% to 30%. Options include repeat FNA for molecular testing or surgery, either thyroid lobectomy or thyroidectomy.
- *Suspicious:* Risk of cancer is 60% to 75%. Surgery consists of either thyroid lobectomy or thyroidectomy.
- *Malignant:* Risk of cancer is greater than 97%. Surgery consists of thyroidectomy.

2. A patient underwent thyroid lobectomy for a suspicious thyroid nodule, and the final pathology report revealed papillary carcinoma. How do you decide whether completion thyroidectomy is necessary?

When electing to undergo lobectomy for an indeterminate or suspicious thyroid nodule, patients should be counseled that if the final pathologic determination is malignant, a second surgical procedure for completion thyroidectomy will be necessary in most cases. Lobectomy may be sufficient treatment for low-risk patients who meet the following criteria: young age ($<$ 45 years), tumor less than 1 cm without invasion, no regional or distant metastases, no history of neck radiation exposure, and no family history of thyroid cancer.

3. Why not just do an intraoperative frozen section on indeterminate thyroid nodules to determine whether to perform lobectomy versus thyroidectomy?

Unfortunately, the accuracy of frozen section for thyroid nodules is not much better than FNA, and frozen section is therefore not routinely used. To distinguish a benign from malignant follicular thyroid lesion requires a detailed assessment for capsular and/or vascular invasion that cannot practically be accomplished intraoperatively. Frozen section can sometimes be useful for definitive diagnosis of cancer in nodules that are in the suspicious category by FNA.

4. What is the role for molecular testing of thyroid nodules?

Fifteen percent to 30% of thyroid nodules are cytologically indeterminate on FNA, and most of these patients undergo surgery to make a definitive diagnosis. However, most of these nodules turn out to be benign on final pathologic examination, in which case the surgery was unnecessary. The goal of molecular testing of thyroid nodules is to stratify the risk of malignancy further in those with indeterminate cytology to decrease the number of patients who undergo unnecessary surgery for benign disease. The most commonly analyzed mutations include those occurring in *BRAF, RAS,* and *RET/PTC*. There are commercially available tests that analyze for these and other mutations; however, it is very important to consider the positive and negative predictive values of these tests, as well as cost, when using them to guide clinical care.

5. What are the differences among total, near-total, and subtotal thyroidectomy?

Total thyroidectomy removes all grossly visible thyroid tissue. Near-total thyroidectomy removes all grossly visible thyroid tissue except for a small amount (< 1 g) adjacent to where the recurrent laryngeal nerve enters the larynx. Total thyroidectomy and near-total thyroidectomy have equivalent oncologic outcomes and are often considered synonymous. Subtotal thyroidectomy leaves more than 1 g of thyroid tissue and is not an appropriate cancer operation. It is used occasionally in patients with benign multinodular goiter or hyperthyroidism in an attempt to leave enough thyroid so that thyroid hormone replacement is not required. However, doing so increases the risk of recurrent disease compared with near-total thyroidectomy.

6. What is the appropriate extent of thyroidectomy for differentiated thyroid carcinoma?

Most patients with differentiated thyroid carcinoma (papillary, follicular, Hürthle cell) should undergo total or near-total thyroidectomy. Several studies have shown that for larger tumors, total or near-total thyroidectomy compared with lesser resections results in lower recurrence rates and improved survival. There appears to be no difference in outcome between patients who undergo lobectomy and those who have near-total or total thyroidectomy when tumor size is less than 1 cm. However, for tumors larger than 1 cm, patients who undergo near-total or total thyroidectomy have lower recurrence and improved survival compared with those who undergo lobectomy. This improved outcome is seen even in the subset of patients with tumors 1 to 2 cm in size. Therefore, most patients should undergo total or near-total thyroidectomy.

7. What is the incidence of lymph node metastasis in well-differentiated thyroid cancer, and when is neck dissection indicated?

Differentiated thyroid cancer (predominantly papillary) involves cervical lymph nodes in 30% to 80% of cases. In most cases, the metastatic lymph nodes are not clinically evident; therefore, all patients should undergo a preoperative full neck ultrasound scan to assess for abnormal nodes. Unlike in many other malignant diseases, the presence of *occult* lymph node metastases does not worsen the outcome for most patients with differentiated thyroid cancer, and routine neck dissection does not clearly improve outcome except for patients in the high-risk group. Moreover, neck dissection may increase the risk of complications. For these reasons, the decision to perform neck dissection for differentiated thyroid cancer is somewhat controversial. The following are some general guidelines:

- All patients with clinically palpable nodes require compartment (central and/or lateral) dissection at the same time as thyroidectomy.
- Any suspicious nodes on ultrasound should undergo FNA and, if positive, should be removed via formal neck dissection as described earlier.
- Physical examination, ultrasound, and intraoperative assessment are insensitive in determining nodal metastasis in the central neck. Whether *prophylactic* central neck dissection at the time of thyroidectomy is indicated for papillary carcinoma is debated. The current American Thyroid Association Guidelines Taskforce state that prophylactic central neck dissection may be indicated in patients with advanced tumors (> 4 cm and/or grossly invasive), and that thyroidectomy alone may be appropriate for noninvasive tumors less than 4 cm.

8. What is central and modified radical neck dissection?

Central neck dissection removes all the perithyroidal and tracheoesophageal groove nodes (level VI) from the hyoid bone superiorly down to the thoracic inlet. Laterally, the dissection extends from the carotid to the carotid artery. The lateral spread of disease usually involves the jugular lymph nodes (levels II–IV) and less commonly the posterior (level V) nodes. Modified radical neck dissection, sometimes referred to as "functional dissection," removes all lymphatic tissue from levels II to IV (and sometimes V) and spares the internal jugular vein, sternocleidomastoid muscle, and spinal accessory nerve because sacrificing these structures (radical neck dissection) does not improve outcome.

9. Describe the appropriate surgical management of medullary thyroid carcinoma.

Medullary thyroid carcinoma accounts for less than 5% of thyroid cancers but occurs as part of an inherited syndrome in 20% to 25% of cases. Thus, all patients with medullary thyroid carcinoma should

be considered for genetic testing. If the patient has multiple endocrine neoplasia type 2 (MEN-2) syndrome, then prophylactic thyroidectomy is indicated; the specific *RET* gene mutation can help determine at what age the surgical procedure should occur. Patients with MEN-2 should also be screened for pheochromocytoma and primary hyperparathyroidism (HPT) so that these conditions can be surgically corrected before or concomitant with the thyroidectomy, respectively. Because medullary thyroid cancer is not sensitive to radioiodine or thyroid-stimulating hormone (TSH) suppression, total thyroidectomy is indicated. Given the high incidence of regional lymph node involvement, central neck dissection is performed at the time of thyroidectomy. Some surgeons also advocate routine bilateral modified neck dissection at the initial surgery; however, despite this aggressive approach, biochemical cure (normalization of calcitonin) is rare in patients with positive lymph nodes. Current guidelines recommend that lateral neck dissection should be performed selectively, based on clinically or ultrasonographically abnormal nodes.

10. Discuss the role of surgery in anaplastic carcinoma of the thyroid.

Anaplastic carcinoma of the thyroid accounts for less than 1% of thyroid cancers but is one of the most aggressive solid tumors known and is rarely curable. At the time of diagnosis, 50% of patients harbor distant metastases, and 95% have local invasion precluding curative resection. Thus, surgery is usually restricted to a diagnostic or palliative role. Palliative surgical debulking and tracheostomy should be reserved for symptoms of dysphagia or airway compromise, respectively, because they do not prolong survival. An attempt at curative resection should be reserved for younger patients without distant disease and only when all gross cervical and mediastinal disease can be resected without excessive morbidity. In this select subgroup of patients, curative-intent surgery combined with adjuvant external beam radiation and/or chemotherapy has been shown to prolong survival compared with patients treated with adjuvant therapy alone.

11. When is surgery indicated for recurrent thyroid cancer?

Suspected recurrent disease in the neck should be evaluated by FNA. Confirmed nodal recurrence should be treated with formal dissection of the involved neck compartment. Recurrence in a neck compartment that has already been subjected to formal neck dissection can be challenging because of scarring of the tissue planes that renders repeat formal neck dissection virtually impossible. In these situations, the risks and benefits of additional surgery must be carefully considered because the risk of complications increases and the likelihood of cure decreases with each subsequent surgical procedure for disease recurrence. Observation may be the best option for patients with low-risk disease. When indicated, nodal recurrences that are palpable can be locally excised. If these recurrences are not palpable, intraoperative ultrasound can be used to guide the excision. For patients who are poor surgical candidates or have had multiple neck operations, percutaneous ethanol injection of nodal metastases is an alternative. Radioiodine is the standard therapy for distant metastatic disease, but isolated metastases can occasionally be surgically resected or treated with external beam radiation.

12. How many times should a thyroid cyst be aspirated if it reaccumulates fluid?

Thyroid cysts are most often benign, and the initial diagnostic and therapeutic procedure is aspiration. Fluid cytology results are typically nondiagnostic. If the nodule does not completely disappear after aspiration, it may be a complex cyst, which is associated with higher malignant potential. Therefore, FNA of the solid component should be performed. Recurrence of thyroid cysts occurs in more than 50%, and controlled studies have shown that aspiration followed by ethanol injection has a higher success rate compared with aspiration alone. If the cyst recurs after a second aspiration, it should be considered for surgical excision.

13. List the indications for thyroidectomy in hyperthyroidism.

In the United States, thyroidectomy is not commonly performed for hyperthyroidism unless the condition is secondary to a single hyperfunctioning adenoma or to a toxic multinodular goiter that is associated with compressive symptoms or contains a suspicious nodule. Despite the excellent success

rate, low recurrence rate, safety, and more rapid return to a euthyroid state, fewer than 10% of patients with hyperthyroidism undergo thyroidectomy. Possible indications for thyroidectomy in patients with hyperthyroidism include:

- Failure of antithyroid medications
- Large goiter and low iodine uptake
- Compression symptoms, such as dysphagia, stridor, or hoarseness
- Nodules suggestive of cancer
- Children
- Pregnant patients who are difficult to treat medically
- Young female patients who want to become pregnant in the near future
- Noncompliance
- Cosmetic concerns
- Severe Graves' ophthalmopathy

14. How should patients with hyperthyroidism be prepared for surgery?

It is important to render patients euthyroid before surgery for hyperthyroidism, to avoid perioperative thyroid storm. Antithyroid medications administered for 4 weeks preoperatively are usually adequate. Some surgeons use saturated solution of potassium iodide (SSKI) or Lugol's solution, 3 to 5 drops three times a day for 3 to 5 days before surgery, to decrease the vascularity of the goiter and reduce the risk of bleeding. Patients who are very symptomatic may benefit from preoperative beta-blockade. For more rapid induction of a euthyroid state, patients may also be given dexamethasone, which can return thyroxine (T_4) and triiodothyronine (T_3) levels to within the normal range in less than 7 days. In cases of severe, refractory hyperthyroidism, plasmapheresis may occasionally be indicated.

15. What are the complications of thyroidectomy?

Thyroidectomy is a safe procedure with a mean length of hospitalization in large series of less than 1.5 days. The incidence rates of specific complications after thyroidectomy include the following:

- Cervical hematoma: 1%
- Recurrent laryngeal nerve injury: 1%
- Superior laryngeal nerve injury: 1%
- Temporary hypocalcemia: 10% to 15%
- Permanent hypoparathyroidism: 1% to 5%
- Mortality: 0.3%

16. What is the significance of a "hot" thyroid nodule incidentally discovered on a positron emission tomography (PET) scan?

Fluorodeoxyglucose (FDG) whole body PET scan is increasingly used in the evaluation and surveillance of patients with various types of cancers. A focal area of increased FDG uptake within the thyroid is incidentally noted in up to 4% of PET scans. The risk of malignancy in these lesions is about 33%. Thus, thyroid incidentalomas noted on PET scans have a high risk of malignancy and warrant appropriate diagnostic evaluation. Diffuse FDG uptake is usually related to underlying thyroiditis and in most cases is not indicative of malignancy.

17. What is the appropriate therapy for an intrathoracic (substernal) goiter?

Intrathoracic goiters are typically cervical goiters with mediastinal extension. Although they are commonly asymptomatic, up to 40% of patients present with compressive symptoms resulting from impingement on the airway, esophagus, vascular structures, or nerves. There is general agreement that medical therapy (thyroid hormone suppression and/or radioiodine) is ineffective for intrathoracic goiters. Whether there is an increased risk of malignancy in intrathoracic compared with cervical goiters is controversial; however, when cases of microcarcinoma are excluded, there does not appear to be an increased risk of malignancy in intrathoracic goiters. Even so, the presence of an intrathoracic goiter is considered by many as an indication for thyroidectomy. Because the arterial supply of intrathoracic goiters originates in the neck, most of these tumors can be resected through

a cervical approach. Extension into the posterior mediastinum, malignancy, or compression of the vena cava may necessitate a combined cervical and sternotomy approach, although this is required in less than 5% of cases.

18. When should thyroglossal duct cysts be removed? Describe the operation.

During the embryologic development of the thyroid, a diverticulum forms from the foramen cecum at the base of the tongue and descends as the thyroglossal duct to the future anatomic position of the thyroid overlying the anterolateral surface of the upper tracheal rings. The thyroglossal duct normally disappears during further development but in rare cases persists as a patent duct or as a thyroglossal duct cyst. Patients may complain of infection, pain, or compressive symptoms, or they may have cosmetic concerns. Because of the risk of infection, thyroglossal duct cysts should be removed; this requires excision of the entire cyst and cyst tract from the origin at the foramen cecum down to the cyst itself. Because the tract nearly always passes through the hyoid bone, the center of the hyoid should be resected to lower the risk of recurrence; this causes no disability and requires no repair.

KEY POINTS 1: THYROID SURGERY

1. All patients with a palpable thyroid nodule should undergo a thyroid ultrasound scan.
2. Fine-needle aspiration (FNA) is the single most important diagnostic test in the evaluation of a thyroid nodule.
3. Near-total or total thyroidectomy (as opposed to thyroid lobectomy) is indicated for all differentiated thyroid cancers 1 cm or larger.
4. Lymph node involvement in thyroid cancer should be treated with systematic compartment node dissection.
5. Incidental thyroid hot spots discovered on positron emission tomography scans have a high rate of malignancy and should be evaluated by ultrasound-guided FNA.

PARATHYROID

19. Which patients with primary HPT should undergo parathyroidectomy?

Patients with classic symptoms of HPT (nephrolithiasis, severe bone disease or fractures, or overt neuromuscular syndrome) should undergo parathyroidectomy; however, most patients with HPT do not have the classic symptoms. The National Institutes of Health (NIH) established criteria to assist clinicians in determining which patients with "asymptomatic" HPT should undergo surgery. In the absence of any of these criteria, continued surveillance is a reasonable option; however, if the patient meets any one of the criteria, then surgery is recommended:

- Calcium greater than 1.0 mg/dL above normal
- Creatinine clearance reduced by more than 30%
- Bone mineral density reduced more than 2.5 standard deviations below mean peak adult value (T score)
- Age less than 50 years
- Patients who do not desire or cannot undergo surveillance

Nonspecific symptoms, such as fatigue, mental slowing, musculoskeletal aches and pains, and depression, were not included in the NIH indications for surgery but are commonly reported by patients. Compared with controls (patients undergoing thyroid surgery), patients with HPT score significantly lower on preoperative quality of life questionnaires. Several studies indicate improvement in these patient-reported outcomes following parathyroidectomy.

20. When should preoperative parathyroid localization studies be performed?

An experienced parathyroid surgeon does not require preoperative localization before initial bilateral neck exploration. However, most patients with primary HPT have a single parathyroid adenoma, so preoperative localization is commonly performed and, when successful, enables minimally invasive parathyroidectomy. Patients with a prior history of neck surgery and certainly all patients with persistent or recurrent HPT should undergo preoperative localization studies before planned re-exploration. The best localization study available is the technetium-99m sestamibi scan, although ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), and parathyroid venous sampling with or without arteriography may all be useful in certain situations, especially persistent or recurrent HPT.

21. What is the best treatment for a 45-year-old woman with primary HPT but negative preoperative localization studies?

Surgery. By the NIH criteria, her age alone warrants parathyroidectomy. Preoperative localization studies fail to localize an abnormal parathyroid approximately 15% of the time. Failure to localize has nothing to do with whether or not a patient has HPT or whether or not the patient should undergo surgery. Most patients with negative preoperative imaging still have a single adenoma as the cause of their HPT, and the success rate of the surgical procedure, if performed by an experienced surgeon, is still high ($>$ 90%–95%).

22. Define minimally invasive parathyroidectomy.

Conventional parathyroidectomy entails bilateral neck exploration, identification of all four glands, and removal of the grossly enlarged gland or glands. The development of accurate preoperative localization studies and a rapid intraoperative parathyroid hormone (ioPTH) assay fostered the development of minimally invasive approaches to parathyroidectomy. A directed unilateral approach uses preoperative imaging to limit the dissection to one side. The abnormal gland is found and removed; after 10 to 15 minutes, a postexcision blood sample is drawn, and the PTH level is compared with a preexcision blood sample. A reduction of the PTH to 50% of the preoperative level and into the normal range predicts successful removal of all hyperfunctioning glands, and the surgical procedure is terminated. If the PTH does not drop appropriately, then all four glands must be identified because the patient likely has multiglandular disease.

23. What is minimally invasive radioguided parathyroidectomy (MIRP)?

MIRP is a second alternative to conventional parathyroidectomy and involves a technetium-99m sestamibi scan the morning of the surgery. An incision is made, either unilateral or bilateral neck exploration is performed, and the abnormal parathyroid glands are removed. A small, hand-held gamma probe is then used to measure the ex vivo radioactive counts of the excised parathyroid to determine whether the gland is hyperfunctioning. Biopsy of normal or borderline enlarged parathyroid glands can also be performed. The ex vivo radioactive counts can be used to confirm that the biopsy represents parathyroid tissue and to determine whether the gland is hyperfunctioning, in which case the rest of the parathyroid is resected. Contrary to common perception, the gamma probe is not used to localize the abnormal parathyroid. An ioPTH assay can also be used to exclude the possibility of multiglandular disease further (5%–10%).

24. Summarize the advantages of minimally invasive approaches.

Multiple studies have shown the minimally invasive approaches to be as safe and effective as conventional parathyroidectomy. However, there are also multiple studies showing that conventional parathyroidectomy (bilateral neck exploration) can similarly be performed through a small incision, on an outpatient basis, and with excellent results. Some studies have found the minimally invasive approaches to be more time and cost efficient because they limit the amount of dissection required and can be done without hospitalization. Because the minimally invasive approach is typically performed through a smaller incision, cosmesis may be improved.

25. How is the ioPTH assay used in parathyroid surgery?

The half-life of PTH is 3 to 5 minutes, and this allows for a rapid assay for ioPTH to be used intraoperatively to assess the functional success of the operation. This test is performed by drawing a sample of blood before the operation and 10 minutes after removal of the suspected abnormal gland or glands. A reduction of the ioPTH by 50% predicts successful removal of all hyperfunctioning glands, and the surgical procedure is terminated. The rate of residual multiglandular disease is approximately 5% when ioPTH is used to determine the completeness of resection, whereas the rate is 10% to 35% when conventional parathyroidectomy is performed (i.e., bilateral neck exploration and removal of grossly enlarged parathyroids). Therefore, the use of ioPTH may prevent the unnecessary removal of glands that appear enlarged but are not hyperfunctional.

26. What is the expected success of surgery for primary HPT?

Parathyroidectomy is highly successful for primary HPT. The procedure corrects hypercalcemia in more than 95% of patients when it is performed by an experienced surgeon. Bone density stabilizes or increases in most patients. Successful parathyroidectomy significantly decreases the risk of kidney stone recurrence. Following successful surgery, most patients experience improvement in the vague nonspecific symptoms of HPT.

27. Describe the appropriate management of a "missing" parathyroid.

Despite meticulous operative technique during conventional parathyroidectomy (identification of all four glands), the surgeon occasionally encounters a "missing gland." Up to 20% of parathyroid glands are ectopic, with the most common locations within the thymus, retroesophageal, and intrathyroidal. A systematic search of the most common ectopic locations is required for successful outcome in these patients. When three normal glands have been identified and the fourth gland is not in a normal position, the most likely ectopic location depends on whether it is a missing upper or lower gland.

28. List the likely locations for an ectopic inferior parathyroid gland.

- Thyrothymic ligament
- Thymus
- Mediastinum outside thymus
- Undescended gland

29. List the likely locations for an ectopic superior parathyroid gland.

- Retroesophageal
- Tracheoesophageal groove
- Posterosuperior mediastinum
- Intrathyroidal

30. What if a patient has multiglandular parathyroid disease?

A single adenoma is by far the most common cause of primary HPT. Depending on the method used to define multiglandular disease (i.e., ioPTH assay versus gross appearance or size), the reported rates range from 5% to 35%. Multiglandular disease can result from either multiple adenomas or four-gland hyperplasia. Hyperplasia may be sporadic or secondary to MEN syndrome, or it may be caused by secondary or tertiary HPT. When four glands are hyperplastic, the patient must undergo either subtotal (removal of 3½ glands [SPTx]) or total parathyroidectomy with autotransplantation of parathyroid tissue (TPTx + AT). The success of either approach depends on finding all four glands. Most patients (95%) have normal calcium and low or normal PTH levels in the early postoperative period; however, recurrent HPT occurs in 10% to 30% of patients.

31. Discuss the advantages and disadvantages of SPTx versus TPTx + AT.

It is generally thought that SPTx has a lower incidence of temporary postoperative hypocalcemia; however, the rate of permanent hypoparathyroidism is similar with either approach (10%–20%). The advantage of TPTx + AT is that persistent or recurrent hypercalcemia can be treated by

partially or completely removing the grafts (usually placed in a forearm muscle) with the use of local anesthesia, whereas the same complication occurring after SPTx requires repeat neck operation with higher morbidity. One very small prospective, randomized trial demonstrated a clear benefit of TPTx + AT for secondary HPT in patients with renal failure; in those patients, TPTx + AT resulted in a more rapid return of normal calcium homeostasis and relief of symptoms.

32. List the complications of parathyroidectomy for primary HPT and their prevalence.

- Persistent or recurrent HPT: 1% to 12%
- Transient hypocalcemia: 10% to 25%
- Permanent HPT: 2% to 5% (< 1% for solitary adenoma)
- Temporary recurrent laryngeal nerve injury: 3%
- Permanent recurrent laryngeal nerve injury: less than 1%
- Mortality: less than 0.5%

33. Define persistent or recurrent HPT.

Persistent HPT is defined as failure of calcium and PTH levels to normalize or remain normal in the initial 6 months after operation, whereas recurrent HPT is defined by recurrence of hypercalcemia after 6 months.

34. What is the most common cause of elevated PTH but normal calcium levels following parathyroidectomy?

Persistent PTH elevation with normal serum calcium can be observed in up to 30% of patients following parathyroidectomy. This can be disconcerting to the patient and surgeon but in most cases is not the result of persistent or recurrent HPT. The origin of this phenomenon is likely multifactorial, but vitamin D deficiency, rapid bone turnover (hungry bone syndrome), and inadequate calcium intake are thought to be the main causes. Postoperative supplementation with calcium and vitamin D decreases this phenomenon. Long-term studies have shown that the PTH eventually returns to normal in most patients, and the long-term recurrence rate is not increased in this subset of patients.

35. Discuss the approach to patients with persistent or recurrent HPT.

The approach to patients with persistent or recurrent HPT requires confirmation of the diagnosis (e.g., exclude familial hypocalciuric hypercalcemia, vitamin D deficiency), estimation of disease severity, careful review of the operative and pathology reports, and preoperative localization. Causes of failure include missed adenoma in a normal location, ectopic glands, inadequate resection in multiglandular disease, and supernumerary glands.

36. Discuss the treatment options for persistent or recurrent HPT.

Although preoperative localization is optional before initial surgery for HPT, it is essential in cases of persistent or recurrent disease because the success rate of the surgery is much higher when the abnormal gland has been accurately localized. Technetium-99m sestamibi scan is the best test, but when negative, ultrasound, CT, MRI, and parathyroid venous sampling with or without arteriography may all be useful. Repeat cervical exploration is successful in normalizing PTH levels in about 85% of patients and may be aided by intraoperative ultrasound and ioPTH assay. Mediastinal parathyroid tissue is most often removed via the transcervical approach, but thoracoscopy or median sternotomy may be required 1% to 2% of the time. Angiographic ablation of mediastinal parathyroid tissue using high doses of ionic contrast may be successful in selected patients with high surgical risk.

37. How does one recognize parathyroid cancer?

Parathyroid cancer is the rarest of all endocrine tumors, with a reported incidence of less than 1% in patients with primary HPT. It is difficult to distinguish parathyroid cancer from the more common benign causes of HPT, and the diagnosis is frequently not suspected preoperatively. Parathyroid cancer should be suspected preoperatively when patients present with rapid onset, severe, symptomatic

hypercalcemia (> 14 mg/dL), very high PTH levels (more than five times normal), a palpable neck mass, or hoarseness. It should be suspected intraoperatively when the tumor is large, firm, fibrotic, or invasive to the thyroid or other surrounding structures. Successful outcome requires early recognition and complete resection of the tumor and any involved structures.

38. Describe the management of parathyroid cancer.

Surgery is the mainstay of treatment for parathyroid cancer given that radiation and chemotherapy have shown little benefit. Local invasion and pathologic nodes should be assumed to represent cancer. Any suspicious parathyroid lesions should be carefully removed without disrupting the parathyroid capsule because such disruption may result in tumor spillage and local recurrence. If a parathyroid gland is obviously abnormal and infiltrating other tissues, those tissues should be resected en bloc with the tumor whenever possible, including the ipsilateral thyroid lobe when necessary. Removal of the central nodes on the side of the tumor is indicated at the initial operation. Any obviously enlarged lateral nodes should be resected by formal neck dissection. Prophylactic neck dissections have shown no benefit. The histopathologic diagnosis of this cancer is also difficult; thus, intraoperative frozen section is rarely useful other than to confirm parathyroid tissue.

39. Give the recurrence and survival rates for parathyroid cancer.

Recurrence rates are high and depend on whether the patient underwent routine parathyroidectomy for presumed benign disease (> 50% recurrence) or en bloc resection for suspicion of cancer (10%–33%). Despite this high recurrence rate, prolonged survival is still possible. The National Cancer Database reports 5- and 10-year survival rates of 85.5% and 49.1%, respectively.

KEY POINTS 2: PARATHYROID SURGERY

1. Indications for parathyroidectomy in primary hyperparathyroidism include the classic symptoms of nephrolithiasis and overt bone or neuromuscular syndrome.
2. Indications in asymptomatic patients include high serum calcium levels (> 1.0 mg/dL above normal), age less than 50 years, osteoporosis, and reduced creatinine clearance.
3. Surgery for primary hyperparathyroidism results in normocalcemia in more than 95% of patients when the procedure is performed by an experienced parathyroid surgeon.
4. Parathyroid cancer is rare but should be suspected in patients with a palpable mass and symptomatic hypercalcemia that is severe and of rapid onset.

ADRENAL GLANDS

40. Should all incidentally discovered adrenal masses be resected?

No. Clinically inapparent adrenal masses are common (up to 6% in autopsy series and 4% in abdominal CT series) and most are benign, hormonally inactive adenomas that require no treatment. The decision to remove an adrenal incidentaloma surgically is based on tumor size, imaging characteristics, and biochemical activity.

41. Summarize the appropriate laboratory evaluation of an adrenal mass.

Hormonally active adrenal tumors should be resected, and up to 20% of adrenal incidentalomas are found to have subclinical hormonal dysfunction. Therefore, patients should be screened for hypercortisolism, "silent" pheochromocytoma, and, if hypertensive, hyperaldosteronism by the following tests:

- 1-mg overnight dexamethasone suppression test
- 24-hour urinary and/or plasma fractionated metanephrines and catecholamines
- In hypertensive patients: a morning plasma aldosterone–plasma renin activity ratio

Routine screening for excess androgens or estrogens is not warranted because sex hormone–secreting adrenal tumors are rare and typically occur in the presence of clinical manifestations.

42. What imaging studies are available for evaluating adrenal disorders?

The appropriate imaging study for adrenal lesions depends on the presumed diagnosis. For incidentally discovered, hormonally inactive adrenal tumors, an "adrenal protocol" CT scan is an appropriate choice. This involves thin-cut imaging through the adrenals with and without intravenous contrast and delayed images to assess how quickly the contrast washes out. For cortisol-producing adenomas and most pheochromocytomas, CT scans are very accurate because the tumors are usually larger than 2 cm by the time they are diagnosed. MRI is essentially equivalent to CT for adrenal tumors; however, it may be superior in recurrent or metastatic disease and for pheochromocytomas. Meta-iodobenzylguanidine (MIBG) scans are best used for recurrent, familial, or nonadrenal pheochromocytomas. Aldosteronomas are typically less than 2 cm in diameter, and therefore the sensitivity of CT scans is only 85%. Adrenal venous sampling should be used in most patients with hyperaldosteronism to exclude bilateral hyperplasia and confirm the correct side in patients with unilateral aldosterone excess.

43. What findings on CT help to distinguish between benign and malignant tumors?

Although most adrenal incidentalomas are benign, a series of more than 2000 patients found that adrenocortical carcinoma accounted for 4.7% of tumors and metastatic cancer another 2.5%. The size of the mass and its appearance on imaging are the two major predictors of malignancy. Adrenocortical carcinoma accounts for 2% of tumors less than 4 cm but up to 25% of tumors greater than 6 cm. The lipid content of the adrenal mass and rapidity of the washout of contrast are also important CT characteristics in differentiating benign tumors from adrenal cancer, pheochromocytoma, and metastatic disease. Benign adenomas typically have high lipid content (low attenuation) and rapid contrast washout ($>$ 50% washout at 10 minutes after contrast). The following imaging characteristics are used to estimate malignant potential of adrenal incidentalomas.

- Benign tumors are typically smaller than 4 cm, are homogeneous with smooth borders, and have low attenuation ($<$ 10 Hounsfield units [HU]) and rapid contrast washout.
- Malignant tumors are typically larger than 6 cm, are heterogeneous with irregular borders, and have increased attenuation ($>$ 10 HU) and slower contrast washout.

44. Discuss the role of percutaneous biopsy in the evaluation of an adrenal mass.

Percutaneous biopsy cannot differentiate an adrenal adenoma from a carcinoma and is rarely indicated in the evaluation of an adrenal mass. However, metastases are the cause of adrenal incidentaloma in approximately half of patients who have a prior history of malignant disease. Therefore, percutaneous biopsy is typically reserved for patients with a history of cancer to evaluate for metastasis and is performed only if the result will influence therapy. It is always necessary to exclude pheochromocytoma first, to avoid the potential for precipitating a hypertensive crisis. The complication rate is 3% with bleeding, pain, infection, and malignant seeding of the biopsy tract most commonly reported.

45. List the indications for surgery.

- Size larger than 4 cm (some sources recommend a threshold of $>$ 6 cm)
- Any size with worrisome radiographic signs (rapid growth, heterogeneous appearance, irregular borders, high attenuation [$>$ 10–20 HU], or delayed washout of contrast)
- All pheochromocytomas
- Unilateral tumor with signs or symptoms of hormonal dysfunction
- Subclinical Cushing syndrome: Whether these patients are best treated medically or surgically is debated. Current guidelines suggest that adrenalectomy should be reserved for younger patients ($<$ 40 years) with worsening hypertension, abnormal glucose tolerance, dyslipidemia, or osteoporosis.

46. Is adrenalectomy best performed laparoscopically or by the open technique?

Advances in laparoscopic surgical techniques have been applied to adrenalectomy, and most endocrine surgeons agree that laparoscopic adrenalectomy is the procedure of choice for benign adrenal tumors. Laparoscopic adrenalectomy has been associated with decreased hospital stay, less postoperative pain,

less blood loss, shorter recovery, and overall increased patient satisfaction compared with the open techniques. However, open adrenalectomy should be performed when malignancy is suspected.

47. What approaches are used for laparoscopic surgery?

The most common technique is via an anterolateral approach in which the patient is positioned on the side. This provides excellent exposure but does not allow removal of both glands without repositioning the patient. An anterior approach provides access to both adrenal glands, but exposure is more difficult. A posterior endoscopic retroperitoneal approach avoids entering the peritoneal cavity altogether. This may be advantageous if the patient has had extensive prior abdominal surgery or needs bilateral adrenalectomy; however, this approach provides a limited working space and may hinder removal of larger lesions. The various laparoscopic approaches are believed to be equivalent in terms of safety and recovery.

48. Summarize the long-term success of adrenalectomy for functional tumors.

Following adrenalectomy for aldosteronomas, blood pressure is improved in 60% to 70% of patients; however, only 33% will require no antihypertensive therapy. The aldosterone level normalizes and hypokalemia is corrected in at least 95%; however, the long-term effect on hypertension is variable. The factors that predict postoperative normotension are younger age ($<$ 40 years), short duration of hypertension ($<$ 6 years), two or fewer antihypertensives, and no family history of hypertension. In older patients with severe, long-standing hypertension associated with renal dysfunction, adrenalectomy may not normalize the blood pressure, but it often results in easier control of hypertension with fewer or lower-dose medications.

Unilateral adrenalectomy is 95% effective in treating cortisol-producing adenomas. Bilateral adrenalectomy, in patients in whom hypophysectomy for adrenocorticotropic hormone–dependent Cushing syndrome fails, is slightly less effective, with approximately 25% of patients having persistent symptoms, hypertension, or diabetes. For patients undergoing unilateral adrenalectomy for Cushing syndrome, the hypothalamic-pituitary-adrenal axis recovers in a mean time of 9 months. Patients who undergo bilateral adrenalectomy require lifelong hormone replacement.

Adrenalectomy for nonfamilial, benign pheochromocytomas is curative in most cases. However, a long-term recurrence rate as high as 15% has been reported. Thus, patients should undergo lifelong surveillance with annual 24-hour urinary catecholamine and metanephrine measurement.

49. Describe the appropriate management of adrenal malignant disease.

Adrenocortical carcinoma is a rare (1–2 per million) and aggressive cancer with a poor prognosis. At the time of diagnosis, approximately 25% of patients will have nodal involvement and 20% will have distant metastases. Approximately 60% of adrenocortical carcinomas are functioning tumors, and the mean size of tumors at the time of diagnosis is greater than 10 cm. The overall 5-year survival rate is around 25% and depends largely on the stage at diagnosis. Patients undergoing complete resection of small tumors ($<$ 5 cm) without local invasion (stage 1) have a 5-year survival of 60%, whereas patients with metastases or invasion into other organs (stage 4) have a median survival less than 12 months. The only chance for cure is surgery, which should be offered to all patients without metastases who have a reasonable surgical risk. Surgery should also be considered for young patients with an isolated, easily resectable metastasis. Despite limited response rates, patients with stage 3 or 4 disease are frequently offered adjuvant therapy with mitotane (with or without cytotoxic chemotherapy) and/or radiotherapy because of the high recurrence rate (up to 85%).

50. Describe the appropriate management of pheochromocytoma.

Most pheochromocytomas are benign, sporadic tumors, and adrenalectomy is curative in nearly all such patients; however, late recurrences have been reported in up to 15% of patients. Therefore, all patients should undergo long-term surveillance with annual biochemical screening. Studies have found that up to 25% of pheochromocytomas are associated with a familial syndrome. It is recommended that most patients, especially younger patients or those with an extraadrenal pheochromocytoma, undergo genetic testing for MEN-2, von Hippel–Lindau syndrome, neurofibromatosis type 1, or defects in the succinate dehydrogenase genes.

The differentiation of benign and malignant pheochromocytoma is difficult histopathologically; however, approximately 10% of pheochromocytomas are malignant. Surgical resection offers the only chance for cure. Therefore, care must be taken not to disrupt the tumor during resection, and en bloc resection of any structure invaded by the tumor should be performed when feasible. The 5-year survival for patients with malignant pheochromocytoma is approximately 40% and depends on the completeness of the resection and on whether distant metastases are present.

51. What is a cortical-sparing adrenalectomy, and when is it indicated?

Approximately 20% to 30% of pheochromocytomas occur in patients with a hereditary predisposition, such as MEN-2, von Hippel–Lindau syndrome, neurofibromatosis type 1, or defects in the succinate dehydrogenase genes. Patients with pheochromocytoma associated with a familial syndrome are at increased risk of developing bilateral and/or recurrent pheochromocytoma. To prevent adrenocortical insufficiency, these patients may undergo a cortical-sparing adrenalectomy. This is actually just a partial adrenalectomy in which the tumor and a margin of normal adrenal are resected. This approach balances the benefit of avoiding the need for lifelong hormone replacement with a slightly higher risk of recurrent pheochromocytoma in the adrenal remnant.

52. How should patients with pheochromocytoma be prepared for surgery?

The stress of anesthesia and/or manipulation of the tumor during surgery can result in a rapid increase in circulating catecholamine levels and can precipitate a hypertensive crisis or arrhythmia even in patients who have not had significant preoperative hypertension. Thus, all patients should undergo preoperative alpha-adrenergic blockade using either phenoxybenzamine or another selective alpha-antagonist. The addition of a beta-blocker can be used to control tachycardia if needed but only after initiation of an alpha-blocker. Beta-blockade should never be started first because the unopposed alpha-adrenergic effect can cause a hypertensive crisis. Calcium channel blockers have been shown to be a safe alternative to adrenergic antagonists. Because of the hyperadrenergic state, patients with pheochromocytoma are typically volume contracted and can develop orthostatic hypotension on initiation of alpha-blockade. Volume expansion is accomplished by instructing patients to increase their fluid and salt intake ($>$ 5 g/day) after starting alpha-blockers. Intraoperatively, the patient's blood pressure can change dramatically during manipulation of the tumor and ligation of the adrenal vein. An experienced anesthesiologist who is prepared for these hemodynamic changes is critical to a safe operation.

KEY POINTS 3: ADRENAL SURGERY

1. Adrenal tumors smaller than 4 cm are rarely malignant; however, 25% of tumors larger than 6 cm are malignant.
2. Cortisol-producing adenoma is the most common functional adrenal tumor.
3. Patients with incidentally discovered adrenal tumors should be evaluated by 1-mg overnight dexamethasone suppression test, plasma or 24-hour urinary fractionated metanephrines and catecholamines, and, in hypertensive patients, a plasma aldosterone–plasma renin activity ratio.
4. Laparoscopic adrenalectomy is now the preferred approach for most adrenal tumors; however, open adrenalectomy should be performed if malignancy is suspected.

NEUROENDOCRINE TUMORS OF THE PANCREAS AND GASTROINTESTINAL TRACT

53. How common are pancreatic neuroendocrine tumors (PNETs)?

PNETs are the most common neuroendocrine tumors occurring in the abdomen, but overall they account for less than 2% of pancreatic tumors. The incidence in the United States is estimated to be 1 to 2 per 1,000,000.

54. Are most PNETs functional?

Although most PNETs secrete biologically inactive peptides such as chromogranins, neuron-specific enolase, and pancreatic polypeptide, 90% of PNETs are considered nonfunctional. PNETs that cause symptoms resulting from overproduction of hormones such as insulin, gastrin, glucagon, vasoactive intestinal peptide (VIP), and somatostatin are considered functional. Nonfunctional PNETs typically manifest similarly to pancreatic adenocarcinoma, with abdominal pain or biliopancreatic duct obstruction, or they are found incidentally. Thus, the definitive diagnosis of a nonfunctional PNET is often not made until final histopathologic examination is performed. Compared with pancreatic adenocarcinoma, patients undergoing resection for malignant PNETs have improved median survival (13 months versus 30 months). In addition, patients with functional tumors tend to have improved survival compared with those with nonfunctional PNETs (50 months versus 25 months).

55. What are the types of functional PNETs?

Insulinoma is the most common functional PNET (60%–70%), and more than 90% are benign. Gastrinoma is the second most common functional PNET (20%–30%), and approximately 50% are malignant. Glucagonoma is the next most common type, and 80% of these tumors are malignant. VIP-secreting tumors (VIPoma) and somatostatinomas are even rarer.

56. How should functional PNETs be imaged?

When a hormonally active tumor is suspected, the diagnosis should be confirmed biochemically before any imaging is performed. This is important not only for reasons of cost effectiveness, but also for patient safety because some localization studies are invasive. Given the small size of many PNETs, preoperative localization can be difficult, and the extent of preoperative imaging needed is controversial. Ultrasound, CT, MRI, and angiography have reported sensitivities around 60%. Octreotide scans are highly sensitive (85%) in locating most PNETs, especially for finding metastases, but they are less sensitive for insulinomas (50% sensitivity). Provocative arterial stimulation (secretin for gastrinomas and calcium for insulinomas) and hepatic venous sampling have higher sensitivity and have replaced portal vein sampling, but their invasiveness and their ability only to regionalize a tumor make them less desirable. Reports have shown endoscopic ultrasound to be the most sensitive preoperative test for localizing PNETs, although it is invasive and highly operator dependent.

57. How important is it to localize functional PNETs before surgery?

When performed by an experienced surgeon, intraoperative palpation with intraoperative ultrasound localizes nearly 100% of PNETs. Therefore, many surgeons believe that exhaustive efforts to localize the tumor preoperatively are unwarranted. They prefer to obtain a preoperative CT scan to identify obviously invasive or metastatic tumors and then rely on intraoperative palpation and ultrasound for tumor localization. However, all patients undergoing re-exploration for PNETs should have thorough preoperative localization studies.

58. What is the appropriate surgical approach for insulinomas?

Insulinomas account for the majority of nonfamilial functional PNETs. The small size of these tumors and the rarity of malignancy allow simple enucleation (60% of cases) or distal pancreatectomy (35% of cases) in most cases. Rarely, formal pancreaticoduodenectomy is required ($<$ 5% of cases), most typically for malignant tumors. Laparoscopy for enucleation or distal pancreatectomy is increasingly used for insulinomas.

59. Describe the surgical approach to gastrinomas.

The surgical approach to gastrinomas is more complex because these tumors are more frequently malignant and occur outside the pancreas in up to 50% of cases. Tumors occurring distal to the pancreatic neck should be removed by formal pancreatic resection because of the high incidence of malignancy. Tumors in the pancreatic head can often be enucleated, reserving formal pancreaticoduodenectomy for more invasive tumors or those in close proximity to the pancreatic duct or superior mesenteric vessels. Careful evaluation of the duodenum by palpation, endoscopic transillumination,

or duodenotomy is necessary to identify tumors within the duodenal wall, which occur commonly and can be quite small. Small submucosal lesions can be enucleated, but full-thickness resection of the duodenal wall may be necessary. Routine duodenotomy has been shown in some studies to improve early and long-term cure rates. The propensity for these tumors to metastasize to lymph nodes necessitates regional lymph node dissection in all patients.

60. Should PNETs occurring in patients with MEN-1 be approached differently from PNETs occurring sporadically?

Yes. Approximately 70% of patients with MEN-1 develop PNETs, and gastrinomas are most common. Because of the multifocal nature of tumors in these patients, aggressive surgery rarely results in biochemical cure. The morbidity and mortality rates of aggressive surgical resection combined with low cure rates and the availability of effective palliative treatment options for symptomatic patients sway many clinicians to treat patients medically unless there is suspicion of malignancy. Other surgeons take a more aggressive approach and cite studies that demonstrate decreased development of liver metastases and improved survival in patients undergoing surgery. Further, the larger tumors seen on preoperative imaging ($>$ 2 cm) often account for symptoms, and therefore surgical extirpation of these tumors may be beneficial. Formal resection of the distal pancreas accompanied by enucleation of tumors in the pancreatic head is necessary. A careful search for duodenal tumors and regional lymph node dissection must accompany resection of the pancreatic tumors.

61. Discuss the role of surgery for liver metastases from neuroendocrine tumors.

Patients who undergo resection of isolated liver metastases from neuroendocrine tumors experience symptomatic improvement in 95% of cases and have prolonged survival (60%–75% versus 25%–30% 5-year survival rates) compared with patients with similar tumor burdens who are not undergoing hepatic resection. Patients with unresectable liver metastases or those with prohibitive surgical risks may benefit from cryosurgical or radiofrequency thermal ablation and/or transarterial chemoembolization.

62. Describe the presentation of nonpancreatic neuroendocrine tumors (carcinoid tumors).

Bronchial carcinoids may manifest with hemoptysis, asthma-like symptoms, or carcinoid syndrome. Gastric carcinoids are frequently found incidentally on endoscopy but may also cause symptoms such as pain or bleeding. Neuroendocrine tumors of the small intestine are the most likely to result in carcinoid syndrome, which typically does not occur until the patient has developed metastases to the liver. These tumors frequently result in a desmoplastic (fibrotic) reaction of the adjacent mesentery that causes bowel obstruction. Hindgut carcinoids do not usually produce active hormones and are typically found incidentally during endoscopy performed for other reasons.

63. Describe the carcinoid syndrome.

Carcinoid syndrome results from the production and release of serotonin from neuroendocrine tumors, most commonly tumors of the small intestine. The liver metabolizes serotonin to inactive products, so most patients do not develop carcinoid syndrome until they have developed liver metastases, which permit serotonin to enter the systemic circulation. Patients frequently experience intermittent abdominal pain, brief flushing episodes, and diarrhea. Asthma-like symptoms, hypotension, and right-sided heart failure (marantic endocarditis) can also occur.

64. Once a patient is diagnosed with carcinoid syndrome, what is the next step?

The tumor must then be localized. This goal may be difficult because of the small size of most carcinoid tumors. Tumors arise in the small bowel and appendix in nearly 70% of patients, and therefore a small bowel contrast study or abdominal CT scan is often the initial study performed. If these tests fail to localize the tumor, a chest radiograph and/or chest CT scan should be obtained to exclude a bronchial carcinoid. Metaiodobenzylguanidine or octreotide scintigraphy is sometimes able to localize tumors not found by conventional methods.

65. Describe the appropriate surgical management for nonpancreatic neuroendocrine tumors (carcinoid tumors).

Bronchial carcinoids tend to spread locoregionally and therefore should be resected by formal lobectomy when possible. Gastric carcinoids are classified into three types. Types 1 and 2 account for most (> 75%) gastric carcinoids and are associated with chronic hypergastrinemia resulting from pernicious anemia and Zollinger-Ellison syndrome, respectively. These tumors are most commonly small (< 1 cm) and multifocal and are typically treated by endoscopic resection and surveillance, with excellent outcomes. Type 3 gastric carcinoids occur sporadically and are usually larger, solitary, and invasive, with more than 50% metastatic at diagnosis. They are treated similarly to gastric adenocarcinoma with formal gastric resection and lymph node dissection. Small intestinal carcinoids without metastases should be excised by segmental resection and lymph node dissection. Appendiceal carcinoids are typically incidentally discovered and occur most commonly at the appendiceal tip. Distal lesions smaller than 2 cm are adequately treated by appendectomy. The presence of a carcinoid near the appendiceal base, size larger than 2 cm, or gross lymph node involvement requires formal right hemicolectomy. Rectal carcinoids often manifest with bleeding or are incidentally found on endoscopy. Extensive surgery for rectal carcinoids offers no survival advantage over local excision.

66. Discuss the role of surgery in carcinoid syndrome.

Patients with surgically resectable hepatic tumors experience improvement in symptoms and survival comparable to that for PNETs metastatic to the liver. The development of somatostatin analogs has allowed successful control of symptoms in most patients with carcinoid syndrome and diffuse hepatic metastases. Systemic chemotherapy and hepatic artery embolization have not been very effective in palliating these patients; however, selective hepatic artery chemoembolization has been successful in decreasing tumor burden and alleviating symptoms in up to 80% of patients. Patients who do not respond to medical palliation may benefit from aggressive tumor debulking by resecting the primary tumor and as many of the liver metastases as feasible.

KEY POINTS 4: NEUROENDOCRINE TUMORS OF THE PANCREAS AND GASTROINTESTINAL TRACT

1. Insulinoma is the most common functional pancreatic neuroendocrine tumor (PNET), is usually benign, and in most cases can be treated by enucleation.
2. Gastrinoma is usually malignant and can occur in the pancreas, duodenum, and lymph nodes.
3. Octreotide scintigraphy and endoscopic ultrasound are the most useful preoperative imaging studies for gastrinoma.
4. PNETs in patients with multiple endocrine neoplasia type 1 (MEN-1) are frequently multifocal and are usually treated medically because of the low surgical cure rate.
5. Resection of isolated liver metastasis from neuroendocrine tumors improves symptoms and prolongs survival.

BARIATRIC SURGERY

67. Define obesity. How common is it?

Obesity is simply defined as the excess of body fat. The degree of body fat relative to weight is calculated by the body mass index (BMI – kg/m^2). Obesity is a BMI of 30 or greater. Morbid obesity is a BMI of 40 or greater. Increasing BMI correlates with increasing health issues including diabetes mellitus,

hypertension, sleep apnea and pickwickian syndromes, asthma, coronary artery disease, cardiomyopathy, gastroesophageal reflux disease, degenerative joint disease, hyperlipidemia, fatty liver, gout, urinary incontinence, gallbladder disease, psychological disorders, menstrual irregularities, and certain cancers (endometrial, colon, postmenopausal breast, kidney). Most important, a BMI greater than 40 increases the risk of death from all causes by twofold. In the United States, 64% or 127 million adults are considered overweight, and 36% or 78 million adults are obese; 17% of children and adolescents are obese.

68. What are the limitations of BMI?

BMI interpretation is limited in those with a higher proportion of fat relative to muscle (elderly persons) or in those with an unusually high proportion of muscle (bodybuilders).

69. How successful is nonsurgical treatment of obesity?

Evidence suggests that nonsurgical treatment (diet and behavior modification, exercise programs, and psychological support) for morbid obesity has more than a 90% failure rate. Similarly, pharmacologic therapy for morbid obesity has been hampered by serious side effects and, overall, has shown disappointing results.

70. What are the indications for surgery for obesity?

An NIH Consensus Conference held in 1991 recommended that the following patients be considered for bariatric surgery:

- BMI of 40 or greater
- A BMI of 35 to 40 is associated with other severe obesity-related medical problems that are likely to improve with weight reduction.

71. Have there been any more recent updates to the classic surgical indications listed earlier?

- The Food and Drug Administration (FDA) in 2011 expanded the use of the lap band to include obese individuals with a BMI of 30 to 34 who also have an existing obesity-related comorbidity.
- The International Diabetes Federation included the following recommendation in the 2011 position statement: Surgery should be considered as an alternative treatment option in patients with a BMI between 30 and 35 when diabetes cannot be adequately controlled by an optimal medical regimen.

72. List the contraindications to bariatric operations.

- Endocrine disorders that cause morbid obesity
- Psychological instability
- Alcohol or drug abuse
- End-stage organ disease or terminal cancer

73. Categorize the various surgical options for weight reduction.

- Restrictive
- Malabsorptive
- Combination restrictive and malabsorptive
- Other

74. List the options for restrictive surgery.

- *Vertical-banded gastroplasty:* A stapling device is used to divide the stomach vertically along the lesser curve starting at the angle of His to create a small (20-mL) pouch. A prosthetic device is then wrapped around the outlet of the pouch to prevent it from dilating over time. This operation is no longer performed because of poor long-term success.
- *Gastric banding:* This procedure is performed laparoscopically and involves placement of an adjustable band around the proximal stomach to create a small (15-mL) pouch. The band is connected to a reservoir placed in the subcutaneous tissue that enables band adjustment. Concerns about long-term success have led to a decline in popularity.

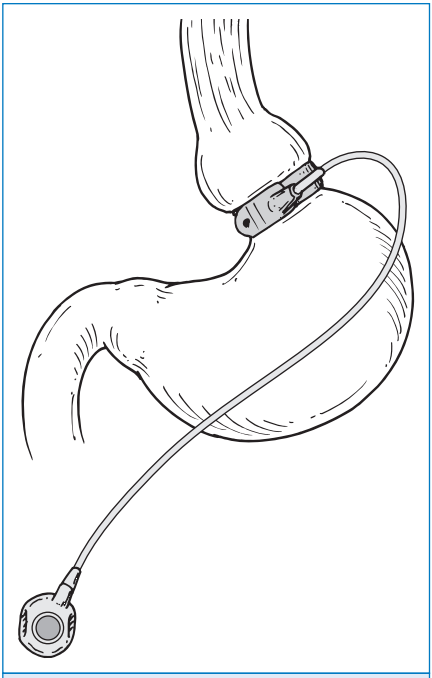

Figure 57-1. Gastric band.

- *Sleeve gastrectomy:* This procedure is gaining in popularity and involves stapling and removing a majority of the gastric body and fundus and leaving the lesser curvature and a small amount of antrum. The pylorus remains intact.

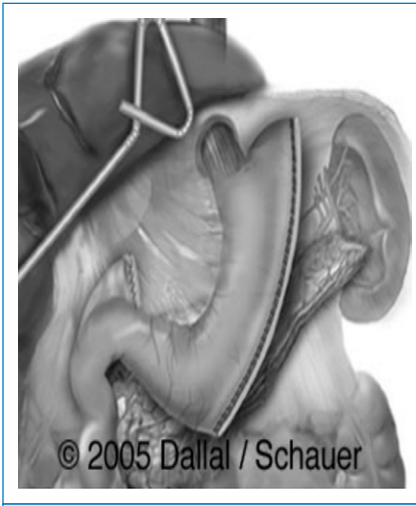

Figure 57-2. Sleeve gastrectomy.

75. What is the option for malabsorptive surgery?

Biliopancreatic diversion with and without a duodenal switch. Subtotal gastrectomy is performed, leaving a gastric remnant of 250 to 500 mL. The small bowel is divided 200 to 300 cm proximal to the ileocecal valve, and the ileum is anastomosed to the stomach. The jejunum is connected to the side of the ileum approximately 50 to 100 cm from the ileocecal valve, the "common channel." This procedure results in malabsorption by creating a short common channel for digestion and absorption of food. Similarly, a "distal" gastric bypass involves creating a short common channel that leads to considerable malabsorption.

76. Explain the combined option.

This procedure is known as the "proximal" Roux-en-Y gastric bypass. The proximal stomach is stapled to create a small, 15- to 30-mL proximal stomach pouch that is completely separated from the excluded remnant stomach. This small reservoir restricts the amount of food that can be ingested at one time. The jejunum is then divided just distal to the ligament of Treitz, and the distal end is anastomosed to the proximal stomach pouch (the Roux limb). The proximal end of the jejunum is then anastomosed to the side of the jejunum 75 to 150 cm distal to the gastrojejunostomy. The length of this Roux limb determines the degree of malabsorption and is typically made longer for patients with very high BMIs. This procedure is performed using laparoscopic technique.

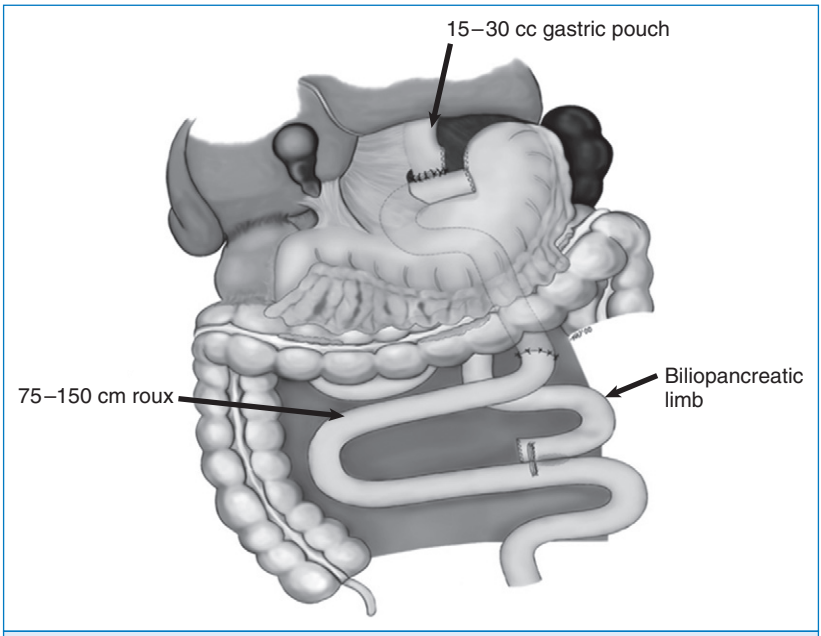

Figure 57-3. The Roux limb.

77. How much weight do patients lose following bariatric surgery?

Success following bariatric surgery is determined by both weight lost and improvement in obesity-related comorbidities. However, most surgical studies report outcome as percentage of excess weight lost (EWL) and consider loss of at least 50% of excess weight as a minimum criterion for success. The lap band typically produces 40% to 60% EWL gradually over 2 to 3 years, but it has a 20% failure rate. The gastric bypass typically produces 60% to 80% EWL rapidly over 2 years, but it has some recidivism and an estimated 10% failure rate. The biliopancreatic diversion is arguably the

most effective weight loss procedure, resulting in 80% EWL, maintained over the long term. The sleeve gastrectomy is currently being studied for long-term success and so far mimics the gastric bypass in terms of weight loss efficacy.

78. What are the effects of bariatric surgery on obesity-related comorbidities?

Long-term weight loss following bariatric surgery has been shown to reduce obesity-related comorbidities significantly. Approximately 85% of patients with diabetes, hyperlipidemia, and obesity hypoventilation syndrome will be improved or cured at 2 years after surgery. In fact, the gastric bypass is now being studied as a surgical option for resolution of type 2 diabetes in patients without severe obesity. Hypertension also improves or resolves in more than two thirds of patients after successful weight loss. Salutary effects on other comorbidities, such as asthma, depression, and arthritic pain, as well as unemployment, are frequently observed following surgery.

79. What are the complications of bariatric surgery?

Perioperative mortality for the lap band is 0.1%; for the gastric bypass, it is 0.3% to 1%; and for the biliopancreatic diversion, it is 1% to 3%. The laparoscopic technique has changed the pattern of perioperative complications. Although wound complications and postoperative cardiopulmonary complications are less frequent, anastomotic stenosis, gastrointestinal bleeding, and bowel obstruction occur more frequently with laparoscopic compared with open techniques. Mean hospital stay following laparoscopic bariatric surgery is 2 to 3 days, significantly shorter than after open surgery (5–7 days). The lap band is usually performed as either an outpatient procedure or a 24-hour stay. Each procedure has its own unique risk of complications; the lap band has the least number of serious complications, and the biliopancreatic diversion has the greatest.

80. Give the incidence of complications following laparoscopic bariatric procedures in general.

- Anastomotic leak: 1% to 2%
- Anastomotic stenosis: 5% to 10%
- Postoperative bowel obstruction: 3%
- Gastrointestinal bleeding: 2%
- Gallstones: 10%
- Protein-calorie malnutrition: 3% to 5%
- Anemia: 30%
- Vitamin deficiency: 30%
- Wound complication (infection, dehiscence, and hernia): 4% to 5%
- Band slippage or erosion into the stomach: 1% to 5%

KEY POINTS 5: BARIATRIC SURGERY

1. Surgery is the only therapy that consistently results in significant, long-term weight loss in morbidly obese patients.
2. Laparoscopic Roux-en-Y gastric bypass, currently the most common bariatric operation performed in the United States, results in loss of 60% to 80% of excess weight.
3. Surgical weight loss significantly reduces obesity-related comorbidities and is the most effective treatment for diabetes mellitus.

WEBSITE

American Association of Endocrine Surgery: www.endocrinesurgery.org.

BIBLIOGRAPHY

Thyroid

Bilimoria KY, Bentrem DJ, Ko CY, et al: Extent of surgery affects survival for papillary thyroid cancer, *Ann Surg* 246: 375–381, 2007.

Burnison CM, Lim S: Multimodal approach to anaplastic thyroid cancer, *Oncology* (Williston Park) 26:378–384, 390–398, 2012.

Cibas ES, Ali SZ: The Bethesda system for reporting thyroid cytopathology, *Am J Clin Pathol* 132:658–665, 2009.

Cooper DS, Doherty GM, Haugen BR, et al: Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer, *Thyroid* 19:1167–1214, 2009.

Kloos RT, Eng C, Evans DB, et al: Medullary thyroid cancer: management guidelines of the American Thyroid Association, *Thyroid* 19:565–612, 2009.

White ML, Doherty GM, Gauger PG: Evidence-based surgical management of substernal goiter, *World J Surg* 32: 1285–1300, 2008.

Parathyroid

Allendorf J, DiGorgi M, Spanknebel K, et al: 1112 consecutive bilateral neck explorations for primary hyperparathyroidism, *World J Surg* 31:2075–2080, 2007.

Bilezikian JP, Khan AA, Potts JT Jr: Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the third international workshop, *J Clin Endocrinol Metab* 94:335–339, 2009.

Coker LH, Rorie K, Cantley L, et al: Primary hyperparathyroidism, cognition, and health-related quality of life, *Ann Surg* 242:642–650, 2005.

Roy M, Mazeh H, Chen H, et al: Incidence and localization of ectopic parathyroid adenomas in previously unexplored patients, *World J Surg* Sep 12, 2012. (E-published ahead of print).

Schulte KM, Talat N: Diagnosis and management of parathyroid cancer, *Nat Rev Endocrinol* 8:612–622, 2012.

Starker LF, Fonseca AL, Carling T, et al: Minimally invasive parathyroidectomy, *Int J Endocrinol* 206:502, 2011.

Adrenal

LaFemina J, Brennan MF: Adrenocortical carcinoma: past, present, and future, *J Surg Oncol* 106:586–594, 2012.

Palazzo FF, Sebag F, Sierra M, et al: Long-term outcome following laparoscopic adrenalectomy for large solid adrenal cortex tumors, *World J Surg* 30:893–898, 2006.

Porterfield JR, Thompson GB, Young WF Jr. et al: Surgery for Cushing syndrome: an historical review and recent ten-year experience, *World J Surg* 32:659–677, 2008.

Webb R, Mathur A, Chang R, et al: What is the best criterion for the interpretation of adrenal vein sample results in patients with primary hyperaldosteronism? *Ann Surg Oncol* 19:1881–1886, 2012.

Young WF Jr: Clinical practice: the incidentally discovered adrenal mass, *N Engl J Med* 356:601–610, 2007.

Zeiger MA, Thompson GB, Duh Q, et al: American Association of Clinical Endocrinologists and American Association of Endocrine Surgeons medical guidelines for the management of adrenal incidentalomas, *Endocr Pract* 15(Suppl 1): 1–20, 2009.

Neuroendocrine Tumors of the Pancreas and Gastrointestinal Tract

Burns WR, Edil BH: Neuroendocrine pancreatic tumors: guidelines for management and update, *Curr Treat Options Oncol* 13:24–34, 2012.

Halfdanarson TR, Rabe KG, Rubin J, et al: Pancreatic neuroendocrine tumors (PNETs): incidence, prognosis and recent trend toward improved survival, *Ann Oncol* 19:1727–1733, 2008.

Huang LC, Poultsides GA, Norton JA: Surgical management of neuroendocrine tumors of the gastrointestinal tract, *Oncology* 25:794, 2011.

Nikfarjam M, Warshaw AL, Axelrod L, et al: Improved contemporary surgical management of insulinomas: a 25-year experience at the Massachusetts General Hospital, *Ann Surg* 247:165–172, 2008.

Norton JA, Fraker DL, Alexander HR, et al: Surgery increases survival in patients with gastrinoma, *Ann Surg* 244:410–419, 2006.

Perez EA, Koniaris LG, Snell SE, et al: 7201 carcinoids: increasing incidence overall and disproportionate mortality in the elderly, *World J Surg* 31:1022–1030, 2007.

Bariatric Surgery

Anthone GJ, Lord RV, DeMeester TR, et al: The duodenal switch operation for the treatment of morbid obesity, *Ann Surg* 238:618–627, 2003.

Biertho L, Steffen R, Ricklin T, et al: Laparoscopic gastric bypass versus laparoscopic adjustable gastric banding: a comparative study of 1,200 cases, *J Am Coll Surg* 197:536–544, 2003.

Brolin RE: Bariatric surgery and long-term control of morbid obesity, *JAMA* 288:2793–2796, 2002.

Buchwald H, et al: Bariatric surgery: a systematic review and meta-analysis, *JAMA* 292:1724–1737, 2004.

Podnos YD, Jimenez JC, Wilson SE, et al: Complications after laparoscopic gastric bypass, *Arch Surg* 138:957–961, 2003.

Schauer PR, Burguera B, Ikramuddin S, et al: Effect of laparoscopic Roux-en Y gastric bypass on type 2 diabetes mellitus, *Ann Surg* 238:467–484, 2003.

Sjöström L, Narbro K, Sjöström CD, et al: Effects of bariatric surgery on mortality in Swedish obese subjects, *N Engl J Med* 357:741–752, 2007.

ENDOCRINOLOGY IN THE MANAGED CARE ENVIRONMENT

CHAPTER 58

Elliot G. Levy

1. Define managed care.

The American College of Physicians/American Society of Internal Medicine has defined *managed care* as "a system of health-care delivery provided by contracted providers in which the entities responsible for financing the cost of health care exert influence on the clinical decision-making of those who provide the health care in an attempt to provide health care that is cost effective, accessible, and of acceptable quality."

2. Is there only one type of managed care?

Managed care is actually a spectrum of health-care delivery systems ranging from managed indemnity insurance through preferred provider organizations (PPOs) and point-of-service (POS) plans to various types of health maintenance organizations (HMOs). Collectively, these organizations are called *managed care organizations* (MCOs). To a greater or lesser extent, all managed care systems attempt to shift financial risk in one way or another to the providers of care.

3. Who is the patient's initial contact in a managed care environment?

In most cases, the patient's initial contact is with a health-care provider, conveniently called a *primary care provider* (PCP). This person is usually a physician, such as a family medicine, family practice, or general practice physician, but often the PCP may be a physician who has specialized in internal medicine or an internist with a subspecialty (e.g., endocrinology) who enjoys practicing primary care in addition to his or her subspecialty or does not have enough subspecialty work to fill his or her schedule. The PCP can also be a physician extender, such as a nurse practitioner or a physician assistant. Some MCOs use physicians in large clinic-type settings in an effort to control costs. In other situations, PCPs function out of their usual private practice offices—in a sense, mixing their private (or non-MCO) patients with their HMO or PPO patients.

4. Do pediatricians and gynecologists function as PCPs?

There has been a movement over the past few years to allow pediatricians to become PCPs for children and for obstetrics and gynecology specialists to become PCPs for women of childbearing years, who often have no need to see other types of physicians.

5. How does the patient make contact with a subspecialist?

A patient is allowed to see a subspecialist, such as an endocrinologist, only with the recommendation of a PCP. Usually, an endocrinologist is not allowed to function as both a PCP and a subspecialist within a given HMO. In these situations, when a fully trained endocrinologist is serving as a PCP, he or she cannot even perform specialty-type procedures and must refer patients to another endocrinologist.

6. What is a meant by the MCO's "panel" of providers?

After an MCO has established itself in a community, it begins to develop a panel of all the providers it requires, including PCPs, medical subspecialists, surgeons and surgical subspecialists, pediatricians, obstetricians-gynecologists, and dermatologists. Simultaneously, the MCO contracts with hospitals (strategically located around the community that it wants to "penetrate"), nursing homes, home health agencies, physical therapy centers, dialysis centers, outpatient diagnostic centers, clinical (commercial) laboratories, and, sometimes, even outpatient diabetes education centers or dietitians.

7. Explain the MCO directory.

The panel of providers is published yearly in a directory that goes by a variety of names (e.g., preferred provider list) and is distributed to all participants of the MCO. This directory is sometimes called the list. It is used by patients to determine which PCP is available for them to use (although in some HMOs, new patients are immediately assigned to a PCP of the HMO's choice). The directory is used by a PCP to know which subspecialists, diagnostic center, and laboratory to use. It is also used by the MCO itself as a marketing tool to solicit business for itself by proudly showing which subspecialists belong to its panel of providers. It is therefore necessary to be on the list to receive referrals from this HMO. However, your presence on the list as a subspecialist does not mean that you will ever receive referrals. The health care for the MCO is then provided by this entire group of health-care providers, all of whom are under contracts with the HMO to provide the care in the manner and for the price negotiated. Thus, the MCO has managed to do what the health-care system was never able to do by itself—organize all the health care into one unit.

8. Explain the POS option.

In some cases, the POS option allows the patient to see any specialist, although the reimbursement schedule is different. In addition, the patient's out-of-pocket expenses (copayment) are often much larger. The POS option differs greatly among insurance companies that offer it.

9. How do MCOs compare with other business units?

When one looks at the managed care system from afar, it is not so different from any other business unit that has to negotiate with vendors to provide services that it cannot provide on its own. Think of a business unit as the cruise ship industry, which negotiates with its own employees, as well as with entertainers, doctors, food suppliers, fuel suppliers, ports, and travel agents, to provide its customers (passengers) a total package for their enjoyment. So have the MCOs attempted to organize the U.S. health-care system. It is clearly a private, non–government-regulated, for-profit (in most cases) system with the primary goal of earning a profit for its shareholders while attempting to contain costs for the entire health-care system. Not-for-profit MCOs are not necessarily any more efficient in providing the care to their members and often have the same fiscal problems as for-profit MCOs.

10. What is the difference between a PPO and an HMO?

A PPO is a plan, as originally conceived in the 1990s, that contracts with independent providers at a discounted fee for service. When the PPO systems first started, their representatives would approach a PCP or a specialist and offer a discounted fee schedule to a physician in exchange for the potential of being specifically referred a group of patients who otherwise would not be able to see that physician. There developed the concept of panels (i.e., the lists discussed earlier), in which a list of accepted providers would be given to patients covered by the plan, who must agree to use only the physicians on such a panel for their care to be covered by the plan. This concept has been modified many times (see question 12).

HMO was originally defined as a prepaid organization that provided comprehensive health-care services to voluntarily enrolled members in return for a prepaid fixed amount of money. Nowadays, an HMO can be a health plan that places some providers at risk for medical expenses or a health plan that uses PCPs as gatekeepers.

11. Are there other types of MCO plans?

As pressure was placed on businesses with large numbers of employees who were not happy with the original types of plans and the costs of the yearly premiums of certain plans, many other insurance options were created.

12. What are blended policies?

Blended policies include PPOs with an assigned PCP and full coverage for specialty referral within the network of contracted providers but partial payment for use of specialists outside the network. Plans can have different deductibles for office visits, hospitalizations, and brand-name versus generic medications.

In some HMOs, an entire clinic provides all the health care, and referrals must be made internally. Other HMOs may contract with certain physicians within a community to be PCPs and with other physicians to be the specialists. Referrals may be scrutinized carefully, and PCPs may be indirectly penalized by withholding bonuses or even reprimanded when they refer too many patients to specialists. There are many more plans as insurance companies try to provide options to employers that meet the needs of employees but keep the cost down to employers. In many MCOs, a physician must provide care for both HMO and PPO patients, although sometimes with different fee schedules. Some MCOs allow physicians to participate in one or the other type of organization.

13. How does an endocrinologist join an HMO?

As many options are there are for a physician to practice, such are the options for joining MCOs. In some cases, an endocrinologist is employed by a faculty group practice of a large medical center or a large group practice, in which all members are participants in the specific plan. He or she is most likely to become a provider as soon as his or her credentials are approved by the MCO. In areas of the country with a shortage of endocrinologists, you will be approached by many MCOs to participate immediately. For the most part, if an endocrinologist decides to practice solo or joins a group practice in an area where the MCO is satisfied with the doctors already on the panel, joining the HMO can be difficult; in some cases, it may be impossible. Trying to open a solo office for general endocrinology in an area of great HMO penetration may be extremely difficult and frustrating. Sometimes, however, the MCO is under pressure to increase the number of endocrinologists, especially in certain geographic areas, and welcomes the applications of new doctors. At other times, MCOs receive specific requests from patients or employers to include in their panels certain groups of doctors who were not previously participants. In general, the process of application, review of application, and final approval for participation can be quite long, maybe even more than 6 months. During this time, a physician cannot see patients for the MCO.

14. How does an HMO patient get to your office?

After a PCP determines that he or she does not have the experience or expertise to treat a certain endocrine problem, the patient is referred to your office. Sometimes the referral is made by the patient's HMO or "center," as it is often called. The patient must have in hand some kind of a referral form, either an authorization form or a special slip of paper giving you the specific authority to evaluate and treat the patient. Without the referral form or some kind of definite referral from the center, you will not be compensated for the consultation visit. Each subsequent visit must also be authorized in the same manner, or payment will be withheld. It can be frustrating when a patient arrives for follow-up at the physician's office without the authorization form. Naturally, the doctor wants to see the patient and has blocked out the time in his or her schedule for the visit. Nonetheless, the HMO will definitely refuse to back-issue a referral form, and, most likely, the doctor will receive no compensation for the visit.

15. What can you expect to be able to do for the patient at the initial consultation or at subsequent follow-up visits?

In general, you will be allowed to perform a history and physical examination and order simple diagnostic tests without hassle. Blood tests should be allowed, although the samples usually have to be sent to the laboratory with which the MCO has contracted (see question 17). Other tests have to be approved in writing by the HMO center or by the main HMO office, depending on the individual company's policy. Approval for simple procedures, such as thyroid scans, ultrasound studies, radioactive iodine treatment, and even fine-needle aspiration (FNA) biopsies can take hours to days. Some HMOs require that PCPs schedule all tests. This can be a problem because you may not know when or where the study is scheduled or when to have the patient return to discuss the results. The more expensive a test is (e.g., magnetic resonance imaging), the more difficult it is to arrange.

16. Can you use your own physician office laboratory (POL) for HMO patients?

Although many endocrinologists have their own laboratories, accredited to perform certain endocrine tests, you usually cannot use POLs for HMO patients. Often the HMO has arranged special fees with

commercial laboratories. This situation can create logistical problems in your office if you work for several HMOs, all of which use different commercial laboratories. Your laboratory technicians must keep straight which specimens go where. In addition, some HMOs require that the patients have all blood tests drawn at the office of the PCP. This requirement is especially a problem because sometimes you will not know whether your patient went to the PCP's office to have the blood drawn, and the test results may not be sent to you until the patient returns for a follow-up visit. You may have to call the PCP's office to have the results given to you over the phone or by fax.

17. What potentially serious problem may arise in regard to pathology services?

Endocrinologists often perform FNA biopsy of a thyroid nodule. Most endocrinologists trust the interpretations by one particular laboratory, often at a university setting. The MCO may not have a contract with that laboratory and may require you to use a totally different laboratory for FNA cytology interpretation. Sometimes the pathologists at that laboratory may not be used to interpreting thyroid FNAs, and the results you receive may not be as accurate. This particular problem is being addressed by the American Thyroid Association and the College of American Pathologists.

18. What happens if your patient changes jobs and receives health insurance from a company for which you are not providing services, or if the patient's employer switches insurance because the price of the original plan was too high?

Obviously, this problem is highly frustrating for both patient and physician. The concept of long-term loyalty has been changed. Occasionally, a POS option may be available in the new plan, but often the patient grows tired of paying the extra copayment. Sometimes a physician will give the patient a discount to continue their professional relationship. At other times, patients feel so strongly about the opinion of their doctor that they pay the fee out of pocket to the physician, especially if the patient must be seen only once or twice a year. There are movements in Congress to allow the continuation of the patient-physician relationship. Until such time, the physician has to understand that losing patients in this way may be unavoidable. He or she should always welcome the patient back to his or her practice if the insurance situation changes.

19. Describe the process by which the endocrinologist submits the bill for patient services.

After endocrinologists finish seeing the patient, they usually complete a "superbill" by entering the type of office visit performed, any diagnostic tests ordered that are performed in house, and the proper diagnosis code covering the patient's medical condition. The doctor then turns the chart and superbill over to a clerical person, thus ending the patient-physician interaction of the day. What happens thereafter is usually a total mystery to most physicians. A secretary or administrative assistant usually enters the charges and the diagnosis into some type of physician management system, in which an insurance claim is generated and sent electronically or by paper to the insurance carrier. The carrier examines the claim, and eventually a check is cut to cover what the carrier deems appropriate. The check returns to the physician's office after some period of time, and a clerical person posts the payment received in the patient's account. There was somewhat of an honor system in the past, whereby the insurance company trusted the physician explicitly. This is no longer the case.

20. Why are payments often delayed?

MCOs are notorious for holding back payments. There are all kinds of excuses:

- Deliberate down-coding (i.e., stating that the service provided was really a level 3 service, even though the claim was submitted at level 4)
- Bundling (e.g., including the charges for the physician component of treatment for a hyperthyroid patient with the cost of the radiopharmaceutical)
- Delayed payments (holding onto the claim for 6–8 rather than 2–3 weeks)
- Wrongful denial of claims (e.g., stating, inappropriately, that there is no coverage, no authorization, a nonexistent preexisting condition, or improper completion of the insurance form)

21. What problems may result from such practices?

These problems result in inappropriate payments (always less than expected), prolonged time before claims are finally resolved, and endless amounts of paperwork, administrative time, and loss of income. In fact, a lawsuit for using such practices that was filed on behalf of the Florida Medical Association, California Medical Association, Texas Medical Association, and Medical Association of Georgia was settled against five MCOs. For this reason, physicians must understand all the potential problems before they enter into contract to see patients for a specific HMO or continue seeing their patients without checking with their billing offices to find out what kinds of problems may exist.

22. Is it advisable to continue seeing patients for MCOs if such problems exist?

This becomes a personal and financial decision that each physician or group practice has to make. Some doctors work for a company strictly on a salary basis. Seeing all patients is just part of what they have to do. Physicians who are in solo practice or small groups must be aware of all the problems so that the decision to begin or continue seeing patients is made for the right economic reasons. Many doctors react out of fear and anger, the worst emotions to invoke when an economic decision has to be made.

23. Explain why doctors must be involved in all aspects of the MCO relationship.

Doctors must be involved in all aspects of the MCO relationship, from contract negotiation to ongoing monitoring of day-to-day problems in seeing patients for the particular MCO and awareness of reimbursement problems. The practice must monitor collections, be on top of claims, and resubmit claims that were rejected, down-coded, or held for a long time without payment. The doctor must make sure that the collection of claims is not forgotten and that all claims are actively pursued, especially when third-party payment (i.e., from an insurance company) is involved. Doctors or their staff must have a policy in force to ensure that referrals are obtained, claims are submitted on time, and proper payments are received.

24. What special concerns apply to doctors in small groups?

Doctors in small groups must make sure that the MCO in question is contributing a significant amount to the gross revenue of the practice to be worth the "hassle" involved in seeing its patients. As a particular doctor becomes busier and busier, it may be more worthwhile to replace patients from an HMO with a low reimbursement schedule with patients from HMOs with higher reimbursement schedules. Perhaps the doctor can see only patients covered by higher-paying PPOs or choose not to be involved in MCOs at all, if there are enough patients to fill his or her schedule. For those physicians new in practice, it may be worthwhile to see more and more patients, despite the associated problems.

25. What pitfalls should doctors avoid in making decisions about participation in MCOs?

The decision to join MCO panels or to resign from a particular panel should not be emotional, such as out of fear that if you do not accept a contract with what you consider an inadequate reimbursement schedule, another endocrinologist will do so. In addition, do not make a decision in anger, when a company denies payment or down-codes a series of claims without good reason. Work out the economics associated with leaving, rather than resigning out of anger. In fact, first try to work it out with the MCO. Then look at all these issues, and decide whether resignation is appropriate for economic reasons, not emotional ones.

26. What factors should be taken into account in deciding whether to renew a specific MCO contract?

Contracts for most HMOs come up for renewal each year. Doctors have a chance to decide whether the contract should be continued. The decision to continue should be based on facts, rather than feelings: revenue tracking, handling of claims, and fee schedule.

27. Explain revenue tracking.

Doctors should track their revenue during each year from all payers to make sure that no single MCO becomes such a large percentage of their practice that dropping the company or, even worse, being dropped by the company would result in a gigantic loss of revenue. No one can say for sure what the ideal percentage should be, but some physicians use 10% to 15% as the ceiling for the cutoff. A doctor must be careful, however, in turning away new referrals from that HMO, because there may be some contractual obligations that must be followed.

28. What factors are relevant to handling of claims?

Practice management software should be able to provide information, such as how many claims for each MCO were down-coded, bundled, or denied. How many claims were delayed in payment for more than 3 weeks? How many times did a billing clerk have to call the company before payment was finally received? Each time a claim is not paid properly or promptly, administrative costs are associated with collecting these fees. These extra costs effectively reduce the expected amount of reimbursement. In addition, talk to the secretaries to find out what kinds of hassles are encountered in receiving referrals, scheduling procedures, and getting laboratory tests done promptly. They can guide you in your decision.

29. How do you evaluate the fee schedule?

After the decision is made to continue seeing the patients for an MCO, the physician must look at the fee schedule. Try not to sign a document that expresses reimbursement in terms of a percentage of Medicare or some other baseline. Try to be specific in providing a list of office visit codes that will be used and agree on criteria for judging what documentation is required for each level. Also provide the company with a list of procedures and tests that you perform in your office, and agree on a fee schedule. Make sure that the company signs off on the reimbursement expected for each item. This strategy will save a major hassle later when down-coding or denials appear.

30. Should doctors consult a lawyer before signing an MCO contract?

Yes. Do not expect to understand the contract that is provided to you. Have an attorney, especially one well versed in health-care law, review it, and point out the potential problems. Many physicians are reluctant to spend the money to do so, but this reluctance is shortsighted.

31. Can doctors negotiate the terms of MCO contracts?

Contracts are always up for discussion. Do not think that you cannot negotiate for terms other than those initially provided.

32. Does the physician have to be a good businessperson to survive in the managed care environment?

Unfortunately, yes. Most physicians go to medical school to learn how to become good doctors. They work hard during their residency and fellowship to learn as much internal medicine and then endocrinology as they can. Most likely, nothing is taught about practice management, contract negotiation skills, and cost-effective medical care. In addition, the traditional role of a physician as a healer of the sick without concern for compensation because doctors “always made a good living” is no longer applicable. It is becoming too expensive to run an office without being aware of the costs of every aspect of the practice, the revenue stream, and the “bottom line.” Some doctors sell their practices to avoid dealing with these problems, only to find out that working for a physician management company or a hospital that acquires practices, or very large groups, creates an entirely different set of problems that they never expected.

To have a financially successful practice, the doctor must have a totally different attitude from that of physicians of a generation ago. The doctor has to view practice as a business, with the provision of health care as only one part of the practice. It takes time, effort, experiential learning, and even mistakes to be successful. Doctors have high intellectual abilities. They must apply these abilities to

learning the business aspects of their practices. Combining a career in clinical endocrinology with a successful income stream is certainly possible and should be the goal of all practicing endocrinologists.

BIBLIOGRAPHY

Levy EG: *Private practice: what you don't learn as a resident,* Chevy Chase, 2007, Endocrine Society Press.

Levy EG: On entering private practice: a personal perspective. A guide for the young endocrinologist about to embark on a career in private practice, *Endocrinologist* 9:119, 1999.

CHAPTER 59

SLEEP AND ENDOCRINOLOGY

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Sleep medicine is a relatively new frontier, especially when intersected with endocrinology. This chapter covers normal human hormonal profiles associated with sleep-wake cycling, with attention to governing neuroendocrine mechanisms. It also reviews endocrine aspects of sleep deprivation and obstructive sleep apnea (OSA) and finishes with the health consequences of disruptive sleep and the improvements that result from successfully treating sleep abnormalities.

1. Why should endocrinologists concern themselves with sleep-wake cycles and circadian rhythmicity?

The 24-hour profile of nearly all pituitary hormones is related to the presence and quality of sleep. Stereotypical changes in nearly all hormonal and metabolic variables are observed in and around sleep, especially the transition to and from sleep. This fact challenges the assertion that hormone release is solely based on feedback loops. Understanding these reproducible changes in view of sleep-wake cycling is fundamental to recognizing normal and early abnormal endocrine processes. For example, appreciation of hormone changes during the day and night provides insight into a patient's laboratory values drawn at varied times through a 24-hour period.

2. Do sleep disorders cause endocrine disease, or does endocrine disease cause sleep disorders?

Both are true. Sleep experts have dubbed sleep symptoms as the "canary in the mine" for serious medical and psychological disease. Sleep quality can be a tool for assessment of disease. Additionally, sleep disorders are common in many endocrine diseases. For example, acromegalic patients are at risk for sleep apnea (also see question 26). Excessive androgens can worsen OSA, as can hypothyroidism. Thyrotoxicosis can contribute to debilitating insomnia, with profound daytime fatigue accompanying other presenting complaints. Disruptive sleep is now associated with increased risk for diabetes and obesity.

3. What are the stages of sleep?

Sleep is organized into non–rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep (Table 59-1). In classic teaching, NREM was organized into four stages. Typically, adults enter sleep through stage 1, which is characterized on electroencephalogram (EEG) by low-amplitude mixed-frequency waves. As one enters stage 2, the EEG displays predominantly sleep spindles and K complexes. The 2007 American Academy of Sleep Medicine (AASM) manual combines stages 3 and 4 into one stage, N3, or slow wave sleep (SWS). In SWS, the EEG slows and is associated with a progressive increase in the number of delta waves, which are characterized by increased amplitude and slowed frequency. It may take up to 100 minutes for the first NREM sleep cycle to finish, but once completed, it heralds the first REM period. Although REM is not defined by characteristic EEG patterns, the EEG can look like that of stage 1. The true hallmark of REM sleep, however, is rapid movement of the eyes in all directions compared with the slow eye movement (SEM) seen on electrooculography (EOG) in stage 1 sleep. Also defining REM is muscle atonia, usually manifested by low electromyography (EMG) tone and absence of chin muscle movement. The only somatic muscles working in REM are the extraocular muscles and the diaphragm.

TABLE 59-1. COMPARISON OF SLEEP STAGES

CHARACTERISTICS	NREM	REM
Responsiveness to stimuli	Reduced	Reduced to absent
Sympathetic activity	Reduced	Reduced or variable
Parasympathetic activity	Increased	Markedly increased
Eye movements	SEMs	REMs
Heart rate	Bradycardia	Tachycardia/bradycardia
Respiratory rate	Decreased	Variable; apneas can occur
Muscle tone	Reduced	Markedly decreased
Upper airway muscle tone	Reduced	Moderately decreased to absent
Cerebral blood flow	Reduced	Markedly increased
Other characteristics	Sleep walks Night Terrors	Dreams

Modified from Chokroverty S: *Disorders of sleep.* In American College of Physicians Medicine, editors: *Neurology,* 2006, WebMD Inc. Rights reserved.
NREMs, Nonrapid eye movements; *REMs,* rapid eye movements; *SEMs,* slow eye movements.

4. What is the progression of sleep stages in a usual night of sleep?

In the human, NREM sleep and REM sleep typically alternate in 90- to 120-minute cycles (Fig. 59-1). Four to six cycles occur during a normal sleep period, depending on the length of sleep. Each cycle is similar, with sleep onset initiating in stage 1, progressing to stage 2, then to SWS, and without significant arousal back to stage 2. In a typical night of adult sleep, stage 1 will comprise up to 5% of total sleep, stage 2 up to 50%, SWS up to 20%, and REM up to 25%. SWS is predominantly experienced in the first third of sleep and REM in the last half of sleep. Achieving predominant SWS or predominant REM sleep likely has neuroendocrine significance.

5. How do the sleep stages change during one's life span?

As we age, total sleep time decreases, and sleep begins to fragment (see Fig. 59-1). The time in sleep declines with age from 16 to 18 hours a day in a newborn to 9 to 10 hours in a 10 year old to 7 ½ to 8 hours in the average adult, to 6 hours in an 80 year old. A newborn's sleep is up to 50% REM sleep, which declines to 25% of sleep by adulthood. There is also a progressive decrease in SWS with aging. This loss of SWS also has endocrine repercussions because anterior pituitary hormone release is associated with SWS.

6. What are the fundamental changes in the nervous system in NREM versus REM sleep, and what other differences are noted between the phases of NREM and REM sleep (see Table 59-1)?

Sleep is characterized by reversible unconsciousness and variable responsiveness to stimuli. There is a shift in the autonomic nervous system (ANS) in sleep, with parasympathetic nervous system (PNS) predominance in NREM sleep and especially in REM sleep. Sympathetic nervous system (SNS) tone decreases in NREM sleep and usually in REM sleep, but sympathetic tone in REM sleep can be variable. In NREM sleep, there are decreases in respiratory rate (RR), heart rate (HR), blood pressure (BP), and cardiac output. Normal REM sleep is characterized by fluctuations in BP, HR, and RR. Dreaming and somatic muscle hypotonia to atonia (which includes reduced to absent upper airway muscle tone) are also REM sleep events. REM sleep can have a few periods of decreased or absent breathing. Cerebral metabolic rates for glucose and oxygen decrease during NREM sleep, but they increase to above waking levels in REM sleep.

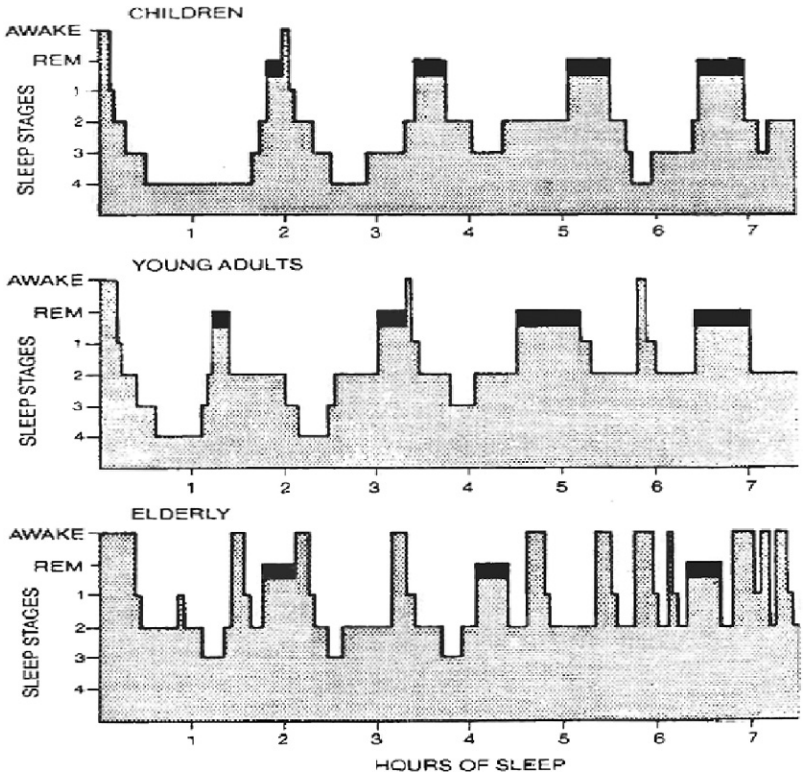

Figure 59-1. Stages of sleep. (From Kales AM, Kales JD: Sleep disorder. *N Engl J Med* 290:487–499, 1974. Used with permission, copyright 1974 Massachusetts Medical Society. All rights reserved.)

7. What are the two basic processes controlling sleep timing and quality and therefore contributing to anterior pituitary hormone cycling in a 24-hour period?

The first process is called *Process-C*, for circadian process (circadian from Latin "approximately a day"). It regulates the timing of sleep. Process-C is regulated in the hypothalamic suprachiasmatic nuclei (SCN), which receives input from environmental cues, the strongest of which is light. Process-C does not just coordinate hormone release; it is the broader of the two processes and transmits circadian output to coordinate behavioral, physiologic, and genetic rhythms. Research has uncovered *core molecular clock* machinery responsive to Process-C in most tissues. For further discussion of the circadian clock field, please see appropriate references.

The second process is sleep-wake homeostasis (SWH), also known as *Process-S*. SWH is dependent on Process-C but the circadian process is not dependent on SWH.

The SWH process relates the amount and intensity of sleep to the duration of prior wakefulness. So, if one has 24 hours with no sleep, there is increased pressure to sleep. The pressure to sleep is least when one is most rested. This pressure increases during the day and peaks just before midnight. The interaction of these two processes, Process-C and Process-S, influences the hypothalamic generators of releasing or inhibiting hormones that influence anterior pituitary function.

8. Discuss the basic neuroendocrinology contributing to Process-C.

The bilaterally paired SCN of the hypothalamus has been regarded as the sole master 24-hour pacemaker. Research since 2000, however, has shown the circadian process to be a decentralized hierarchy of oscillations within the SCN and downstream oscillations within the brain and other tissues. Interactions among several hypothalamic nuclei are also involved in Process-C. SCN timing is genetically determined to be slightly greater than 24 hours and must be modified or reset (synchronized) to the 24-hour day-night cycle by environmental stimuli (*zeitgebers*, German for time givers or time cues). SCN cytoarchitecture reveals functional organization. The SCN projects into the periventricular hypothalamic nucleus (PVH), mediating melatonin and corticosteroid synthesis. SCN projections to other hypothalamic nuclei are also critical to sleep-wake cycling.

9. What is the relationship of "entrainment" and "synchronization" with circadian rhythms?

Circadian rhythms are synchronized to the 24-hour day through the process of entrainment. The SCN is the neural pacemaker for biologic rhythms, but it is set at greater than 24 hours. Entrainment is the phase shift caused by daily stimuli. This phase shift corrects for the difference between the intrinsic period of the pacemaker (slightly greater than 24 hours) and the environmental cycle. For example, light is the dominant time cue, capable of inducing sleep phase or wake phase changes. Aside from photic stimuli, there are other nonphotic stimuli or time cues, such as exercise, social interaction, temperature variation, and even feeding, all capable of shifting circadian rhythms. The interaction between photic and nonphotic clues is complex. The magnitude of contributions to the human system remains to be determined. At this point, it can be said that stable entrainment likely reflects integration of both central and peripheral parameters.

10. How is melatonin involved in regulation of sleep and circadian rhythm?

Melatonin levels in the pineal gland are inhibited by light; they increase at sundown and peak at mid-darkness. This makes the neurohormone, melatonin, the chemical message communicating a photoperiod "fine tuning" to the autonomous master clock in the SCN. Melatonin also communicates a chemical message of light-dark cycling to the remainder of the body. This communication occurs through specific melatonin receptors. The MT1 and MT2 melatonin receptors are G-protein coupled, with characteristic seven transmembrane domains. These two receptor families are distributed throughout the brain and peripheral tissues, for example, in the SCN itself, the adipocytes, macrophages, platelets, gastrointestinal tract, liver, heart, kidneys, and adrenals. The melatonin receptors are only receptive at the light-/dark transitions, so exogenous administration of melatonin is most effective at these transitions.

11. Name the two hormones elevated early in sleep and the two hormones elevated late in sleep.

The SWS predominates in the first third of sleep, and REM predominates in the last half of sleep. Growth hormone (GH) and prolactin (PRL) are entrained to SWS (Table 59-2). Regardless of age and gender, most of the PRL released occurs when the individual is asleep. The nighttime GH and PRL

TABLE 59-2. PRIMARY INFLUENCE ON 24-HOUR VARIATION

HORMONE	SLEEP-WAKE HOMEOSTASIS	CIRCADIAN
Growth hormone	+++	+
PROLACTIN	+++	++
Thyroid-stimulating hormone	++	+++
Testosterone	++	++
Cortisol	+	+++

surges are associated with the first period of SWS. In fact, the GH surge immediately after sleep onset is the largest of the 24-hour period for both genders, although girls and women burst less than boys and men. Girls and women have two evening GH bursts; the first is before sleep onset late in evening, and a second is with SWS. Boys and men have few daytime GH pulses compared with girls and women. The surge of PRL and GH is lost if the patient goes sleepless and returns if the patient gets recovery sleep. It is the onset of sleep and not the time of day that triggers the release of these hormones. The hormones that increase later in sleep are cortisol and testosterone. Testosterone rises just after midnight and cortisol begins its rise at 2 AM, peaking at 6 to 9 AM. The timing and amount of REM sleep are related to the late-sleep rise of these two hormones in men. However, the 24-hour rhythm for both testosterone and cortisol is primarily controlled by circadian rhythmicity (Process-C) and not SWH (Process-S).

12. How does gonadotropin release change from youth to adulthood, and is the LH adulthood pattern of release solely responsible for testosterone release?

They vary with sleep according to gender and stage of maturity. Before puberty, there is daytime pulsatile gonadotropin release, which is augmented with sleep onset. One of the hallmarks of puberty for the child is increased nocturnal amplitude of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) pulses. Both Process-S and Process-C contribute to this nocturnal surge in pubertal children. As the pubescent boy enters adulthood, there is increased daytime LH as well, thus making the variation on a 24-hour cycle less apparent. Accumulating evidence in adult men indicates that the testosterone profile is significantly influenced by NREM-REM cycling. The nighttime LH surges of puberty dampen in height and decrease in frequency in adulthood. The early morning male testosterone rise starts with sleep onset and increases to maximum levels during last half of sleep (REM predominant). This surge of testosterone is different from that of cortisol, which is quiescent in early sleep. In addition, during the early phase of sleep, there is no corresponding LH surge. The characteristic nighttime LH bursts occur later on, in the last half of sleep. A testosterone surge was observed during adult daytime recovery sleep, and a testosterone decrease followed as the patient remained awake after the daytime recovery sleep. All this suggests that sleep itself, and not only the LH bursts, is contributing to testosterone release. The mechanisms for this increase are not yet known. The 24-hour testosterone profile and its response to sleep deprivation and daytime recovery sleep are more like PRL (Fig. 59-2). For example, when the sleep-deprived male internal medicine resident finally gets some sleep, his testosterone will surge during his recovery sleep; during the normal day and in one who has not slept, testosterone levels are on a decline. To take this example to clinical application, if low testosterone is found in an individual, it may be from sleep deprivation, OSA, or even shift work. It is fair to tell our patients to have their testosterone levels drawn first thing in the morning in a rested state, based on the observations that sleep increases testosterone, wakefulness decreases it, and the circadian influence may be less potent than SWH.

13. Is the LH pattern the same in women?

In women, plasma LH is significantly influenced by the menstrual cycle. However, some sleep modulation of LH levels occurs because the LH pulse frequency slows during sleep. In the early follicular and early luteal phases, the LH pulse amplitude actually increases, although the frequency decreases, and the nocturnal LH pulse frequency slowing becomes more evident. In middle and late follicular and luteal phases, this slowing is less apparent or absent. In postmenopausal women, FSH and LH levels are elevated without circadian variation.

14. Do the gonadal steroid hormones follow the LH and FSH changes mentioned in the earlier questions?

No. Gonadotropins have pulse amplitude and frequency that are not reflected in the gonadal steroids (i.e., gonadal steroids do not have similar pulsations). For pubertal girls, there is a daytime estradiol elevation. For pubescent boys, the testosterone increase coincides with elevation of the gonadotropins as described, with minimal testosterone levels in the late evening and highest levels in early

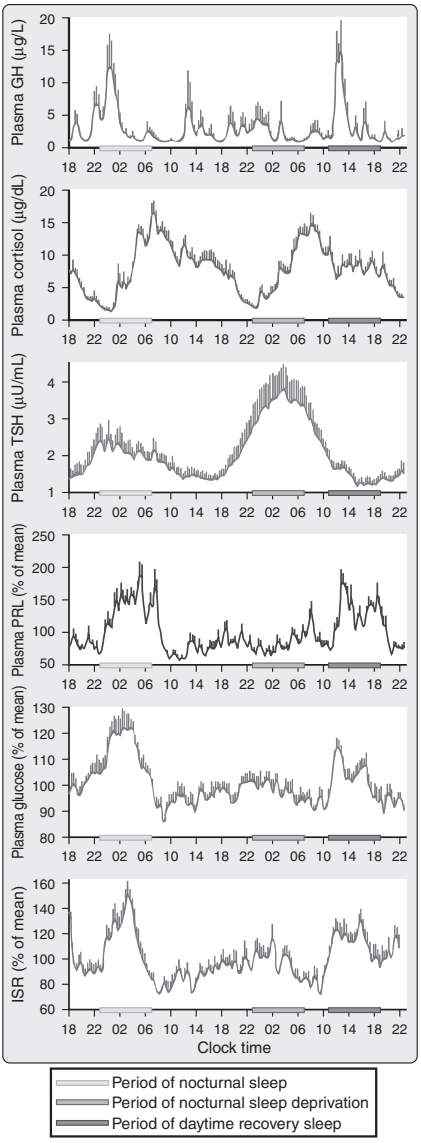

Figure 59-2. Mean 24-hour profiles of plasma growth hormone (GH), cortisol, thyrotropin (thyroid-stimulating hormone [TSH]), prolactin (PRL), glucose, and insulin secretion rates (ISR) in a group of eight healthy young men (20 to 27 years old) studied during a 53-hour period including 8 hours of nocturnal sleep, 28 hours of sleep deprivation, and 8 hours of daytime sleep. The *vertical bars* on the tracings represent the standard error of the mean (SEM) at each time point. The horizontal bars are the following periods: light gray is nighttime sleep, medium gray is nocturnal sleep deprivation, and darkest gray is daytime recovery sleep. Caloric intake was exclusively under the form of a constant glucose infusion. Shifted sleep was associated with an immediate shift of GH and PRL release. In contrast, the secretory profiles of cortisol and TSH remained synchronized to circadian time. Both sleep-dependent and circadian inputs can be recognized in the profiles of glucose and ISR. (From Van Cauter E, Tasali E: Endocrine physiology and relationship to sleep and sleep disturbances. In Kryger MH, Roth T, Dement WC, editors: *Principles and practice of sleep medicine,* ed 5, Philadelphia, 2011, Elsevier Saunders.)

morning. In postmenopausal women, the gonadotropins increase in an attempt to make estradiol, and there is no consistent circadian gonadotropin pattern.

15. What factors influence thyroid-stimulating hormone (TSH) release?

TSH release is primarily related to the circadian rhythm, although there is a strong Process-S influence. TSH release in healthy young male subjects shows an early evening circadian elevation and then a decline in levels shortly after sleep onset that continues until the nadir in late afternoon. The inhibitory influence of sleep on TSH is thought to occur in SWS. Therefore, clinicians may need to consider withholding therapeutic decisions on the sole basis of midafternoon TSH values. With acute sleep loss, TSH takes its usual early evening upturn at approximately 6 PM but continues to rise to nearly twice normal maximum through the middle of the usual sleep period. TSH normalizes when this sleep-deprived individual gets daytime recovery sleep. The loss of an inhibitory effect of sleep on the circadian TSH elevation may contribute to the elevated TSH values seen in acutely ill hospitalized patients.

16. Given that TSH and cortisol release are circadian, why are their levels not parallel through the night and day?

Essentially, TSH is influenced both by the quality and duration of sleep (SWH), as well as the time of day (circadian). However, corticotropin (adrenocorticotropic hormone [ACTH]) release is primarily influenced by the time of day. Cortisol is thus primarily influenced by the circadian process, with some influence from Process-S (see Table 59-2). The normal 24-hour cortisol profile does not have a significant change in shape when compared with those with daytime sleep deprivation in sequence with daytime recovery sleep. The wave shape of the two hormone profiles is highest in sleep compared with daytime; TSH starts to rise just before sleep onset and is highest in SWS, whereas cortisol starts its rise in REM-predominant sleep, followed by a burst on awakening. This burst is not seen with TSH. Therefore, a change to one's sleep-wake cycle influences the release of both hormones, but to different extents. In general, TSH fluctuations precede cortisol; cortisol peaks later, with bursts on awakening. TSH begins to rise under circadian rhythm, reaches maximum levels around midnight to 2 AM, and has a nadir at 1.5 mU/L by midafternoon. TSH then levels off, stopping a would-be ascent after sleep onset, thus reflecting sleep suppression of TSH. In a study of healthy young men during nocturnal sleep deprivation from 10 PM to 6 AM (SWS suppression removed), TSH more than doubled; that is, TSH went from its afternoon nadir of approximately 1.5 mU/L to a new peak of approximately 3.8 mU/L at 2 AM. In the follow-on recovery sleep (10 AM to 6 PM), TSH returned to a mean of 1.25 mU/L. Cortisol, conversely, begins its rise abruptly after midnight, peaks around 6 to 9 AM, and then declines throughout the day (reaching a nadir at midnight). It is well documented that interruptions to nocturnal sleep are associated with short-term TSH elevations. TSH levels normalize when normal nocturnal sleep is resumed. Repeated and prolonged nocturnal sleep interruptions result in elevations of cortisol.

17. Jet lag is not uncommon. How are some of its symptoms attributable to the observed changes in cortisol and TSH?

Jet lag is a sleep disorder arising from crossing time zones in a short period of time. Essentially, the circadian process becomes misaligned with the destination time zone. This is particularly true when flying east, which moves the clock ahead but the individual's circadian clock remains set the time zone of take off. This puts the individual at risk for insomnia. Persons with insomnia, whose ratio of total time asleep to total time in bed is less than 70% of normal, have significantly higher evening and early sleep cortisol levels. In a study of young adults whose circadian rhythms were perturbed by a flight from Europe to the United States, GH secretory patterns adjusted within a few days to the new sleep-wake cycle, but the cortisol levels remained dissociated for 2 weeks. This dissociation is thought to contribute to the symptoms of jet lag syndrome. Disruption of the hypothalamic-thyroid axis during prolonged flight has also been studied. The inhibitory effects of sleep on TSH secretion may not be present in prolonged air travel, thus translating to an overall TSH elevation, paralleled by a small, temporarily prolonged increase in triiodothyronine (T_3) levels. The study related the fatigue and discomfort of jet lag syndrome to the prolonged elevation of thyroid hormone, as well as to the desynchronization of multiple circadian rhythms.

18. How do circadian and sleep-wake processes influence glucose and insulin levels?

Glucose and insulin levels are influenced by both Process-C and SWH. Studies in normal adults demonstrated a 30% increase in glucose and a 60% increase in insulin levels during nocturnal sleep. In sleep deprivation, glucose and insulin secretion rates increase at habitual sleep time, although to a much lesser degree, a finding suggesting circadian modulation. In recovery sleep, however, secretion rates of both insulin and glucose markedly increase, a finding suggesting modulation by sleep itself.

19. How does aging change hormonal release?

Changes to sleep architecture with aging are thought to lead to hormonal changes. Normal aging is associated with loss of SWS and REM sleep, with increased sleep fragmentation (see Fig. 59-1). GH and PRL rise primarily in relation to the SWS of NREM sleep, whereas TSH, cortisol, and testosterone have primarily circadian increases. In younger men, there is a dose response relationship between SWS and GH secretion. For example, in 16- to 25-year-old boys and men, SWS is nearly 20% of the sleep period and tails off to 5% to 10% after age 40 years. This is associated with GH release during sleep of approximately 350 μg in the 16 to 25 year olds, but not more than 100 μg in individuals more than 35 years old. Most of the PRL released during a 24-hour period is during sleep regardless of gender. There is nearly a 50% decrement in nocturnal PRL release with aging. The extent of circadian changes in cortisol and TSH are less dramatic with aging. Day-night TSH fluctuations also dampen with age.

20. What is the definition of sleep-disordered breathing (SDB), and how does this differ from OSA?

Confusion arises when the terms sleep-related breathing disorders (SRBD), SDB, and OSA are used interchangeably in the literature and in sleep laboratory reports. SRBD and SDB are disease headings under which other diseases are arranged, much like chronic obstructive pulmonary disease (COPD) comprises a general reference for other specific disease entities. SRBD contains adult and pediatric central apnea syndromes and OSA syndromes. OSA, in contrast, is a specific disorder that is diagnosed with polysomnography (PSG). OSA can be suspected on the basis of complaints by the patient or his or her bed partner. Such complaints include the following: unintentional sleep episodes during wakefulness; daytime sleepiness; unrefreshing sleep; fatigue or insomnia; waking from sleep with breath holding, gasping, or choking; loud snoring; and breathing interruptions. The PSG criteria are not as stringent if they are associated with patient or bed partner complaints. Accompanied by complaints, the PSG must have five or more respiratory events per hour of sleep associated with increased respiratory effort. Without a history of complaints, the PSG instead must contain 15 or more such respiratory events. In either case, rendering the diagnosis of OSA includes ruling out current medical, neurologic, and/or substance abuse disorders. Some prescribed medications can also increase the risk for OSA.

21. What are respiratory events?

Respiratory events are apneas, hypopneas, and respiratory effort–related arousals (RERAs). An apneic episode is an airflow decrease of at least 90% from baseline that lasts at least 10 seconds (try holding your own breath for 10 seconds). Hypopnea is defined as 10 seconds of at least a 30% decrease in airflow, which results in 4% or more of desaturation on pulse oximetry. Conversely, RERA criteria should be sought if an observed event does not meet apnea or hypopnea criteria. RERA is defined as a sequence of breaths more than 10 seconds in duration that is associated with increased respiratory effort and results in arousal from sleep. The AASM directs apneas, hypopneas, and RERAs, if present, to be scored in the routine PSG interpretation. The average number of apneas and hypopneas in 1 hour is referred to as the apnea-hypopnea index (AHI). However, if RERAs are present, then the average number of apneas, hypopneas, and RERAs should be calculated. This is called the respiratory disturbance index (RDI). The AHI does not equal the RDI, even though the terms are sometimes used interchangeably—such an interchange could create confusion.

22. What is the prevalence of OSA?

The prevalence depends on the definition of OSA. The earliest epidemiologic investigations, primarily of white men, estimated that up to 4% had OSA (60%–90% were obese). The classic prevalence of OSA for adults 30 to 60 years old is 24% in men and 9% in women. In nonobese patients, genetic craniofacial features such as retrognathia are correlated with OSA. As OSA data mature, the prevalence may become unique to populations or ethnicities. In Asian nonobese male office workers, body mass index (BMI) and age were positively correlated, but weight was less so than in white, non-Asian subjects. Risk factors for OSA other than adiposity, such as pharyngeal narrowing, retrognathia or micrognathia, and pharyngeal collapsibility are thought to assume greater pathologic significance in Chinese populations.

23. Define sleep deprivation. How common is it?

Sleep deprivation can be acute or chronic. By definition, going without sleep for 24 hours is acute sleep loss, whereas sleeping less than 6 hours a night for 6 nights or greater is considered chronic sleep deprivation. People in industrialized nations are sleeping less. In the United States, for example, more than 30% of adults less than 64 years of age report sleeping less than 6 hours per night, a finding leaving no doubt that many patients are accumulating chronic sleep deprivation.

24. What are the key features of sleep deprivation versus sleep apnea?

In sleep deprivation, one does not sleep but breaths normally. In OSA, one sleeps but does not breathe well during sleep. The AASM classifies volitional sleep deprivation as behaviorally induced insufficient sleep syndrome as long as it is associated with daytime sleepiness. One can objectively measure excessive daytime sleepiness (EDS) with a standardized tool such as the Epworth Sleepiness Scale (ESS). In the ESS the interviewer gives the patient 8 different life circumstances, asking them to rate their own sleep pressure in that circumstance using a four point scale, 0-3, with 0 meaning the patient feels no sleep pressure in that circumstance, whereas a patient assessment of themselves of 3 in that circumstance means they feel significant sleep pressure in that circumstance. The cumulative score from all these 8 life circumstances [the patient must answer all eight questions] has been validated in clinical practice. An ESS score of greater than 9 is consistent with EDS. Patients with acute or chronic shortening of sleep resist the drive to sleep with no impairment of gas exchange. In OSA, there is a repetitive collapse of the upper airway, which induces apneic and hypopneic episodes despite persistent thoracic and abdominal respiratory effort. This leads to mechanical loading on the upper airway, chest wall, and diaphragm. What follows are hypoxia, hypercarbia, and a marked increase in adrenergic tone. OSA often leads to disruption or fragmentation of the usual sleep-wake cycle and endocrine responsiveness. Both can contribute to fatigue and daytime sleepiness. If EDS is secondary to sleep deprivation, the patient's sleep continuity is normal and is often associated with an increase in SWS. Recall the inhibitory influence of daytime recovery sleep on TSH; that is, if daytime recovery sleep follows nocturnal sleep deprivation, the inhibitory influence of sleep will decrease TSH (see question 15).

25. In view of increased SNS tone in OSA (see question 24), does the comorbidity of OSA interfere with the assessment of metanephrines and catecholamines when screening for pheochromocytoma?

Yes. OSA results in an appropriate release of catecholamines in response to physiologic stress or disease, just as myocardial infarctions, cerebral vascular accidents, and acute heart failure are associated with appropriate acute catecholamine increases. If a 24-hour urinary collection is performed in the setting of undiagnosed or poorly treated OSA, it would likely contain elevated metanephrine and catecholamine levels. This may falsely suggest a diagnosis of pheochromocytoma.

26. What endocrine diseases are associated with OSA?

The most common diseases are hypothyroidism, acromegaly, and polycystic ovary syndrome (PCOS). Although it was once thought that all patients with OSA had subclinical hypothyroidism, this has now been shown not to be the case. Evidence suggests that the prevalence of OSA in hypothyroid patients

is about 30%. OSA is reversible in most such patients once they are treated appropriately with thyroid hormone replacement. In one prospective study of nonobese, middle-aged men and women with newly diagnosed symptomatic hypothyroidism, 30% had OSA by PSG at study onset. Eighty-four percent of these subjects had reversal of OSA with normalization of their TSH. Finally, insulin levels and measures of glucose tolerance in PCOS are strongly correlated with the risk and severity of OSA. Additionally, among those women with PCOS who have normal glucose tolerance, insulin levels are significantly higher in those at high versus low OSA risk, independent of BMI. Therefore it is reasonable to assess measures of restorative sleep, sleep habits, and sleep behaviors in all patients with PCOS.

27. How is the sleep apnea of GH excess different from the sleep apnea of thyroid hormone deficiency?

GH excess is associated with a high proportion of central sleep apnea, whereas hypothyroidism is almost uniformly associated with OSA. Up to 60% of patients with acromegaly are eventually found to have sleep apnea by PSG studies. In one series, more than 30% had central sleep apnea. Endoscopy revealed little occlusive posterior tongue movement during sleep, so this is not from macroglossia. This assertion is further supported by the observation that these patients have lower arterial carbon dioxide levels while awake and have increased ventilatory responsiveness when compared with patients with OSA. The mechanism for central sleep apnea in these patients is not clear.

28. How does sleep deprivation influence glucose tolerance?

In one study, after 1 week of sleeping 4 hours per night, increases in postbreakfast insulin resistance were noted. During sleep restriction, glucose tolerance is nearly 40% worse when compared with a group with sleep extension. It is first-phase insulin release that has been found to be markedly reduced. When sleep-deprived individuals go into recovery sleep (sleeping during the day because of prior sleep deprivation), there are marked elevations of glucose and insulin levels, indicating that sleep also exerts modulatory influences on glucose regulation independent of the circadian rhythm.

29. What is the evidence linking OSA to abnormal glucose metabolism?

Snoring, sleep deprivation, and OSA have all been linked to type 2 diabetes mellitus (DM2) risk. Data from diverse patient populations suggest that OSA severity is a risk for DM2 development. At present, available data do not definitively prove direct causation. Snoring, in nonobese Asians and especially in those who are obese, has been independently associated with abnormal oral glucose tolerance tests and higher hemoglobin A_{1C} (HbA_{1C}) percentages. In epidemiologic studies, sleep quality has been positively correlated with the risk of developing DM2. Observational studies have shown that patients who report less than 6 hours of sleep per night have an increased prevalence of glucose intolerance and DM2. It was found that the duration of sleep (<6 and >8 hours per night) was predictive of an increased incidence of DM2. OSA, as diagnosed by PSG, is independently associated with abnormal glucose metabolism. Another article extended this independent association through rigorous assessment of the potential confounders of overweight and obesity. In this cross-sectional analysis of 2588 patients, it was shown that impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and occult diabetes are associated (but to different degrees) with OSA in both the normal-weight (BMI <25 kg/m^2) and overweight or obese subgroups. This finding suggests that individuals with OSA are at special risk for DM2 and its cardiovascular complications.

30. What are the two main mechanisms underlying the development of abnormal glucose metabolism in patients with sleep apnea?

The hallmark of OSA is airflow reduction, which is typically associated with intermittent hypoxemia, sleep fragmentation, and SNS stimulation. In animal studies, insulin sensitivity has been shown to vary with intermittent hypoxemia, independent of activation of the SNS. Additionally, it has been shown that in nondiabetic overweight to mildly obese males, every 4% decrease in oxygen saturation is associated with an odds ratio that approaches 2 for worsened glucose tolerance. Sleep fragmentation has been associated with abnormal glucose metabolism. In one study of healthy adults, selective

suppression of SWS (without decreasing total sleep time) was associated with decreases in insulin sensitivity by nearly 25%. This finding suggests that the low levels of SWS in elderly and obese persons may contribute to their increased incidence of DM2. In a study of consecutive adults with DM2, aged 41 to 77 years, BMI 20 to 57 kg/m^2, mild OSA was associated with a mean HbA_{1C} of 7.22% and severe OSA with an HbA_{1C} of almost 9.42%. After adjustments for age, gender, race, BMI, number of diabetic medications, level of exercise, years of diabetes, and total sleep time, the severity of OSA by AHI correlated with higher mean HbA_{1C} values.

31. With respect to causality, does the use of continuous positive airway pressure (CPAP) improve abnormal glucose metabolism parameters?

Yes. This is seen in nondiabetic patients, in nonobese diabetic patients, and in patients with poorly controlled diabetes. Caveat: In this body of work, the reader must discern from the trial whether there was a published measure of CPAP compliance. Trials reporting CPAP adherence definitions and those demonstrating no change in BMI during the study period do show improvement. A study of nondiabetic patients with moderate to severe OSA reported that CPAP significantly improved insulin sensitivity after only 2 days of treatment and that the improvement persisted at the 3-month follow-up with no significant changes in body weight. This influence was most pronounced in nonobese subjects. In contrast, this same research laboratory showed no improvement in insulin sensitivity in obese patients with DM2. In other trials, postprandial blood glucose levels improved most significantly after CPAP use in patients with DM2 and OSA.

32. How well are providers in diabetes clinics screening their patients for OSA? What are good tools for screening by history and physical examination?

A study of diabetic patients that used a validated clinical measurement and questionnaire to quantify OSA risk and sleepiness revealed that 56% of patients reported snoring, 29% had fatigue on awakening, and 34% reported feeling tired during wake time. The authors of the study concluded that 56% of those questioned were at high risk of OSA. This finding supports a call for greater vigilance in screening for OSA in diabetic patients, given the high prevalence of SDB found in that patient population. Certain screening tools may be helpful to this end. BMI is proportional to OSA risk; neck size greater than 17 inches is the most sensitive physical finding. Some craniofacial changes, such as retrognathia, also place a patient at high risk. A patient with OSA is often unaware of the neurocognitive changes that have developed slowly over time, and thus he or she may not volunteer a history consistent with OSA unless directly queried.

33. Does the effective use of CPAP in patients with OSA lead to weight loss?

Yes it does, apparently through two distinct mechanisms. First, patients with treated sleep apnea usually wake more rested and with a sense of improved vitality or energy. Once they are receiving treatment, patients with OSA have even been shown to exercise more. Second, treatment of sleep apnea results in normalization of serum leptin (from the Greek word *leptos*, meaning "thin"), the so-called satiety hormone. As discussed in the next question, leptin is suppressed during sleep deprivation and untreated sleep apnea.

34. What are the effects of sleep deprivation on leptin (satiety hormone) and ghrelin (hunger hormone)?

With sleep deprivation, leptin decreases and ghrelin (from the original root *ghre* meaning "to grow") increases. In longer than average sleep, leptin increases and ghrelin decreases. It has been documented that leptin release is blunted in sleep-deprived subjects and that over a 6-month period, sleep-deprived subjects gain an average of 10 pounds more than do rested subjects.

35. Is the testosterone decline observed with aging related to changes associated with the sleep pattern of aging?

It probably is. As discussed previously, aging is associated with less time in sleep and less time in SWS. In older men, LH pulses show lower amplitude but increased frequency. The sleep-related rise

TABLE 59-3. ANDROGEN CHANGES IN COMMON CIRCUMSTANCES

CONDITION	SHBG	TOTAL TESTOSTERONE	FREE TESTOSTERONE
Aging	↑	↓	↓
Obesity	↓	↓	Normal
OSA	↓	↓	↓

OSA, Obstructive sleep apnea; *SHBG,* sex hormone–binding globulin.

of testosterone is still seen, although the magnitude is less, and it is no longer associated with time to the first REM period.

36. How do androgens influence sleep?

Exogenous testosterone may worsen existing OSA or lead to changes associated with sleep apnea. One randomized controlled trial revealed that high-dose testosterone administration in hypogonadal, otherwise healthy, elderly men shortened total sleep time and worsened coexisting undiagnosed sleep apnea. Although there have been no substantiated reports of decreased cognition and impaired driving ability with hypogonadism, it is incumbent on the prescriber to screen patients for the possibility of undiagnosed OSA.

37. How does the testosterone panel change with OSA? Does OSA treatment influence the panel?

The androgen changes of OSA are distinct from those seen in aging and obesity (Table 59-3). In OSA, there are decreases in sex hormone–binding globulin and free and total testosterone without concomitant increases in gonadotropins. In fact, one study showed LH pulse disturbances with untreated OSA. Testosterone levels improve with OSA treatment, whether by CPAP or with uvulopalatopharyngoplasty. These findings point to a hypothalamic mechanism for low testosterone levels in untreated OSA.

KEY POINTS 1: SLEEP AND ENDOCRINOLOGY

1. Endocrine diseases associated with abnormal sleep include acromegaly, hyperthyroidism, hypothyroidism, and polycystic ovary syndrome.
2. Normal sleep preserves normal 24-hour hormone cycling. Sleep deprivation and obstructive sleep apnea can impair hormone cycling.
3. Mechanisms responsible for 24-hour hormone cycling are circadian, sleep-wake homeostatic, or both. These sleep mechanisms are complex, distinct, and superimposed on classic feedback loop mechanisms.
4. Sleep architecture changes with aging include less total sleep time and less slow wave sleep (SWS).
5. Obstructive sleep apnea (OSA) requires polysomnography for diagnosis.
6. Acute sleep loss eliminates the nocturnal thyroid-stimulating hormone suppression.
7. Sleep deprivation disrupts SWS, which is associated with decrease in hormone levels entrained to SWS (growth hormone and prolactin).

Continued

KEY POINTS 1: SLEEP AND ENDOCRINOLOGY—cont'd

8. Short-term sleep deprivation increases cortisol levels, suppresses insulin secretion, and diminishes glucose tolerance. It also decreases serum leptin and increases ghrelin levels such that sleep-deprived subjects gain weight compared to non-sleep-deprived subjects.
9. OSA results in less predictable hormone changes depending on the extent of sleep fragmentation, elevation of adrenergic tone, and hypoxia. It is associated with decreased insulin sensitivity and worsened glucose tolerance proportional to the severity of OSA.
10. Effective treatment of OSA improves sleep architecture, normalizes hormone release, and improves abnormal glucose metabolism.

WEBSITES

Sleep Research Society: www.sleepresearchsociety.org.

National Institutes of Health, National Heart Lung, and Blood Institute, National Center on Sleep Disorders Research: www.nhlbi.nih.gov/about/ncsdr/index.htm.

American Academy of Sleep Medicine: www.aasmnet.org.

BIBLIOGRAPHY

Aronsohn RS, Whitmore H, Van Cauter E, Tasali E. et al: Impact of untreated obstructive sleep apnea on glucose control in type 2 diabetes, *Am J Respir Crit Care Med* 181:507–513, 2010.

Aurora RN, Punjabi NM: Sleep apnea and metabolic dysfunction: cause or correlation? *Sleep Med Clin* 2:237–250, 2007.

Brzezinski A: Melatonin in humans, *N Engl J Med* 336:186–195, 1997.

Chokroverty S: Disorders of sleep, In American College of Physicians Medicine, editors: *Neurology,* 2006, WebMD Inc.

Czeiler CA and Buxton OM: The human circadian timing system and sleep wake regulation. In Kryger MH, Roth T, Dement WC, editors: *Principles and practice of sleep medicine,* ed 5, Philadelphia, 2011, Elsevier-Saunders, pp 402–419.

Gooley JJ, Saper CB: Anatomy of the mammalian circadian system. In Kryger MH, Roth T, Dement WC, editors: *Principles and practice of sleep medicine,* ed 5, Philadelphia, 2011, Elsevier Saunders, pp 376–389.

Guardiola-Lemaitre B, Quera-Salva MA: Melatonin and the regulation of sleep and circadian rhythms. In Kryger MH, Roth T, Dement WC, editors: *Principles and practice of sleep medicine,* ed 5, Philadelphia, 2011, Elsevier-Saunders, pp 420–430.

Iber C, Ancoli-Israel S, Chesson AL, et al: *The American Academy of Sleep Medicine manual for the scoring of sleep and associated events: rules, terminology and technical specifications,* Westchester, Ill, 2007, American Academy of Sleep Medicine.

Ip MS, Bing L, Lauder IJ, et al: A community study of sleep disordered breathing in middle-aged Chinese men in Hong Kong, *Chest* 119:62–69, 2001.

Jha A, Sharma SK, Tandon N, et al: Thyroxine replacement therapy reverses sleep disordered breathing patients with primary hypothyroidism, *Sleep Med* 7:55–61, 2006.

Johns, M.W. A new method for measuring daytime sleepiness: The Epworth sleepiness scale. *Sleep*, *14*, 540–545, 1991.

Jun J, Polotsky VY: Sleep disordered breathing and metabolic effects: evidence from animal models, *Sleep Med Clin* 2:263–277, 2007.

Kales A, Kales JD: Sleep disorders: recent findings in the diagnosis and treatment of disturbed sleep, *N Engl J Med* 290:487–499, 1974.

Kelly E, Cullen G, McGurk C, et al: Are we missing OSAS in the diabetic clinic? *Eur J Intern Med* 19:e13, 2008.

Knutson KL, Spiegel K, Penev P, Van Cauter E, et al: The metabolic consequences of sleep deprivation, *Sleep Med Rev* 11:163–178, 2007.

Liu PY, Caterson ID, Grunstein RR, Handelsman DJ, et al: Androgens, obesity and sleep-disordered breathing in men, *Endocrinol Metab Clin North Am* 36:349–363, 2007.

Parish JM, Adam T, Facchiano L, et al: Relationship of metabolic syndrome and obstructive sleep apnea, *J Clin Sleep Med* 3:467–472, 2007.

Punjabi NM, Sorkin JD, Katzel LI, et al: Sleep-disordered breathing and insulin resistance in middle-aged and overweight men, *Am J Respir Crit Care Med* 165:677–682, 2002.

Rosenwassen AM, Turek FW: Physiology of the mammalian circadian system. In Kryger MH, Roth T, Dement WC, editors: *Principles and practice of sleep medicine,* ed 5, Philadelphia, 2011, Elsevier Saunders, pp 390–401.
Sack RL: Jet lag, *N Engl J Med* 362:440–447, 2010.
Seicean S, Kirchner HL, Gottlieb DJ, et al: Sleep disordered breathing and impaired glucose metabolism in normal-weight and overweight/obese individuals: the Sleep Heart Health Study, *Diabetes Care* 31:1001–1006, 2008.
Spiegel K, Leproult R, L'hermite-Balériaux M, et al: Leptin levels are dependent on sleep duration: relationships of sympathovagal balance, carbohydrate regulation, cortisol, and thyrotropin, *J Clin Endocrinol Metab* 89:5762–5771, 2004.
Spiegel K, Leproult R, Van Cauter E, et al: Impact of sleep debt on metabolic and endocrine function, *Lancet* 354: 1435–1439, 1999.
Tasali E, Mokhlesi B, Van Cauter E, et al: Obstructive sleep apnea and type 2 diabetes: interacting epidemics, *Chest* 133:496–506, 2008.
Tasali E, Leproult R, Ehrmann DA, Van Cauter E, et al: Slow wave sleep and the risk of type 2 diabetes in humans, *Proc Natl Acad Sci USA* 105:1044–1049, 2008.
Tasali E, Van Cauter E, Ehrmann DA, et al: Relationships between sleep disordered breathing in glucose metabolism in polycystic ovarian syndrome, *J Clin Endocrinol Metab* 91:36–42, 2006.
Tuomilehto H, Peltonen M, Partinen M, et al: Sleep duration is associated with an increased risk for prevalence of type 2 diabetes in middle-aged women: the FIN-D2D survey, *Sleep Med* 9:221–227, 2008.
Turek FW: Chronobiology. In Kryger MH, Roth T, Dement WC, editors: *Principles and practice of sleep medicine,* ed 5, Philadelphia, 2011, Elsevier-Saunders.
Van Cauter E, Tasali E: Endocrine physiology and relationship to sleep and sleep disturbances. In Kryger MH, Roth T, Dement WC, editors: *Principles and practice of sleep medicine,* ed 5, Philadelphia, 2011, Elsevier-Saunders, pp 291–311.
Young WF, Jr: Endocrine hypertension. In Kronenberg HM, et al, editors: *Williams textbook of endocrinology,* ed 11, Philadelphia, 2008, Saunders.
Zee PC, Manthena P: The brain's master circadian clock: implications and opportunity for therapy of sleep disorders, *Sleep Med Rev* 11:59–70, 2007.

CHAPTER 60

ENDOCRINE CASE STUDIES

Michael T. McDermott

1. A 34-year-old woman has new-onset hypertension. Her serum potassium level is 2.7 mmol/L. Initial hormone screening shows a plasma aldosterone (PA) of 55 ng/dL (normal [nl], 1–16) and a plasma renin (PR) of 0.1 ng/mL/hour (nl, 0.15–2.33). What is the probable diagnosis?

The presence of hypertension and hypokalemia suggests primary aldosteronism (Conn syndrome). The PA level is elevated, the PR is suppressed, and the PA/PR ratio is greater than 20, supporting this diagnosis. The diagnosis can be confirmed by demonstrating the failure of PA to suppress after volume expansion with intravenous saline or oral salt loading. The next step is to establish whether the cause is an aldosterone-producing adenoma or bilateral adrenal hyperplasia. Abdominal computed tomography (CT) should be performed. Because of her young age and very low serum potassium level, an aldosterone-producing adrenal adenoma is the most likely cause. The treatment for an aldosterone-producing adrenal adenoma is surgery. Spironolactone should be given to control blood pressure and to normalize the serum potassium preoperatively (see Chapter 27).

2. A 32-year-old business executive develops amenorrhea. She has not recently lost weight but states that her job is very stressful. Evaluation reveals the following laboratory results: serum estradiol = 14 pg/mL (nl, 23–145), luteinizing hormone (LH) = 1.2 mIU/mL (nl, 2–15), follicle-stimulating hormone (FSH) = 1.5 mIU/mL (nl, 2–20), prolactin = 6.2 ng/mL (nl, 2–25), thyroid-stimulating hormone (TSH) = 1.2 mU/L (nl, 0.5–5.0), and a serum pregnancy test is negative. A magnetic resonance imaging (MRI) scan of her pituitary gland is normal. What is the probable diagnosis?

The patient has secondary amenorrhea with low estradiol and gonadotropin levels. This clinical picture is most consistent with hypothalamic amenorrhea, which may occur in women who exercise excessively or have stressful jobs. The disorder results from reduced gonadotropin-releasing hormone (GnRH) pulse frequency in the hypothalamus. Treatment consists of stress management and, if menses do not resume, estrogen replacement therapy (see Chapter 47).

3. A nulliparous 48-year-old woman presents with symptoms of thyrotoxicosis. She has a modest, nontender goiter and no exophthalmos. She takes no medications and has had no recent radiology procedures. The following results are found on thyroid evaluation: free thyroxine (T_4) = 3.5 ng/dL (nl, 0.8–1.8), TSH less than 0.1 mU/L, 24-hour radioactive iodine uptake (RAIU) = 1% (nl, 20%–35%), thyroglobulin = 35 ng/mL (nl, 2–20), and sedimentation rate = 10 mm/hour. What is the likely diagnosis?

The patient has clinical and biochemical thyrotoxicosis, but the RAIU is low. The differential diagnosis includes postpartum thyroiditis, silent thyroiditis, subacute thyroiditis, factitious thyrotoxicosis, and iodine-induced thyrotoxicosis. She has never been pregnant and denies medication use and recent iodine exposure. The nontender gland, elevated thyroglobulin, and normal sedimentation rate are most consistent with silent thyroiditis. A transient (1–3 months) thyrotoxic phase followed by a transient (1–3 months) hypothyroid phase is expected before the condition resolves; 20% of patients, however, remain hypothyroid. If symptomatic, the thyrotoxic phase is best treated with

beta-blockers, and the hypothyroid phase can be managed, if necessary, with levothyroxine (see Chapters 33 and 35).

4. A 38-year-old man has coronary artery disease, xanthomas of the Achilles tendons, and the following serum lipid profile: cholesterol = 482 mg/dL, triglyceride (TG) = 125 mg/dL, high-density lipoprotein (HDL) cholesterol = 42 mg/dL, and low-density lipoprotein (LDL) cholesterol = 415 mg/dL. What is the probable diagnosis?

Significant elevations of total cholesterol and LDL cholesterol, normal TG, tendon xanthomas, and premature coronary artery disease are most consistent with a diagnosis of heterozygous familial hypercholesterolemia. This disorder is usually the result of deficient or abnormal LDL receptors or an abnormal apoprotein B-100 molecule. Aggressive lipid lowering with a combination of statins, ezetimibe, bile acid resins, and niacin is needed. In many cases, LDL apheresis is also indicated (see Chapter 6).

5. A 28-year-old man presents because of infertility. He is found to have small, firm testes and gynecomastia. Laboratory testing shows the following abnormalities: testosterone = 206 ng/dL (nl, 300–1000), LH = 88 mIU/mL (nl, 2–12), and FSH = 95 mIU/mL (nl, 2–12). What is the likely diagnosis?

The patient has hypergonadotropic hypogonadism with small firm testes and gynecomastia, which is most consistent with a diagnosis of Klinefelter syndrome. Such patients usually have a 47XXY karyotype. Androgen replacement therapy is the treatment of choice (see Chapters 43 and 44).

6. A 38-year-old nurse presents in a stuporous state; the blood glucose level is 14 mg/dL. Additional blood is drawn, and the patient is quickly resuscitated with intravenous glucose. Further testing on the saved serum reveals the following: serum insulin = 45 μU/mL (nl, <22), C-peptide = 4.2 ng/mL (nl, 0.5–2.0), and proinsulin = 7 pmol/L (nl, <5). A sulfonylurea screen is negative. What is the probable diagnosis?

The patient has hyperinsulinemic hypoglycemia. The differential diagnosis includes insulinoma, surreptitious insulin injection, and oral sulfonylurea ingestion. The elevated serum C-peptide and proinsulin levels are most consistent with an insulinoma. After an appropriate localizing procedure, surgical removal is the treatment of choice (see Chapter 53).

7. A 28-year-old woman develops amenorrhea. She has type 1 diabetes mellitus. Further testing reveals the following serum hormone values: estradiol = 15 pg/mL (nl, 23–145), LH = 78 mIU/mL (nl, 2–15), FSH = 92 mIU/mL (nl, 2–20), prolactin = 12 ng/mL (nl, 2–25), TSH = 1.1 mU/L; a pregnancy test is negative. What is the most likely diagnosis?

The patient has secondary amenorrhea with low estradiol and elevated gonadotropin levels. In a patient with another autoimmune disease (type 1 diabetes mellitus), the most likely diagnosis is premature ovarian failure resulting from autoimmune ovarian destruction. Hormone replacement therapy is the treatment of choice (see Chapter 47).

8. A 34-year-old woman presents with galactorrhea, amenorrhea, headaches, fatigue, and weight gain. Laboratory evaluation reveals the following: prolactin = 58 ng/mL (nl, 2–25), free T_4 = 0.2 ng/dL (nl, 0.8–1.8), and TSH greater than 60 mU/L (nl, 0.5–5.0). She has an enlarged pituitary gland on MRI scan. What is the probable diagnosis?

The patient has moderately increased serum prolactin levels, pituitary enlargement, and severe primary hypothyroidism. Her entire clinical picture is most likely explained solely by the hypothyroidism, which is well known to cause secondary hypersecretion of prolactin and pituitary enlargement from thyrotroph hyperplasia. All abnormalities should resolve after adequate thyroid hormone replacement is established (see Chapters 20 and 47).

9. A 6-year-old girl has recently developed breast enlargement and some pubic hair. She has not complained of headaches and has had good health otherwise. Her older sister entered puberty at approximately 8 years of age. Her height is at the 90th percentile for her age, and her physical examination reveals Tanner stage III breast development and stage II pubic hair growth. Abdominal and pelvic examinations are normal. Laboratory tests show the following results: LH = 7 mIU/mL (nl, 2–15), FSH = 8 mIU/mL (nl, 2–20), prolactin = 6 ng/mL (nl, 2–25), TSH = 1.9 mU/L (nl, 0.5–5.0), and a normal pituitary MRI scan. Her bone age is 1.8 years ahead of the chronologic age. What is the probable diagnosis?

The patient has gonadotropin-dependent true precocious puberty. The etiology includes pituitary and hypothalamic tumors, but most cases in girls are idiopathic. The normal pituitary MRI points to a diagnosis of idiopathic precocious puberty. A long-acting GnRH analog should successfully arrest her premature development and allow her to enter puberty at a later, more appropriate time (see Chapter 43).

10. A 19-year-old man presents with excessive thirst and urination. Laboratory evaluation shows the following: serum glucose = 88 mg/dL, serum sodium = 146 mmol/L, serum osmolality = 298 mOsm/kg, and urine volume = 8800 mL/24 hour. A water deprivation test is performed, and it shows a urine osmolality of 90 mOsm/kg with no response to water deprivation and an increase in urine osmolality to 180 mOsm/kg after the administration of vasopressin. What is the likely diagnosis?

The patient has polyuria and polydipsia with maximally dilute urine. The differential diagnosis includes central diabetes insipidus, nephrogenic diabetes insipidus, and primary polydipsia. The lack of response to water deprivation and the more than 50% increase in urine osmolality after administration of vasopressin are most consistent with central diabetes insipidus. This may be caused by inflammatory or mass lesions in the hypothalamus but is often idiopathic. An MRI scan of the pituitary-hypothalamic region should be performed. The treatment of choice is intranasal or oral desmopressin (see Chapters 18 and 24).

11. A 25-year-old woman presents with a cushingoid appearance. The results of hormone testing are as follows: 24-hour urine cortisol = 318 μg (nl, 20–90), morning serum cortisol = 28 μg/dL (nl, 5–25), and morning plasma adrenocorticotropic hormone (ACTH) = 65 pg/mL (nl, 10–80). After an 8-mg oral bedtime dose of dexamethasone, the morning serum cortisol = 3 μg/dL. What is the probable diagnosis?

Cushingoid features and significantly elevated urinary cortisol excretion confirm the diagnosis of Cushing syndrome. The cause is usually an ACTH-secreting pituitary adenoma (65%–80%), ectopic production of ACTH (10%–15%), or a cortisol-producing adrenal adenoma (10%–15%). The normal plasma level of ACTH, which is inappropriate for the elevated serum cortisol level, and suppression of serum cortisol with high-dose dexamethasone are most consistent with a pituitary adenoma (Cushing's disease). This should be confirmed with an MRI scan of the pituitary gland and possibly inferior petrosal sinus sampling. Transsphenoidal surgical removal is the treatment of choice (see Chapter 23).

12. An 8-year-old boy with known adrenal insufficiency complains of paresthesias of the lips, hands, and feet and intermittent muscle cramps. He has positive Chvostek's and Trousseau's signs on examination. Results of blood testing are as follows: calcium = 6.2 mg/dL (nl, 8.5–10.2), phosphorus = 5.8 mg/dL (nl, 2.5–4.5), intact parathyroid hormone (PTH) = 3 pg/mL (nl, 10–65), and 25-hydroxyvitamin D = 42 ng/mL (nl, 30–100). What is the most likely diagnosis?

Hypocalcemia, hyperphosphatemia, and a low serum PTH level are diagnostic of primary hypoparathyroidism. This disorder, which is often autoimmune, may occur in association with adrenal insufficiency as part of the autoimmune polyendocrine syndrome type 1 (APS 1). Hypoparathyroidism must be treated with both calcium and calcitriol supplementation. Calcitriol is necessary because PTH, the missing

hormone, is necessary for normal renal conversion of 25-hydroxyvitamin D into 1,25-dihydroxyvitamin D, the active vitamin D metabolite that is necessary for normal intestinal calcium absorption. A thiazide diuretic is also often helpful to increase the serum calcium further and to reduce treatment-induced hypercalciuria (see Chapters 16 and 52).

13. A 52-year-old man has a personal and family history of early coronary artery disease, minimal alcohol consumption, and no xanthomas on examination. He has the following results on serum testing: cholesterol = 328 mg/dL, TG = 322 mg/dL, HDL = 35 mg/dL, LDL = 229 mg/dL, apoprotein B = 178 mg/dL (nl, 60–130), apoprotein E phenotype = E3/E3, TSH = 2.1 mU/L (nl, 0.1–4.5), and glucose = 85 mg/dL. What is the probable diagnosis?

The patient has elevations of both serum cholesterol and TG and no detected disorders that cause secondary dyslipidemia. The differential diagnosis includes familial combined hyperlipidemia and familial dysbetalipoproteinemia. The elevated level of apoprotein B and the normal apoprotein E phenotype are most consistent with familial combined hyperlipidemia. The top treatment priority is LDL reduction with a statin. After LDL cholesterol is lower than the National Cholesterol Education Program (NCEP) goal, persistent TG elevations should be addressed with the possible addition of a fibrate, niacin, or fish oils (see Chapter 6).

14. A 58-year-old man has recently developed diabetes mellitus, weight loss, and a skin rash that is most prominent on the buttocks; a dermatologist diagnoses this as necrolytic migratory erythema. What is the probable underlying diagnosis?

Diabetes mellitus, weight loss, and necrolytic migratory erythema are virtually diagnostic of a glucagon-secreting pancreatic endocrine tumor (glucagonoma). The diagnosis can be confirmed by finding an elevated serum level of glucagon. After appropriate localizing procedures, surgery is the treatment of choice, if possible. Chemotherapy should be considered for unresectable malignant tumors or tumor remnants (see Chapter 53).

15. A 29-year-old woman has asymptomatic hypercalcemia. Her mother and a sister also have hypercalcemia and have had failed neck explorations for presumed parathyroid tumors. Further testing results: serum calcium = 11.0 mg/dL (nl, 8.5–10.2), phosphorus = 3.0 mg/dL (nl, 2.4–4.5), creatinine = 0.9 mg/dL, intact PTH = 66 pg/mL (nl, 10–65), 25-hydroxyvitamin D = 42 ng/mL (nl, 30–100), 24-hour urine calcium = 13 mg (nl, 100–300), and creatinine = 1100 mg. What is the probable diagnosis?

Most patients with hypercalcemia and a mildly elevated serum PTH level have primary hyperparathyroidism. However, in this case, the very low urinary calcium excretion and family history of unsuccessful parathyroid surgical procedures point to a likely diagnosis of familial hypocalciuric hypercalcemia. The diagnosis is confirmed by finding a calcium/creatinine clearance ratio (urine calcium × serum creatinine/serum calcium × urine creatinine) of less than 0.01. This autosomal dominant disorder results from a heterozygous inactivating mutation in the gene that encodes the calcium sensor receptor. The mutant sensor receptors, present in parathyroid and renal tubular cells, have a raised threshold for calcium recognition. The result is a physiologic equilibrium, in which hypercalcemia coexists with mild elevations of PTH and low urinary calcium excretion. The disorder causes no morbidity and does not require treatment (see Chapters 13 and 14).

16. A 39-year-old human immunodeficiency virus (HIV)-positive man with *Pneumocystis carinii* pneumonia has the following serum thyroid hormone values: free T_4 = 0.8 ng/dL (nl, 0.8–1.8), total triiodothyronine (T_3) = 22 ng/dL (nl, 90–200), and TSH = 0.5 mU/L (nl, 0.5–5.0). What is the most likely endocrine diagnosis?

The very low T_3, low normal free T_4, and low normal TSH are most consistent with the euthyroid sick syndrome. This is not a primary thyroid disorder but is instead a set of circulating

thyroid hormone abnormalities that occur in the presence of nonthyroidal illnesses; it corrects when the underlying illness resolves. Treatment of the condition with thyroid hormone administration is not currently recommended, although this remains controversial (see Chapter 39).

17. An 18-year-old woman has not yet begun menstruating. She has a height of 56 inches, a small uterus, and no breast development. The results of hormone tests are as follows: estradiol = 8 pg/mL (nl, 23–145), LH = 105 mIU/mL (nl, 2–15), FSH = 120 mIU/mL (nl, 2–20), prolactin = 14 ng/mL (nl, 2–15), and TSH = 1.8 mU/L (nl, 0.5–5.0). What is the probable diagnosis?

Primary amenorrhea, short stature, low serum estradiol, and elevated gonadotropins are most consistent with a diagnosis of Turner syndrome. This disorder, characterized by ovarian dysgenesis, is associated with a 45XO karyotype. These patients should be given hormone replacement therapy with estrogen and progesterone. Growth hormone (GH) therapy should be considered because it improves longitudinal growth and final height (see Chapters 43 and 47).

18. A 62-year-old woman presents for evaluation of recent nephrolithiasis and low back pain. Her estimated calcium intake is 800 mg/day, and she takes no vitamins. Her physical examination is unremarkable. Spinal radiographs reveal a compression fracture of the second lumbar vertebra (L2). Laboratory evaluation shows the following: serum calcium = 13.0 mg/dL (nl, 8.5–10.5), phosphorus = 2.3 mg/dL (nl, 2.5–4.5), albumin = 4.4 g/dL (nl, 3.2–5.5), intact PTH = 72 pg/mL (nl, 11–54), and 24-hour urine calcium = 312 mg (nl, 100–300). What is the most likely diagnosis?

Hypercalcemia, hypophosphatemia, and elevated serum PTH levels are characteristic of primary hyperparathyroidism. Hyperparathyroidism is usually the result of a solitary parathyroid adenoma; familial cases and those associated with multiple endocrine neoplasia (MEN) syndromes more often have four-gland hyperplasia. Surgical indications include serum calcium levels greater than 1 mg/dL above the normal range, renal impairment, osteoporosis, age less than 50 years, or symptoms related to hyperparathyroidism. Observation alone or bisphosphonate therapy may be appropriate for patients with mild, asymptomatic disease or only mild bone loss. This patient should be referred for parathyroid surgery (see Chapter 14).

19. A 32-year-old woman presents with the recent onset of fatigue, palpitations, profuse sweating, and emotional lability. She gave birth to her second child 8 weeks ago. Her pulse is 100/minute, and she has mild lid retraction, a fine hand tremor, and a slightly enlarged, nontender thyroid gland. She is not breast-feeding her child. Laboratory tests are as follows: TSH less than 0.03 mU/L (nl, 0.5–5.0), free T_4 = 3.8 ng/dL (nl, 0.8–1.8), and RAIU less than 1% at 4 and 24 hours. What is the probable diagnosis?

Postpartum thyrotoxicosis is most often secondary to Graves' disease or postpartum thyroiditis. The RAIU will distinguish the two; it is high in Graves' disease and low in postpartum thyroiditis. RAIU is contraindicated in patients who are breast-feeding; in those cases, measurement of TSH receptor antibodies (TRAb) is often useful, being positive in Graves' disease and negative in postpartum thyroiditis. This patient has postpartum thyroiditis, a condition caused by lymphocytic inflammation with leakage of thyroid hormone from the inflamed gland. There is often a thyrotoxic phase (lasting 1–3 months) followed by a hypothyroid phase (lasting 1–3 months) and eventual return to euthyroidism, although nearly 20% remain permanently hypothyroid. Treatment consists of beta-blockers, if necessary, for symptom control in the thyrotoxic phase, and levothyroxine, if necessary, for symptom control in the hypothyroid phase and for those who remain permanently hypothyroid (see Chapters 33 and 35).

20. A 70-year-old man complains of a 1-year history of weakness, weight loss, and hand tremors. He has been treated with amiodarone for nearly 3 years for paroxysmal atrial flutter. Laboratory tests show the following: TSH less than 0.01 mU/L (nl, 0.5–5.0), free T_4 = 3.35 ng/dL (nl, 0.8–1.8), and RAIU = 2.7% at 6 hours and 4.1% at 24 hours. Thyroid scan showed patchy tracer uptake. What is the likely diagnosis?

This man has amiodarone-induced thyrotoxicosis (AIT). The condition occurs in up to 10% of patients using amiodarone, which has a very high iodine content. There are two subtypes: type 1 AIT results from iodine overload and occurs mainly in patients with underlying goiters; type 2 AIT results from amiodarone-induced thyroid follicular damage. Both are associated with a low RAIU. No tests reliably distinguish the two subtypes, although an underlying goiter and detectable RAIU are more common in type 1 AIT. Type 1 AIT is best treated with methimazole, whereas type 2 AIT responds better to steroid therapy. Difficult cases may require both these medications, dialysis, plasmapheresis, or thyroidectomy (see Chapter 33).

21. A 20-year-old man presents for failure to enter puberty. He has small, soft testes, no gynecomastia, normal visual fields, and decreased sense of smell. Laboratory evaluation is as follows: serum testosterone = 70 ng/dL (nl, 300–1000), LH = 2.0 mIU/mL (nl, 2–12), FSH = 1.6 mIU/mL (nl, 2–12), prolactin = 7 ng/mL (nl, 2–20), and TSH = 0.9 mU/L (nl, 0.5–5.0). An MRI scan of the pituitary gland is normal. What is the probable diagnosis?

This picture is most consistent with idiopathic hypogonadotropic hypogonadism, also known as Kallmann syndrome. This disorder is caused by a deficiency of GnRH, resulting from failure of fetal migration of the GnRH-secreting neurons from the olfactory placode to the hypothalamus. Mutations of the Kal gene have been detected in some patients. Maldevelopment of the olfactory lobe causes the associated anosmia. Androgen therapy is indicated to promote appropriate masculinization. When desired, these patients can also become fertile by receiving treatment with GnRH or gonadotropin preparations (see Chapters 43 and 44).

22. A 32-year-old man complains of impotence and retroorbital headaches intermittently for the past year. He is adopted and does not know his natural family history. He has bitemporal visual field loss, but his examination is otherwise normal. Laboratory tests reveal the following: serum calcium = 11.8 mg/dL (nl, 8.5–10.5), phosphorus = 2.5 mg/dL (nl, 2.5–4.5), albumin = 4.8 g/dL (nl, 3.2–5.5), intact PTH = 58 pg/mL (nl, 11–54), and prolactin = 2650 ng/mL (nl, 0–20). What is the likely diagnosis?

This patient has a prolactinoma, manifested by impotence, headaches, bitemporal hemianopsia, and a significantly elevated serum prolactin level. Hypercalcemia with an elevated serum PTH level indicates that he also has hyperparathyroidism. The MEN type 1 (MEN-1) syndrome, which consists of hyperparathyroidism, pituitary tumors, and pancreatic endocrine tumors, results from an inherited mutation in the Menin gene. This patient should be screened for gastrinoma by ordering a fasting serum gastrin and for insulinoma by measuring serum glucose, insulin, C-peptide, proinsulin, and beta-hydroxybutyrate following an overnight fast or during a prolonged supervised fast. After pituitary imaging studies, he should be treated with a dopamine agonist, transsphenoidal surgery, or both, and subsequently with parathyroid surgery (see Chapters 20 and 51).

23. A 52-year-old woman complains of a 1-year history of progressive fatigue, puffy eyes, dry skin, and mild weight gain. She had acromegaly treated with transsphenoidal surgery and radiation therapy 10 years ago. Physical examination shows normal visual fields, mild periorbital edema, and dry skin. Laboratory testing reveals the following: GH = 1.2 ng/mL (nl, < 2.0), insulin-like growth factor-I (IGF-I) = 258 ng/mL (nl, 182–380), TSH = 0.2 mU/L (nl, 0.5–5.0), and free T_4 = 0.5 ng/dL (nl, 0.8–1.8). What is the most likely cause of this patient's symptoms?

She has central hypothyroidism resulting from pituitary damage from the combined effects of surgery and radiation treatment of her pituitary tumor 10 years earlier. Such a lengthy delay in the development of this condition is not uncommon. The diagnosis of central hypothyroidism is based on the presence of

symptoms of thyroid hormone deficiency, a low serum free T_4, and a low or low-normal serum TSH. Treatment consists of levothyroxine replacement in doses sufficient to relieve symptoms and to maintain the serum free T_4 level in the midnormal or upper-normal range. Because TSH secretion is impaired, the serum TSH level cannot be used to monitor this patient's response to therapy. Assessment of her pituitary-adrenal axis is also indicated (see Chapters 18 and 34).

24. A 32-year-old woman complains of deep pain in both thighs. She was diagnosed as having type 1 diabetes mellitus at age 20 years. She currently has two to three bowel movements each day. Her menses are regular. Her diet is well balanced with adequate calcium intake, and she takes a multivitamin. Physical examination is normal. Laboratory studies show the following: serum calcium = 8.2 mg/dL (nl, 8.5–10.5), phosphorus = 2.3 mg/dL (nl, 2.5–4.5), alkaline phosphatase = 312 U/L (nl, 25–125), PTH = 155 pg/mL (nl, 11–54), and 25-hydroxyvitamin D = 7 ng/mL (nl, 30–100). Explain the findings in this patient, and suggest a probable underlying diagnosis.

Her biochemical profile of hypocalcemia, hypophosphatemia, elevated alkaline phosphatase, and significant secondary hyperparathyroidism suggests vitamin D deficiency, which is confirmed by the low serum 25-hydroxyvitamin D level. The elevated serum alkaline phosphatase suggests that the vitamin D deficiency has been sufficiently severe and prolonged to result in osteomalacia. Lactose intolerance can cause chronic diarrhea but seldom results in vitamin D and calcium malabsorption. Celiac disease (gluten sensitive enteropathy), which occurs with increased frequency in patients with type 1 diabetes mellitus, should be suspected. The diagnosis can be confirmed by the measurement of tissue transglutaminase antibodies or by a small bowel biopsy. The treatment is elimination of gluten (wheat, rye, barley, oats) from the diet and supplementation with calcium and vitamin D (see Chapter 11).

25. A 42-year-old man presents for evaluation of a skin rash that has recently developed. He has known type 2 diabetes mellitus. He drinks two to three alcoholic beverages several nights each week. Physical examination shows eruptive xanthomas (red papules with golden crowns) all over his body, most prominently on the buttocks, thighs, and forearms. Laboratory studies reveal the following: glucose = 310 mg/dL, hemoglobin A_{1C} (HbA_{1C}) = 12.9%, cholesterol = 1082 mg/dL, and TG = 8900 mg/dL. Discuss the cause and treatment of this lipid disorder

The patient has severely elevated serum TG. This condition usually results from combining a secondary cause of TG elevation (uncontrolled diabetes mellitus, excess alcohol use) with an inherited TG disorder (familial hypertriglyceridemia or familial combined hyperlipidemia). His LDL cholesterol cannot be assessed until the serum TG levels are less than 400 mg/dL. Because he is at high risk of developing acute pancreatitis, the priority is to lower his serum TG level quickly to less than 1000 mg/dL. This goal can be achieved most effectively with a temporary very low-fat (<5% fat) diet, blood glucose control, and discontinuation of alcohol. TG levels will fall by about 20% a day on this regimen. A fibrate or fish oil (or both) should then be added, and he should be switched to an American Heart Association diet. Diabetes control must be continued and further alcohol intake discouraged (see Chapter 6).

26. A 26-year-old woman requests to be tested for a type of thyroid cancer that has recently been found in her mother and two of five siblings. She notes that she has had intermittent headaches and palpitations for the past year. Her blood pressure is 164/102. She has a 1-cm, left-sided thyroid nodule without associated lymphadenopathy. Laboratory testing shows the following results: serum calcium = 11.2 mg/dL (nl, 8.5–10.5), phosphorus = 2.4 mg/dL (nl, 2.5–4.5), albumin = 4.5 g/dL (nl, 3.2–5.5), intact PTH = 55 pg/mL (nl, 11–54), calcitonin = 480 pg/mL (nl, 0–20), and 24-hour urine catecholamines = 1225 μg (nl, 0–200). Discuss her diagnosis and management.

The thyroid nodule, elevated serum calcitonin, and family history make medullary carcinoma of the thyroid (MCT) likely. Hypertension, headaches, palpitations, and high urinary catecholamines indicate

a probable pheochromocytoma. She also has hyperparathyroidism. MEN type 2A (MEN-2A) consists of MCT, pheochromocytoma, and hyperparathyroidism. It is an autosomal dominant syndrome that results from a germline mutation in the Ret gene. After alpha-blocker initiation and blood pressure control, treatment should consist of removal of the pheochromocytoma(s), followed by later removal of the abnormal thyroid and parathyroid glands. Screening at-risk family members for the Ret/MCT oncogene should also be performed (see Chapters 37 and 51).

27. A 68-year-old man complains of a 10-year history of progressive pain in the shins, knees, and left arm. He also notes progressive hearing loss. Physical examination reveals tenderness above the left elbow and enlarged, bowed shins. Bone scan shows intense uptake in both tibias and the left humerus. Skeletal radiographs show enlargement with multiple focal lytic and sclerotic areas in the tibias and the distal left humerus. Laboratory evaluation reveals serum calcium = 9.8 mg/dL (nl, 8.5–10.5) and alkaline phosphatase = 966 U/L (nl, 25–125). What is the probable diagnosis?

Bone pain and deformity, reduced hearing, and markedly elevated serum alkaline phosphatase levels suggest a diagnosis of Paget's disease. Intense radioisotope uptake on bone scanning supports this diagnosis, and the characteristic findings on skeletal radiographs confirm it. Treatment options include analgesics, intravenous bisphosphonates (zoledronic acid preferred), subcutaneous denosumab, and calcitonin, all of which may control but will not cure the disease (see Chapter 12).

28. A 19-year-old man has experienced fatigue, muscle weakness, and dizziness for the past 3 weeks. This morning he fainted when he went outdoors to exercise. His blood pressure is 95/60 mm Hg, and his pulse is 110. His skin is cool, dry, and tanned. His thyroid feels normal. Laboratory testing shows the following: hematocrit = 36%, glucose = 62 mg/dL, sodium = 120 mmol/L, potassium = 6.7 mmol/L, creatinine = 1.4 mg/dL, and blood urea nitrogen (BUN) = 36 mg/dL. What endocrine disorder should be considered and evaluated?

Hyponatremia with hyperkalemia always suggests primary adrenal insufficiency (Addison's disease). Fatigue, weakness, hypotension, tanned skin, anemia, azotemia, and hypoglycemia are also consistent with this diagnosis. The most common cause is autoimmune destruction of the adrenal glands. The diagnosis is made by a basal serum cortisol level lower than 3 μg/dL or by a cosyntropin stimulation test that shows a low basal serum cortisol level that fails to increase after ACTH administration. During an adrenal crisis, however, one does not have time to wait for the test results. When this diagnosis is suspected, one should draw blood for a serum cortisol measurement and then start treatment with intravenous fluids and glucocorticoids (hydrocortisone, 100 mg every 6–8 hours). Precipitating conditions should be actively sought and treated. After the patient is stable, he can be switched to oral hydrocortisone and fludrocortisone for chronic maintenance (see Chapter 30).

CHAPTER 61

FAMOUS PEOPLE WITH ENDOCRINE DISORDERS

Pratima Kumar, Kenneth J. Simcic†, and Michael T. McDermott

1. Name the former college basketball star from Gonzaga University who was diagnosed with type 1 diabetes at age 14 years.

Adam Morrison. After his final college season, Morrison shared college basketball's Player of the Year Award with J.J. Redick of Duke. He was then selected third overall in the 2006 National Basketball Association (NBA) draft by the Charlotte Bobcats.

2. This female track star recovered from Graves' disease and went on to win the title of "Fastest Woman in the World" at the 1992 Summer Olympics in Barcelona. Who is she?

Gail Devers. Devers repeated as champion in the women's 100 meters at the 1996 Olympics in Atlanta. She enjoyed remarkable longevity in her sport. In February 2007, at age 40 years, she won the 60-meter hurdles at the Melrose games with a time of 7.86 seconds.

3. Name the dwarf actor who gained fame for his role as Tattoo on the television series *Fantasy Island* (1977–1984).

Herve Villechaize (1943–1993). Villechaize's short stature was secondary to achondroplasia. His adult height was only 3 feet, 2 inches.

4. Television and film actress Mary Tyler Moore has what endocrine disorder?

Type 1 diabetes. Moore was diagnosed at age 33 years. Her diabetes has been complicated by retinopathy and recurrent foot infections.

5. George Bush and his wife Barbara were both diagnosed with Graves' disease during his presidency (1989–1993). How did the president's Graves' disease manifest clinically?

Atrial fibrillation. (Mrs. Bush's Graves' disease was also complicated by ophthalmopathy. In addition to radioactive iodine for her hyperthyroidism, she also required treatment with glucocorticoids and orbital radiation therapy for her eye disease.)

KEY POINTS 1

1. Because many endocrine disorders are common, it is not surprising that famous people have or have had endocrine disorders.
2. Most endocrine disorders are either curable or treatable.
3. Many famous people have accomplished great things despite their endocrine disorders.
4. The lives of these famous people can serve as sources of encouragement to patients who suffer from similar endocrine conditions.

†Deceased.

6. Pulitzer Prize–winning film critic Roger Ebert was diagnosed with what endocrine disorder at age 59 years?
Papillary thyroid cancer (treated with thyroidectomy and radioactive iodine). Ebert has a major risk factor for papillary thyroid cancer. As a child, he was given radiation treatment for an ear infection. He is unable to speak, but he uses a computer program to turn text into speech.

7. Name the acromegalic giant who played the character Jaws in the James Bond films *The Spy Who Loved Me* (1977) and *Moonraker* (1979).
Richard Kiel (Kiel is 7 feet, 2 inches tall).

8. Name the 2-foot, 8-inch, dwarf actor best known for his role as Mini-Me in the film *Austin Powers: The Spy Who Shagged Me* (1999).
Vern Troyer. Troyer's dwarfism is secondary to chondrodysplasia. He has had acting roles in more than 15 feature films.

9. Name the Chicago Bear NFL quarterback who developed type 1 diabetes in 2007.
Jay Cutler. He lost 35 pounds at the time of his diagnosis and has made Web videos for Lilly on diabetes.

10. Ancient Egyptian sculptures and paintings suggest that Tutankhamen (1357–1339 BC) and other pharaohs of the Eighteenth Egyptian Dynasty had what endocrine disorder?
Gynecomastia. Familial aromatase excess syndrome is a possible explanation for this historical finding.

11. What famous male ice skater overcame growth failure related to a childhood illness to win the gold medal at the 1984 Winter Olympics in Sarajevo?
Scott Hamilton. As a child, Hamilton suffered from Shwachman syndrome, a rare disorder of the pancreas. His adult height is 5 feet, 3 inches. Hamilton was also diagnosed with testicular cancer at age 38 years and with a craniopharyngioma at age 46 years.

12. How was Scott Hamilton's craniopharyngioma treated?
After a biopsy to confirm the diagnosis, Hamilton was treated with gamma knife radiosurgery.

13. Name the late professional wrestler (and actor) who was well known for his height and acromegalic facial features.
Andre "The Giant" Rousimoff (1947–1993).

14. Charles Sherwood Stratton (1838–1883) reached an adult height of only 3 feet, 4 inches. What was his circus name?
General Tom Thumb. In 1863, Stratton married fellow diminutive circus performer Lavinia Warren, whose height was only 2 feet, 8 inches.

15. Actress Catherine Bell, who starred as Lt. Col. Sarah "Mac" MacKenzie on the television series *JAG* (1995–2005), has been treated for what thyroid disorder?
Papillary thyroid cancer.

16. Oscar award–winning actress Halle Berry was diagnosed with what endocrine disorder at age 21 years?
Diabetes (probably type 1).

17. After successful treatment for Graves' disease, this professional golfer captained the United States team to the 1999 Ryder Cup in what has been called the greatest comeback in Ryder Cup history. Who is he?
Ben Crenshaw.

18. Vocalist Rod Stewart has had surgery for what endocrine disorder?
Thyroid cancer (most likely papillary). It took 9 months for Stewart's voice to recover from the surgery.

19. Ron Santo won six Golden Glove Awards and played in nine All Star games while playing third base for the Chicago Cubs. He was diagnosed with type 1 diabetes at what age?
Eighteen years, just after signing his first contract to play major league baseball. Since his retirement from baseball, Santo has suffered the following macrovascular complications of his diabetes: coronary artery disease, requiring a quadruple coronary artery bypass operation and implantation of an automatic cardiac defibrillator device, and bilateral below-knee amputations for peripheral vascular disease.

20. Name the 3-foot, 7-inch, 65-pound midget who batted one time for the St. Louis Browns on August 19, 1951.
Eddie Gaedel (1925–1961). Gaedel was walked on four pitches by Detroit Tigers' pitcher Bob Cain.

21. Gheorghe Muresan of the Washington Bullets is the tallest player in the history of the NBA (7 feet, 7 inches). What treatments has he received for his acromegaly and gigantism?
Transsphenoidal pituitary surgery, pituitary radiation, and somatostatin analog injections. (Note: Shaquille O'Neal is 7 feet, 1 inch tall.)

22. In his 6-year NBA career (Washington Bullets 1993–1997; New Jersey Nets 1998–2000), Muresan twice led the league in what category?
Field goal percentage (1995–1996 season: .584; 1996–1997 season: .604).

23. Regardless of acting ability, it seems that every famous giant gets an acting role in a movie. Gheorghe Muresan starred in what movie with Billy Crystal?
My Giant (1998).

24. The late actor Rondo "The Creeper" Hatton had severe acromegalic facial features. He played the villain in numerous horror films such as the *Pearl of Death* (1944), *House of Horrors* (1946), and *The Brute Man* (1946). How old was Hatton at the time of his death?
Hatton died of a myocardial infarction at age 51 years. At the time of his death, he also reportedly suffered from diabetes and loss of vision. All these conditions were probably sequelae of his untreated acromegaly.

25. Nicole Johnson was 24 years old when she was crowned Miss America 1999. At age 19, she was diagnosed with what endocrine disorder?
Type 1 diabetes.

26. Name the former chief justice of the U.S. Supreme Court who died of anaplastic thyroid cancer at age 80 years.
William Rehnquist. Rehnquist was diagnosed with anaplastic cancer in October 2004, and he died less than 1 year later, in September 2005.

27. Grammy award–winning vocalists Johnny Cash (1932–2003), Ella Fitzgerald (1917–1996), Waylon Jennings (1937–2002), and Luther Vandross (1951–2005) all died of complications of what endocrine disorder?
Type 2 diabetes.

28. Track star Carl Lewis competed in five consecutive Olympics. He is one of only three athletes who have won nine gold medals in an Olympic career. With what endocrine disorder was he diagnosed at age 35 years?
Primary hypothyroidism (secondary to Hashimoto's thyroiditis).

29. Name the American swimmer who was diagnosed with type 1 diabetes 18 months before he won two gold medals at the 2000 Olympics in Sydney, Australia.
Gary Hall, Jr.

30. Carla Overbeck, women's soccer star and captain of the 1996 U.S. gold medal Olympic team, was diagnosed with what endocrine disorder at age 32 years?
Graves' disease.

31. Based on a true story, the film *Lorenzo's Oil* (1992) portrays a family's struggle with what rare adrenal disorder?
Adrenoleukodystrophy. The film's main character, Lorenzo Odone, was diagnosed with this condition at age 5 years.

32. Despite his type 1 diabetes, this former National Hockey League star led the Philadelphia Flyers to back-to-back Stanley Cup championships in 1973 to 1974 and 1974 to 1975.
Bobby Clarke. Clarke's diabetes was diagnosed at age 13 years.

33. The demanding ironman Triathlon requires a 2.4-mile swim followed by a 112-mile bike ride and a 26.2-mile run. Name the three-time member of the U.S. National Team for Long Course Triathlon who was diagnosed with type 1 diabetes at age 24 years.
Jay Hewitt. Hewitt began competing in the Triathlon after his diagnosis of diabetes.

34. Name the Supreme Court justice who has type 1 diabetes.
Justice Sonia Sotomayor was diagnosed with type 1 diabetes at age 7 years. She went to Princeton University and earned a law degree from Yale. She became the first Latina Supreme Court justice in 2009.

TOP SECRETS

1. Although type 1 diabetes is a serious disease, athletes with this condition have been able to compete and succeed at the professional level in almost every sport.
2. The accomplishments of track star Gail Devers emphasize the excellent prognosis of properly treated Graves' disease.
3. Perhaps the most fascinating of all endocrine disorders are the disorders of growth. This explains why dwarfs and giants have been so popular as circus performers and movie actors.
4. The curability of most thyroid cancers is illustrated by the lives of Rod Stewart, Catherine Bell, and Roger Ebert.
5. The high mortality of untreated acromegaly is illustrated by the short lives of wrestler Andre "The Giant" Rousimoff and actor Rondo Hatton.

BIBLIOGRAPHY

D'Arrigo T: Hot shot NBA rookie Adam Morrison scores with control, *Diab Forecast February*:42–45, 2007.
Dawson LY: Skating at the cutting edge: Bobby Clarke, *Diab Forecast March*:6–19, 1994.
Drimmer F: *Very special people*. New York, 1991, Carol Publishing Group.
Falcon M, Shoop SA: *Roger Ebert reviews his thyroid cancer (April 5, 2002)*. USA Today, March 20, 2003. Retrieved from: www.usatoday.com/news/health/spotlight/2002/03/20-ebert.htm.
Famousheights.com: www.famousheights.com, 2003.
Ford-Martin P: *Famous people who have diabetes*. Retrieved from: www.diabetes.about.com//cs/diabetesfame.
Jay Cutler Foundation: www.jaycutlersix.com/news.
Lerner BH: *When illness goes public*, Baltimore, 2006, Johns Hopkins University Press.
Mandernach M: Short hitter, long memory, *Sports Illustrated* 2:5, 1996.
Mazur M: Here she is, Miss America, *Diab Forecast July*:49–51, 1999.
Montville L: Giant, *Sports Illustrated* 2:50–56, 1995.
Paulshock BZ: Tutankhamen and his brothers: familial gynecomastia in the Eighteenth Dynasty, *JAMA* 244:160–164, 1980.
Shomon M: *Famous people with thyroid conditions*. Retrieved from: www.thyroid.about.com/cs/famouspeople.
USA Today (June 21, 2011): *Sotomayor opens up about her diabetes*. Retrieved from: http://usatoday30.usatoday.com/news/washington/judicial/supremecourtjustices/2011-06-21-sotomayor-diabetes-court_n.htm
http://www.endocrineweb.com/conditions/thyroid/celebrities-thyroid-disorders
www.imdb.com/name/nmo613837/

INTERESTING ENDOCRINE FACTS AND FIGURES

CHAPTER 62

Michael T. McDermott

1. Who is the tallest man on record?

The man with the greatest medically documented height was Robert Wadlow of Alton, Illinois. He was 8 feet, 11.1 inches tall and weighed 439 pounds when he died in 1940 at age 22 years; he was 7 feet, 1.75 inches at age 13 years. His condition was the result of a growth hormone–secreting pituitary tumor that developed before closure of the skeletal epiphyseal plates (gigantism). The tallest currently living man is Xi Shun of China, who stands 7 feet, 8.95 inches tall.

2. Name the tallest woman on record.

Zeng Jinlian of Hunan Province, China, is the tallest woman on record. She was 8 feet, 1.75 inches just before her death at age 17 years in 1982 and had been 7 feet, 1.5 inches tall at age 13 years. She also had a growth hormone–secreting tumor that developed during childhood.

3. How tall was the shortest man on record?

Gul Mohammed of India was measured at 22.5 inches (57 cm) tall in 1990; he died in 1997. The shortest currently living man is Younis Edwan of Jordan, who is 25.5 inches (65 cm) tall.

4. Who is the shortest woman on record?

The shortest adult woman on record was Pauline Musters of the Netherlands. She was 23.2 inches tall and weighed 9 pounds shortly before her death at age 19 years in 1895. Because of her relatively normal proportions, she is believed to have had pituitary growth hormone deficiency, although growth hormone assays were clearly not available in 1895.

5. Who had the most variable adult stature?

Adam Rainer of Austria was a 3-feet, 10.45-inch dwarf at age 21 years but rapidly grew into a 7-foot, 1.75-inch, giant at age 32 years in 1931. He was 7 feet, 8 inches tall when he died in 1950 at age 51 years.

6. Which is the tallest tribe in Africa?

The Watusi (or Tutsi) tribe of Sudan, Rwanda, Burundi, and Central African Republic are the tallest in the world. The men average 6 feet, 5 inches, and the women average 5 feet, 10 inches. Their tall stature is believed to be a genetic adaptation.

7. Which is the shortest tribe?

The Mbuti pygmies of central Africa have the lowest mean height. The men average 4 feet, 6 inches, and the women 4 feet, 5 inches. Their short stature is thought to result from genetic resistance to growth hormone, possibly secondary to deficient growth hormone receptors.

8. Who was the heaviest man on record?

Jon Brower Minnoch of Bainbridge Island, Washington, was 6 feet, 1 inch tall and weighed approximately 1400 pounds at age 37 years, when he was admitted to the hospital with congestive heart failure. He remained in the hospital for 2 years on a 1200-calorie diet and was discharged at 476 pounds; his weight loss of 924 pounds is also a record. He weighed 798 pounds when he died at age 42 years in 1983. His wife weighed 110 pounds.

9. How much did the heaviest woman on record weigh?

The heaviest woman on record was Rosalie Bradford, who weighed 1199 pounds in 1987. She also holds the record for weight loss, having shed 917 pounds over the subsequent 7 years.

10. What is the greatest rate of weight gain ever recorded?

Arthur Knorr of the United States gained 294 pounds during the last 6 months of his life; this is an average weight gain of 1.6 pounds a day. Given that a pound of fat has about 3500 kcal, this represents an excess intake (above caloric expenditures) of 5600 kcal a day. Doris James holds the record for women, by having gained 328 pounds in the last year of her life (3150 kcal/day excess) before she died at age 38 years, weighing 675 pounds.

11. What is the largest recorded waist size?

Walter Hudson of New York, who stood 5 feet, 10 inches tall, had a peak weight of 1197 pounds and a waist size of 119 inches.

12. Who are the heaviest twins on record?

Billy McCrary and Benny McCrary of Hendersonville, North Carolina, weighed 743 and 723 pounds, respectively. Both had 84-inch waists. One brother died in a motorcycle accident, but the other is alive at the time of this printing.

13. What is the longest anyone has ever survived without food or water?

Andreas Mihavecz of Austria was put in jail in 1979. The guards forgot about him and gave him no food or water for 18 days, after which he was found still alive, but barely.

14. What is the greatest known number of children born to one woman in a lifetime?

A peasant woman from Shuya, east of Moscow, Russia, gave birth to 69 children from 1725 to 1765. She had 27 pregnancies, producing 16 pairs of twins, 7 sets of triplets, and 4 sets of quadruplets. Sixty-seven of the children survived infancy. Her husband had 18 more children with a second wife.

15. Who is the oldest known woman to give birth?

Adriana Emilia Illiescu of Romania gave birth to a daughter by cesarean section in 2005, at age 66 years, 230 days. Donna Maas of California, the oldest woman to give birth to twins, delivered twin boys by cesarean section in 2004 at age 57 years, 286 days.

16. What is the highest reported number of multiple births for a single gestation?

Ten births (decaplets) were reported in Brazil (1946), China (1936), and Spain (1924). Nine births (nonuplets) were recorded in Australia (1971), Philadelphia (1972), and Bangladesh (1977). The largest number to survive a multiple gestation is seven (septuplets), which has happened on three occasions; the mothers were Bobby McCaughey of Nebraska (1997), Nikem Chukwu of Texas (1998), and Hasna Mohammed Humair of Saudi Arabia (1998).

17. What is the highest single birth weight ever recorded?

Anna Bates, living in Seville, Ohio, gave birth to a 23-pound, 12-ounce (10.8 kg) baby boy who died 11 hours later in 1879. Anna was 7 feet, 5.5 inches tall. Carmelina Fedele of Italy gave birth in 1955 to the largest surviving baby, who weighed 22 pounds, 8 ounces (10.2 kg).

18. What is the oldest age to which a human has been documented to live?

Jeanne Louise Calment of Arles, France, lived to be 122 years, 164 days old. She died on August 4, 1997. The oldest man was Shigechiyo Izumi of Japan, who lived to be 120 years, 237 days old before he died in 1986.

19. What is the highest blood glucose level ever reported?

A 12-year-old boy with new-onset diabetes mellitus was still conscious when he was discovered to have a blood glucose level of 2350 mg/dL in 1995.

20. What is the record for most kidney stones produced by one individual?

Don Winfield of Canada passed 3711 kidney stones over a 15-year period (1986–2001).

21. What is the largest tumor ever reported?

A 328-lb ovarian cyst was removed from a woman in Texas in 1905.

22. What is the longest hair ever recorded?

Hoo Sateow of Thailand had his hair measured at 16 feet, 11 inches in 1997. He had not cut his hair for 70 years.

23. What is the record distance walked by an individual in 24 hours?

The record for men is 142.25 miles, by Jesse Castenda of the United States in 1976. The record for women is 131.27 miles, by Annie Van der Meer-Timmerman of the Netherlands in 1986. The 24-hour record for an individual in a wheelchair is 77.58 miles, by Nik Nikzaban of Canada in 2000.

24. Did King David of Israel have an endocrine disorder?

"When King David was old and advanced in years, though they spread covers over him, he could not keep warm. His servants therefore said to him, 'Let a young virgin be sought to attend you, lord king, and to nurse you. If she sleeps with your royal majesty, you will be kept warm.' . . . The maiden, who was very beautiful, nursed the king and cared for him, but the king did not have relations with her" (I Kings 1:1–4). Some speculate that King David was afflicted with hypothyroidism.

25. What endocrine disorder could Goliath of Gath have had?

Goliath of Gath, who was killed by a stone from David's sling (I Samuel 17:1–51), probably stood about 6 feet, 10 inches. His tall stature may have resulted from a growth hormone–secreting pituitary tumor. Others add that the ease with which David's stone became embedded in Goliath's skull may have been the result of hyperparathyroidism, and his bizarre behavior may have resulted from hypoglycemia caused by an insulinoma. Goliath may thus have had the earliest known case of multiple endocrine neoplasia type 1 syndrome.

26. What endocrine disorder did President John F. Kennedy have?

Kennedy had primary adrenal insufficiency—Addison's disease. He was sustained throughout the later years of his life and his presidency by therapy with oral glucocorticoids.

WEBSITE

Guinness World Records: www.guinnessworldrecords.com.

BIBLIOGRAPHY

Baumann G, Shaw MN, Merimee TJ: Low levels of high affinity growth hormone-binding protein in African Pygmies, *N Engl J Med* 320:1705–1709, 1989.

In Farlan D, editor: *The Guinness book of world records,* New York, 1991, Bantam Books.

In Folkard C, editor: *The Guinness book of world records,* New York, 2003, Bantam Books.

In Glenday C, editor: *The Guinness book of world records,* New York, 2007, Bantam Books.

The New American Bible, Camden, NJ, 1971, Catholic Publishers, Thomas Nelson, Inc.