Endocrinology and Metabolism Topics

Disorders of Glucose Metabolism

Diabetes Mellitus

Diabetes mellitus is a chronic metabolic disease characterized by elevated plasma glucose levels as a consequence of insulin deficiency, impaired action of insulin secondary to insulin resistance, or a combination of both abnormalities. Prediabetes is defined as elevated plasma glucose levels below the diagnostic criteria for diabetes, but above the normal range.

Screening for Diabetes Mellitus

Patients with diabetes mellitus may exhibit classic symptoms (polyuria, polydipsia, polyphagia), or more commonly, they can be asymptomatic. Diabetes screening may detect an early asymptomatic phase. Current guidelines do not recommend routine screening for type 1 diabetes as there is no consistent evidence that early treatment during the asymptomatic stage prevents progression of the disease. Similarly, it has not been firmly established that screening improves clinical outcomes in type 2 diabetes. However, microvascular and macrovascular disease can be present at the time of diagnosis of type 2 diabetes, which is indicative of ongoing organ damage during the asymptomatic phase. Furthermore, there is evidence that the microvascular and macrovascular disease associated

with type 2 diabetes may be reduced with improved glucose control early in the disease course and that treatment of prediabetes may delay the onset of type 2 diabetes. In 2008, the U.S. Preventive Services Task Force (USPSTF) recommended screening for type 2 diabetes only in asymptomatic adults with a sustained blood pressure level (treated or untreated) greater than 135/80 mm Hg. Updated USPSTF draft guidelines from 2014 have expanded screening recommendations to all adults in primary care settings with risk factors for the development of diabetes (Table 1). In contrast, the American Diabetes Association (ADA) recommends screening for type 2 diabetes based on BMI (≥25) with additional risk factors, including a history of gestational diabetes, or age (≥45 years).

Table 1. OPEN IN NEW WINDOW Screening Guidelines for Type 2 Diabetes Mellitus in Asymptomatic Adults

	ADA	USPSTF
Screening criteria	**BMI ≥25[a] and at least one additional risk factor:** Physical inactivity First-degree relative with diabetes High-risk race/ethnicity (black, Latino, Native American, Asian American,	**2008 guidelines:** Sustained BP >135/80 mm Hg treated or untreated **2014 updated draft:** Screening of adults in primary care settings with at least one of the following risk factors for IFG, IGT, or type 2 diabetes mellitus: Age ≥45 years Overweight or obese First-degree relative with diabetes History of GDM History of polycystic ovary syndrome High-risk race/ethnicity (black, American Indian/Alaska Native, Asian American, Hispanic/Latino, and Native Hawaiian/Pacific Islander)

Table 1. OPEN IN NEW WINDOW Screening Guidelines for Type 2 Diabetes Mellitus in Asymptomatic Adults

	ADA	USPSTF
	Pacific Islander) Delivery of a baby weighing >4.1 kg (9 lb) History of GDM Hypertension (≥140/90 mm Hg or on antihypertensive medication) HDL cholesterol <35 mg/dL (0.90 mmol/L) and/or triglyceride level >250 mg/dL (2.82 mmol/L) Polycystic ovary syndrome Hemoglobin A_{1c} ≥5.7%, IGT, or IFG on previous testing Other	

Table 1. OPEN IN NEW WINDOW Screening Guidelines for Type 2 Diabetes Mellitus in Asymptomatic Adults

	ADA	USPSTF
	conditions associated with insulin resistance (severe obesity, acanthosis nigricans) History of CVD	
Additional screening criteria	All patients age 45 years or older	Patients age 45 years or younger with any of the other risk factors in the screening criteria
Additional screening considerations	Use of glucocorticoids or antipsychotics	—
Screening intervals	3-year intervals if results are normal. Yearly testing if prediabetes (hemoglobin A_{1c} between 5.7% and 6.5%, IGT, IFG) is	3-year intervals if low-risk and normal plasma glucose values. In high-risk adults or those with near abnormal test values, yearly testing may be beneficial.

Table 1. OPEN IN NEW WINDOW Screening Guidelines for Type 2 Diabetes Mellitus in Asymptomatic Adults

	ADA	USPSTF
	diagnosed.	

- [a]At-risk BMI may be lower in some ethnic groups.
- ADA = American Diabetes Association; BP = blood pressure; CVD = cardiovascular disease; GDM = gestational diabetes mellitus; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; USPSTF = U.S. Preventive Services Task Force.
- Data from American Diabetes Association. Classification and diagnosis of diabetes. Sec. 2. *In* Standards of Medical Care in Diabetes-2015. Diabetes Care 2015;38 Suppl 1:S8-16. PMID: 25537714

Diagnostic Criteria for Diabetes Mellitus

Related Questions

Question 51

Question 57

Prediabetes and diabetes can be diagnosed based on the elevated results from one of the following screening tests repeated on two separate occasions: fasting plasma glucose (FPG), 2-hour postprandial glucose during an oral glucose tolerance test (OGTT), or hemoglobin A_{1c}(**Table 2**). A random plasma glucose level greater than or equal to 200 mg/dL (11.1 mmol/L) with classic hyperglycemic symptoms is diagnostic of diabetes and does not warrant repeat measurement. The diabetes screening tests have several advantages and disadvantages to consider. FPG is cheaper and more readily available in most countries compared with hemoglobin A_{1c}, but the requirement for overnight fasting can be problematic. OGTT best reflects the pathophysiology of diabetes by identifying postprandial hyperglycemia secondary to pancreatic beta-cell deficiency; however, the test is time-intensive. Hemoglobin A_{1c} testing is more convenient with no fasting requirement, is unaffected by acute stress or illness, and provides an accurate reflection of the average plasma glucose over the previous 3 months. By contrast, hemoglobin A_{1c} testing can miss

early glucose abnormalities, such as postprandial hyperglycemia. Another disadvantage is its decreased reliability in the setting of anemia, hemoglobinopathies, or kidney or liver disease. Furthermore, conditions that affect the turnover of erythrocytes, such as anemias/hemoglobinopathies and pregnancy, can affect the reliability of hemoglobin A_{1c}.

Table 2. OPEN IN NEW WINDOW Diagnostic Criteria for Diabetes Mellitus [a]

Test	Normal Range	Increased Risk for Diabetes (Prediabetes)	Diabetes
Random plasma glucose	—	—	Classic hyperglycemic symptoms plus a random plasma glucose ≥200 mg/dL (11.1 mmol/L)
Fasting plasma glucose[b]	<100 mg/dL (5.6 mmol/L)	100-125 mg/dL (5.6-6.9 mmol/L)	≥126 mg/dL (7.0 mmol/L)
Plasma glucose during a 2-hour 75-g OGTT	<140 mg/dL (7.8 mmol/L)	140-199 mg/dL (7.8-11.0 mmol/L)	≥200 mg/dL (11.1 mmol/L)
Hemoglobin A_{1c}	<5.7%	5.7%-6.4%	≥6.5%

- OGTT = oral glucose tolerance test.

- [a]In the absence of hyperglycemic symptoms, an abnormal fasting plasma glucose, OGTT, or hemoglobin A_{1c} should be confirmed by repeat testing. The same test should be used when repeating the measurement for confirmation. If two different tests are performed and only one has abnormal results, the American Diabetes Association recommends repeating the test with the abnormal results.
- [b]Fasting for at least 8 hours.
- Data from American Diabetes Association. (2) Classification and diagnosis of diabetes. Diabetes Care 2015 Jan;38 Suppl:S8-S16. PMID: 25537714

Classification of Diabetes Mellitus

Categories for classification of diabetes encompass a range of insulin abnormalities, including absolute or relative insulin deficiency, insulin resistance, or a combination of these abnormalities (**Table 3**).

Insulin Deficiency

Type 1 Diabetes Mellitus

Related Questions

Question 63

Question 83

Type 1 diabetes occurs in the setting of insulin deficiency. It accounts for 5% of diagnosed diabetes cases. The underlying mechanism is destruction of insulin-producing pancreatic beta cells, which can be autoimmune-mediated, idiopathic, or acquired.

Autoimmune-mediated type 1 diabetes mellitus can result from a combination of genetic, environmental, and autoimmune factors. There is a strong association between type 1 diabetes and specific HLA antigens. One or more precipitating events, such as viral infections, can trigger the autoimmune process of beta-cell destruction in genetically susceptible persons. Autoantibodies (one or more) can be present at the time of diagnosis, including antibodies to the following: islet cells, glutamic acid decarboxylase (GAD65), tyrosine phosphatases IA-2 and IA-2β, insulin, and zinc transporter autoantibodies. Measurements of autoantibodies to GAD65 and IA-2 are recommended for initial confirmation as both of these assays are highly automated. In addition, autoantibodies to GAD65 persist longer than those to islet cells after the development of diabetes.

Autoimmune-mediated type 1 diabetes has classically been considered a disease of children and young, thin adults, although it can occur at any age or BMI range. The initial presentation can range from modest elevations in plasma glucose levels to diabetic ketoacidosis (DKA). The time course for beta-cell destruction is also variable, although it is frequently more rapid in children compared with adults. Upon initiation of insulin therapy for type 1 diabetes, the remaining functioning pancreatic beta cells may temporarily regain the ability to produce some insulin during a "honeymoon" phase lasting several weeks to many months, although this is not an adequate or sustained effect. Insulin therapy is therefore recommended during the honeymoon phase to reduce the metabolic stress on the functioning beta cells to preserve any residual function for as long as possible. Late autoimmune diabetes in adults (LADA) presents in patients with autoantibodies to pancreatic beta-cell antigens and beta-cell destruction who did not require insulin initially but eventually progressed to an insulin requirement. Patients with autoimmune-mediated type 1 diabetes are at an increased risk to develop other autoimmune diseases, such as thyroiditis and celiac disease most commonly. Thus, screening for associated autoimmune diseases should be considered at the time of diagnosis and/or the development of signs and symptoms. Consensus on the frequency and effectiveness of repeat screening for associated autoimmune diseases is lacking.

Idiopathic type 1 diabetes can present with relative insulin deficiency and episodic DKA without evidence for autoimmunity. There is a strong genetic history of diabetes, and Asian and African ancestry appears to be a predisposing factor.

Acquired type 1 diabetes can be caused by diseases affecting the exocrine pancreas, infections, or drugs. Diffuse damage to the pancreas and beta cells or impaired insulin secretion with subsequent insulin deficiency occurs in these scenarios.

Key Points

- Prediabetes and diabetes mellitus can be diagnosed based on the elevated results from one of the following screening tests repeated on two separate occasions: fasting plasma glucose, 2-hour postprandial glucose during an oral glucose tolerance test, or hemoglobin A_{1c}.

- Measurements of autoantibodies to GAD65 and IA-2 are recommended for initial confirmation of autoimmune-mediated type 1 diabetes mellitus.

Insulin Resistance

Insulin resistance is characterized by the inability of the peripheral cells to utilize insulin effectively, with a compensatory increase in the amount of insulin secreted by the pancreatic beta cells in response to hyperglycemia. The pancreas exhibits a relative insulin deficiency when it cannot produce enough insulin to overcome the hyperglycemia. Obesity predisposes to the development of insulin resistance.

Metabolic Syndrome

Metabolic syndrome is the coexistence of a group of risk factors that increases a person's probability for the development of type 2 diabetes mellitus and cardiovascular disease (CVD). In addition to impaired glucose metabolism, these risk factors include central body obesity, hypertension, and hyperlipidemia (**Table 4**). Metabolic syndrome increases the relative risk of developing CVD by twofold and diabetes by fivefold, although it is not clear whether the combination of factors associated with metabolic syndrome imparts a greater risk than that attributable to each individual risk factor present. In the presence of one or more risk factors for metabolic syndrome, the Endocrine Society recommends a 3-year screening interval for the metabolic syndrome components including waist circumference, fasting lipid profile, fasting plasma glucose, and blood pressure. Calculation of the 10-year CVD risk is recommended in persons with metabolic syndrome to determine the need for lifestyle modifications and therapeutic interventions to prevent or delay progression to type 2 diabetes or CVD. The Framingham Risk Score and the new Pooled Cohort Equation from the American College of Cardiology/American Heart Association are frequently used within the United States to assess CVD risk.

Table 4. OPEN IN NEW WINDOW AHA/NHLBI Criteria for the Definition of the Metabolic Syndrome

Clinical Criteria (Must meet at least 3 of the 5 criteria)	Qualifying Measurements
Waist circumference[a]	Men 40 in (102 cm)[b]
	Women 35 in (89 cm)[c]
Fasting TG	≥150 mg/dL (1.7 mmol/L) or
	Drug therapy targeting increased TG
HDL cholesterol	Men <40 mg/dL (1.0 mmol/L)
	Women <50 mg/dL (1.3 mmol/L) or
	Drug therapy targeting decreased HDL
Blood pressure	Systolic ≥130 mm Hg or
	Diastolic ≥85 mm Hg or

Table 4. OPEN IN NEW WINDOW AHA/NHLBI Criteria for the Definition of the Metabolic Syndrome

Clinical Criteria (Must meet at least 3 of the 5 criteria)	Qualifying Measurements
Fasting glucose	Drug therapy for hypertension
	Blood glucose ≥100 mg/dL (5.6 mmol/L) or
	Drug therapy for increased glucose

- AHA = American Heart Association; HDL = high-density lipoprotein cholesterol; NHLBI = National Heart, Lung, and Blood Institute; TG = triglycerides.
- [a]Some individuals with minimally elevated waist circumference measurements [e.g., (men 37-39 in or 94-99 cm) or (women 31-34 in or 79-86 cm)] may still be at risk for type 2 diabetes or cardiovascular disease and will benefit from lifestyle interventions.
- [b]A lower waist circumference of 35 in (89 cm) should be used for Asian American men.
- [c]A lower waist circumference of 31 in (79 cm) should be used for Asian American women.
- Data from Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement: Executive Summary. Circulation. 2005 Oct 25;112(17):2735-52. PMID: 16157765

Type 2 Diabetes Mellitus

Related Question

Question 6

Type 2 diabetes mellitus accounts for most (90%-95%) diagnosed diabetes cases. It affects 10.9 million (26.9%) of adults in the United States aged 65 years or older. Asian Americans, American Indians, Alaska Natives, Hispanics, and non-Hispanic black persons are at an increased risk for developing diabetes compared with non-Hispanic white persons. The

etiology of type 2 diabetes is likely multifactorial. There is often a strong family history of type 2 diabetes among first-degree relatives, although the specific genes responsible for the glucose abnormalities remain unidentified.

Insulin resistance from obesity in the setting of relative insulin deficiency contributes to the development of type 2 diabetes in the majority of patients. The degree of hyperglycemia depends on the extent of beta-cell function, which can decline over time.

Type 2 diabetes generally has an insidious onset of prolonged asymptomatic hyperglycemia. Most patients do not present with the classic symptoms of polydipsia, polyphagia, or polyuria. Patients with type 2 diabetes may present first with macrovascular or microvascular changes. Although type 2 diabetes is often considered an adult disease, the incidence is increasing along with obesity rates in children and adolescents.

Residual insulin production from the beta cells is insufficient to control glucose adequately, but it is able to suppress lipolysis for most persons with type 2 diabetes. Under extreme metabolic stress, such as an illness, some patients with type 2 diabetes cannot suppress lipolysis and present with DKA. Ketosis-prone patients with type 2 diabetes are more likely to be overweight or obese, middle-aged, male, and of black or Latino ethnicity. Insulin use during the time of metabolic stress can often restore the beta cells from the glucose toxicity with a return to diet, exercise, and oral hypoglycemic agents for glucose control. Prior to switching from insulin to oral therapy, pancreatic beta-cell function should be assessed with fasting C-peptide and glucose measurements.

Lifestyle modifications alone or combined with therapeutic interventions can prevent or delay the development of type 2 diabetes in high-risk persons. Lifestyle modifications are a cost-effective intervention. Several randomized controlled trials provide evidence that diet changes, increased daily exercise, and weight loss targets of 5% to 7% can significantly decrease the risk of developing type 2 diabetes in persons with prediabetes by 41% to 58%. Additionally, metformin has been shown to reduce the risk of diabetes in patients with prediabetes, although this effect was not as robust as lifestyle interventions. In the setting of impaired glucose tolerance, impaired fasting glucose values, or hemoglobin A_{1c} values

between 5.7% and 6.4%, the ADA recommends considering metformin for prevention of type 2 diabetes.

Additional therapeutic agents, such as lipase inhibitors, α-glucosidase inhibitors, and thiazolidinediones, have been evaluated to delay or prevent type 2 diabetes; however, the effectiveness, cost, and potential side effects must be considered before implementation (Table 5).

Table 5. OPEN IN NEW WINDOW Strategies to Prevent or Delay Onset of Type 2 Diabetes Mellitus

Intervention	Effectiveness
Diet and exercise	Sustained weight loss of 7%, with at least 150 minutes of moderate exercise per week, shown to delay onset of diabetes by up to 3 years
Smoking cessation	Modestly effective as long as it does not cause weight gain, but is always recommended
Bariatric surgery	Effective if used in morbidly obese persons (BMI >40)
Metformin[a]	Shown to delay onset of diabetes by up to 3 years
Lipase inhibitors (orlistat)	Shown to delay onset of diabetes by up to 3 years
α-Glucosidase inhibitors (acarbose, voglibose)	Shown to delay onset of diabetes by up to 3 years

Table 5. OPEN IN NEW WINDOW Strategies to Prevent or Delay Onset of Type 2 Diabetes Mellitus

Intervention	Effectiveness
Thiazolidinediones (troglitazone, rosiglitazone, pioglitazone)	Shown to delay onset of diabetes by up to 3 years
Insulin and insulin secretagogues (sulfonylureas, meglitinides)	Ineffective
ACE inhibitors and angiotensin receptor blockers	Ineffective
Estrogen-progestin	Modest effect only

- [a]Preferred.

Key Points

- Lifestyle modifications are a cost-effective intervention that has been proven to decrease the risk of patients with prediabetes developing type 2 diabetes by 41% to 58%.
- In high-risk persons, the American Diabetes Association recommends considering metformin for prevention of type 2 diabetes, particularly in patients who are younger than 60 years of age, have a BMI greater than 35, or have a history of gestational diabetes.

Gestational Diabetes Mellitus

Relative insulin deficiency during the increased insulin resistance associated with pregnancy can result in the development of gestational diabetes mellitus. Pregnant women at high risk for developing gestational diabetes include those from certain racial or ethnic groups

(Hispanic/Latino Americans, blacks, and American Indians), overweight or obese women, women older than 25 years of age, and women with a strong family history of type 2 diabetes. An estimated 2% to 10% of pregnant women have gestational diabetes. Complications related to gestational diabetes include miscarriage, fetal deformities, large for gestational age infants, macrosomia, preeclampsia, complications during labor and delivery, increased perinatal complications, and mortality. Complication risk is on a continuum with increasing hyperglycemia.

Disagreement exists among consensus groups regarding the definition, screening methods, and diagnostic criteria for gestational diabetes. High-risk pregnant women should be screened for overt diabetes at the initial prenatal visit using criteria for nonpregnant women, according to the International Association of Diabetes and Pregnancy Study Group (IADPSG) and the ADA. In the absence of overt diabetes at the initial office visit, diabetes screening should occur between 24 and 28 weeks' gestation. Once a diagnosis of gestational diabetes is made, glucose monitoring should be performed at least four times daily initially, to include fasting and 1-hour or 2-hour postprandial values. Postprandial hyperglycemia in pregnancy may predict worse fetal outcomes and complications.

Lifestyle interventions and/or pharmacologic agents should be implemented when glucose goals for gestational diabetes are not met. Nutrition requirements for gestational diabetes should allow for appropriate maternal weight gain for normal fetal growth while obtaining goal glucose values. A moderate exercise program is recommended for glycemic control.

Insulin has traditionally been the mainstay of therapy for gestational diabetes when glycemic goals are not met with diet and exercise. Off-label use of metformin and glyburide in pregnancy has been studied and there appears to be equivalence in efficacy with insulin; however, long-term safety data are lacking.

Gestational diabetes resolves after pregnancy for most women; however, the risk of developing type 2 diabetes is 5% to 10% after delivery and 35% to 60% in the subsequent 10 to 20 years. The ADA recommends diabetes screening for women with a history of

gestational diabetes using standard criteria at 6 to 12 weeks postpartum and every 3 years thereafter.

Key Points

- Lifestyle interventions should be implemented to meet glycemic goals in women with gestational diabetes; however, when these are not met, insulin should be initiated.
- For women with a history of gestational diabetes, diabetes screening using standard criteria should occur at 6 to 12 weeks postpartum and every 3 years thereafter.

Uncommon Types of Diabetes Mellitus

Genetic defects in beta-cell function and insulin action cause some uncommon forms of diabetes (see **Table 3**). Maturity-onset diabetes of the young (MODY) is an autosomal dominant monogenetic defect that affects beta-cell function but not insulin action. MODY should be suspected in non-obese patients with a strong family history for diabetes when the onset of diabetes occurs before 25 years of age in the absence of autoantibodies. Genetic defects in insulin action cause insulin resistance with varying degrees of hyperglycemia, as seen with congenital lipodystrophy.

Table 3. OPEN IN NEW WINDOW Classification of Diabetes Mellitus

Insulin Deficiency[a]
Immune-mediated
Type 1 diabetes
LADA
Rare forms: “stiff man” syndrome, anti-insulin receptor antibodies

Table 3. OPEN IN NEW WINDOW Classification of Diabetes Mellitus

Insulin Deficiency[a]
Idiopathic (seronegative)
Acquired
Diseases of the exocrine pancreas: pancreatitis, trauma/pancreatectomy, neoplasia, cystic fibrosis, hemochromatosis, fibrocalculous, pancreatopathy
Infections: congenital rubella
Drug-related: Vacor (rat poison), intravenous pentamidine
Insulin Resistance
Type 2 Diabetes[b]
Ketosis prone[c]
Other or Rare Types
Genetic defects in beta-cell function (including six distinct MODY syndromes)
Genetic defects in insulin action

Table 3. OPEN IN NEW WINDOW Classification of Diabetes Mellitus

Insulin Deficiency[a]
Endocrinopathies:
(acromegaly, Cushing syndrome, glucagonoma, pheochromocytoma, hyperthyroidism)[d]
(somatostatinoma, aldosteronoma)[e]
Drug-related:
(glucocorticoids, thiazides, β-blockers, diazoxide, tacrolimus, cyclosporine, niacin, HIV protease inhibitors, atypic antipsychotics [clozapine, olanzapine])[f]
Genetic syndromes:
Down syndrome[g]
Wolfram syndrome (DIDMOAD)[h]
(Klinefelter, Turner, and Prader-Willi syndromes; myotonic dystrophy)[d]

- DIDMOAD = diabetes insipidus, diabetes mellitus, optic atrophy, and deafness; LADA = late autoimmune diabetes in adults; MODY = maturity-onset diabetes of the young.
- [a]Beta-cell destruction usually leading to absolute insulin deficiency.
- [b]Insulin resistance with progressive relative insulin deficiency.
- [c]More common in nonwhite patients who present with diabetic ketoacidosis but become non-insulin dependent over time.
- [d]Impaired insulin action.

- [e]Impaired insulin secretion.
- [f]Impaired insulin secretion, impaired insulin action or altered hepatic glucose metabolism.
- [g]Insulin deficiency, immune-mediated.
- [h]Insulin deficiency.

Several endocrinopathies can impair insulin action or secretion as a consequence of excess hormone production. Conditions such as Cushing syndrome and pheochromocytoma decrease the action of insulin secondary to excess cortisol and epinephrine, respectively. The hypokalemia induced by hyperaldosteronism can inhibit the secretion of insulin.

Management of Diabetes Mellitus

The most effective management of diabetes mellitus includes a multidisciplinary approach, including patient education and support, engaging patients in their care and decision making, lifestyle modifications with diet and exercise, reduced caloric intake for overweight and obese patients, and pharmacologic therapies when necessary to meet individualized glycemic goals (Table 6).

Patient Education

Diabetes self-management education (DSME) and diabetes self-management support (DSMS) are recommended at the time of diagnosis of prediabetes or diabetes and throughout the lifetime of the patient. DSMS is an individualized plan that provides opportunities for educational and motivational support for diabetes self-management. DSME and DSMS jointly provide an opportunity for collaboration between the patient and health care providers to assess educational needs and abilities, develop personal treatment goals, learn self-management skills, and provide ongoing psychosocial and clinical support. Improved outcomes and reduced costs have been associated with DSME and DSMS.

Self-Monitoring of Blood Glucose Related Questions

Question 4

Question 53

Question 69

Blood glucose monitoring can involve a variety of modalities, including self-monitoring of blood glucose (SMBG), hemoglobin A_{1c}, or continuous glucose monitoring (CGM).

SMBG is recommended for patients on multiple daily injection (MDI) insulin therapy or continuous subcutaneous insulin infusion (CSII) therapy. SMBG should be performed frequently during several critical time periods: preprandial, bedtime, before and after exercise, periods of symptomatic hypoglycemia or hyperglycemia, and before important activities such as operating dangerous machinery. Monitoring blood glucose levels 1 to 2 hours after food consumption (postprandial) can be useful to assess prandial insulin coverage in patients with at-goal preprandial readings but with hemoglobin A_{1c} not at goal. Overnight blood glucose monitoring can help detect hypoglycemia or dawn phenomenon. Success with SMBG requires the physician and patient to act upon the information that it provides. This can include insulin dose adjustments, changes in meal content, or changes in activity level to reach individualized glycemic goals. The data for the role and cost-effectiveness of SMBG are less clear for regimens without multiple daily insulin injections and noninsulin regimens.

It is often necessary to combine both SMBG and hemoglobin A_{1c} to determine if adequate control of glucose has been achieved. There is a strong correlation between hemoglobin A_{1c} and the average 3-month plasma glucose value. Therefore, the ADA and the American Association for Clinical Chemistry advocate reporting both the hemoglobin A_{1c} and the estimated plasma glucose levels (Table 7).Hemoglobin A_{1c} monitoring should be measured at the time of diagnosis and every 3 months while making changes to achieve glycemic goals. Testing intervals can be decreased to twice yearly after glycemic goals have been met.

Table 7. OPEN IN NEW WINDOW Comparison of Hemoglobin A_{1c} Value and Estimated Plasma Glucose Level

Hemoglobin A_{1c} (%)	Estimated Average Plasma Glucose Level mg/dL (mmol/L)

Table 7. OPEN IN NEW WINDOW Comparison of Hemoglobin A_{1c} Value and Estimated Plasma Glucose Level

Hemoglobin A_{1c} (%)	Estimated Average Plasma Glucose Level mg/dL (mmol/L)
6	126 (7.0)
7	154 (8.6)
8	183 (10.2)
9	212 (11.8)
10	240 (13.4)
11	269 (14.9)
12	298 (16.5)

- Adapted with permission of American Diabetes Association, from Translating the A1C assay into estimated average glucose values. Nathan DM, Kuenen J, Borg R, Zheng H, Shoenfeld D, Heine RJ; A1C-derived average glucose study group. [erratum in Diabetes Care. 2009;32(1):207]. Diabetes Care. 2008;31(8):1476. PMID: 18540046

CGM technology measures real-time glucose values from the interstitial fluid every few seconds through the temporary placement of a sensor subcutaneously for 3 to 7 days. The sensor is connected to a transmitter that sends the data through wireless radiofrequency to a display device. CGM glucose values average +/- 15% from a laboratory glucose measurement. CGM may be useful in persons with frequent hypoglycemia, hypoglycemic

unawareness, or extreme fluctuations in glucose levels. CGM systems can rapidly identify hypo- or hyperglycemia that is not always detected with SMBG or hemoglobin A_{1c} measurements. Additionally, the ADA endorses the use of CGM combined with intensive insulin therapy in adults (≥25 years of age) with type 1 diabetes as a successful modality to lower hemoglobin A_{1c} levels. The greatest improvements in glycemic control are associated with longer periods of CGM use. In patients using a CGM system, it is important to note that it does not replace SMBG. Calibration with SMBG is required at least twice daily with CGM systems. All CGM glucose values that warrant an immediate intervention should be confirmed with SMBG prior to action due to a lag time ranging from 5 to 21 minutes for several CGM brands between capillary blood glucose and interstitial glucose. Rapid glucose fluctuations further increase the lag time.

Key Points

- Blood glucose monitoring, including self-monitoring of blood glucose levels, hemoglobin A_{1c}levels, or continuous glucose monitoring, is recommended for patients with diabetes mellitus requiring multiple daily insulin injections or continuous intravenous insulin injection therapy.
- The data for the role and cost-effectiveness of self-monitoring of blood glucose levels are less clear for regimens without multiple daily insulin injections and noninsulin regimens; generally this should be avoided.

Nonpharmacologic Approaches Related Question

Question 49

Nonpharmacologic approaches to diabetes management should be implemented throughout the lifespan of the patient. These approaches can be used alone or as adjunct therapy in type 2 diabetes to improve the success rate of pharmacologic agents. Medical nutrition therapy and exercise can be used in conjunction with insulin therapy for patients with type 1 diabetes.

Medical nutrition therapy is an essential component of any successful management plan for patients with prediabetes or diabetes. Modest weight loss (2.0-8.0 kg [4.4-17.6 lb] or 7%) through caloric reduction can benefit some overweight or obese adults with type 2 diabetes.

Consistent exercise provides beneficial effects on glucose control, weight, and cardiovascular status. For persons with diabetes in whom no contraindications exist, aerobic exercise should consist of at least 150 minutes/week at a moderate intensity level, 75 minutes/week at a vigorous activity level, or a combination of these two. Resistance training should be incorporated into the exercise routine at least 2 days per week. Hypoglycemia and extreme hyperglycemia can worsen if present at the time of exercise and should be corrected before proceeding with increased physical activity.

Bariatric surgical procedures (restrictive and bypass) can be considered in obese patients with type 2 diabetes. Weight loss and diabetes remission rates are significant with these procedures, but the long-term benefits require additional studies. See MKSAP17 Gastroenterology and Hepatology and MKSAP 17 General Internal Medicine for more information.

Depression, anxiety, and diabetes-related stress are common among patients with diabetes and may impair their ability to achieve success with a diabetes management plan. Screening should occur continuously during the course of diabetes treatment.

Pharmacologic Therapy Related Question

Question 14

An individualized treatment goal will help guide the selection of the optimal treatment regimen. For many persons with diabetes, a reasonable goal for hemoglobin A_{1c} is less than 7.0% (or less than 6.5%, if this can be achieved without significant hypoglycemia). If severe recurrent hypoglycemia is present, there is no recommended hemoglobin A_{1c} goal, as modification of the patient's diabetes regimen to resolve severe recurrent hypoglycemia should take precedence. The increased risks of hypoglycemia outweigh the risks of diabetes complications in older patients with longer disease duration, which necessitates consideration of a less-stringent glycemic goal. The recommended goals from the ADA for blood glucose and hemoglobin A_{1c} levels are located in **Table 6**.

Table 6. OPEN IN NEW WINDOW American Diabetes Association Recommended Outpatient Glycemic Goals for Adults with Diabetes Mellitus

State of Health	Characteristics of Patients	Hemoglobin A_{1c}[a]	Preprandial Capillary Glucose[a]	Postprandial Capillary Glucose (1-2 hours after meal)[a]
Healthy	Early in disease course Few comorbidities Preconception Patient preference Life expectancy >10 years	<7.0% without severe recurrent hypoglycemia (<6.5% for select patients)[b]	70-130 mg/dL (3.9-7.2 mmol/L)	<180 mg/dL (10.0 mmol/L)
Complex health issues	Significant comorbidities, including advanced atherosclerosis or microvascular complications Longer duration of diabetes Frequent hypoglycemia Hypoglycemia	<8.0% without severe recurrent hypoglycemia		

Table 6. OPEN IN NEW WINDOW American Diabetes Association Recommended Outpatient Glycemic Goals for Adults with Diabetes Mellitus

State of Health	Characteristics of Patients	Hemoglobin A_{1c}[a]	Preprandial Capillary Glucose[a]	Postprandial Capillary Glucose (1-2 hours after meal)[a]
	unawareness Life expectancy <10 years			
Older adults	Few comorbidities Extended life expectancy No impairment of cognition or function	<7.0%-7.5% without severe recurrent hypoglycemia	90-130 mg/dL (5.0-7.2 mmol/L)	
	Multiple comorbidities Hypoglycemic risk Fall risk Mild impairments in cognition and function	<8.0% without severe recurrent hypoglycemia	90-150 mg/dL (5.0-8.3 mmol/L)	

Table 6. OPEN IN NEW WINDOW American Diabetes Association Recommended Outpatient Glycemic Goals for Adults with Diabetes Mellitus

State of Health	Characteristics of Patients	Hemoglobin A_{1c}[a]	Preprandial Capillary Glucose[a]	Postprandial Capillary Glucose (1-2 hours after meal)[a]
	Poor health Chronic comorbidities with end-stage disease Long-term care placement Moderate-to-severe impairment in cognition and function Limited life expectancy	<8.5% without severe recurrent hypoglycemia	100-180 mg/dL (5.6-10.0 mmol/L)	
Pregnant women	Preexisting type 1 or type 2 diabetes	<6.0% without severe recurrent hypoglycemia	60-99 mg/dL (3.3-5.5 mmol/L)	100-129 mg/dL (5.6-7.1 mmol/L)
	Gestational diabetes		≤95 mg/dL (5.3 mmol/L)	1-hour after meal: ≤140 mg/dL (7.8 mmol/L) 2-hours after meal: ≤120 mg/dL (6.7 mmol/L)

- [a]Recommended if goal can be met without severe recurrent hypoglycemia. If severe recurrent hypoglycemia is present, there is no recommended hemoglobin A_{1c} goal, as modification of the patient's diabetes mellitus regimen to resolve severe recurrent hypoglycemia should take precedence. When severe recurrent hypoglycemia is resolved, an hemoglobin A_{1c} goal can be chosen, and treatment decisions can again be made based on that individualized hemoglobin A_{1c} goal without frequent hypoglycemia.
- [b]This can be considered for patients with an early diagnosis of diabetes mellitus, no significant cardiovascular disease, or managed with lifestyle modifications or metformin.
- Data from American Diabetes Association. Glycemic targets. Sec. 6. In Standards of Medical Care in Diabetes-2015. Diabetes Care. 2015;38(Suppl 1):S33-S40. PMID: 25537705. (Modification of Table 6.2 (p. S37).
- Data from American Diabetes Association. Older adults. Sec. 10. In Standards of Medical Care in Diabetes-2015. Diabetes Care. 2015;38(Suppl 1):S67-S69. PMID: 25537711. (Modification of Table 10.1 (p. S68).
- Data from American Diabetes Association. Management of diabetes in pregnancy. Sec. 12. In Standards of Medical Care in Diabetes-2015. Diabetes Care. 2015;38(Suppl 1): S77-S79. PMID: 25537713.

Therapy for Type 1 Diabetes Mellitus

Related Question

Question 38

Lifelong insulin therapy is the first-line treatment for type 1 diabetes. Physiologic insulin therapy, also known as intensive insulin therapy, is the ideal insulin regimen as it attempts to mimic the actions of normal pancreatic beta cells. Intensive insulin therapy includes multiple daily injections (MDI) (≥3 per day) with an intermediate or long-acting insulin for basal coverage and multiple preprandial injections throughout the day with analogue or regular insulin. Intensive insulin therapy can also include continuous subcutaneous insulin infusion (CSII) and meal-time boluses with an insulin pump. Data support targeting normal glycemic levels with a goal hemoglobin A_{1c} of less than 7% for most persons with type 1 diabetes to reduce long-term complications. Long-term physiologic insulin therapy reduces early microvascular disease by 34% to 76% and reduces cardiovascular events by 42% to 57%. Intensive insulin therapy has risks, including significant increases in hypoglycemia and weight gain. Therapy should therefore be individually tailored for each patient's preferences, lifestyle, education level, financial resources, and comorbidities.

Available insulin preparations and their activity profiles are indicated in **Table 8**. Most persons with type 1 diabetes are sensitive to the effects of exogenous insulin therapy, with initial total daily doses of insulin typically ranging from 0.3 to 1 U/kg/d. A basal insulin dose

should account for half of the total daily dose of insulin, while the remaining insulin should be divided to cover the number of meals consumed during the day. Basal insulin coverage can be provided with one to two daily injections of insulin detemir, glargine, or neutral protamine Hagedorn (NPH) insulin. CSII can also provide basal coverage with analogue insulin. For prandial coverage, analogue or regular insulin is injected prior to meal consumption or analogue insulin is bolused with CSII prior to meals. Insulin dosing immediately after a meal is appropriate in certain situations, particularly when food intake is unpredictable. Postprandial insulin dosing allows for a reduction in the insulin dose that is commensurate with the amount of food ingested to avoid hypoglycemia that could have resulted from the full insulin dose. For example, the postprandial insulin dose is reduced by 50% if only half of the meal is consumed.

Table 8. OPEN IN NEW WINDOW Pharmacokinetic Properties of Insulin Products [a]

Insulin Type	Onset	Peak	Duration
Rapid-acting or analogue (lispro, aspart, glulisine)	5-15 min	45-90 min	2-4 h
Short-acting (regular)	0.5-1h	2-4 h	4-8 h
NPH insulin	1-3 h	4-10 h	10-18 h

Table 8. OPEN IN NEW WINDOW Pharmacokinetic Properties of Insulin Products [a]

Insulin Type	Onset	Peak	Duration
Detemir	1-2 h	None[b]	12-24 h[c]
Glargine	2-3 h	None[b]	20-24+ h
Pre-mixed insulins			
70% NPH/30% regular	0.5-1 h	2-10 h	10-18 h
50% NPH/50% regular	0.5-1 h	2-10 h[d]	10-18 h
75% NPL/25% lispro	10-20 min	1-6 h	10-18 h
50% NPL/50% lispro	10-20 min	1-6 h[d]	10-18 h

Table 8. OPEN IN NEW WINDOW Pharmacokinetic Properties of Insulin Products[a]

Insulin Type	Onset	Peak	Duration
70% NPA/30% aspart	10-20 min	1-6 h	10-18 h

- NPA = neutral protamine aspart; NPH = neutral protamine Hagedorn; NPL = neutral protamine lispro.
- [a]The time course of each insulin varies significantly between persons and within the same person on different days. Therefore, the time periods listed should be considered general guidelines only.
- [b]Both insulin detemir and insulin glargine can produce a peak effect in some persons, especially at higher doses.
- [c]The duration of action for insulin detemir varies depending on the dose given.
- [d]Premixed insulins containing a larger proportion of rapid- or short-acting insulin tend to have larger peaks occurring at an earlier time than mixtures containing smaller proportions of rapid and short-acting insulin.

Regular insulin requires a longer time interval between prandial injection and food consumption compared with analogue insulin due to its longer onset of action. Classic carbohydrate counting with prandial analogue insulin allows flexibility and variety in the types and sizes of meals consumed by adjusting the dose based on the number of carbohydrates ingested. Typically, 1 U of analogue insulin is used to cover every 10 to 20 g of carbohydrate in the meal. Modified carbohydrate counting for patients who are unwilling or cannot count carbohydrates includes fixed prandial doses of regular or analogue insulin that can be adjusted by 50% based upon the size of the meal: regular (100% dose), small (50% dose), or large (150% dose). In the setting of pre-meal hyperglycemia, the prandial dose of insulin determined by the classic or modified carbohydrate counting methods can be combined with a supplemental insulin dose to correct the hyperglycemia. There are a variety of methods to determine the supplemental insulin dose needed for correction; however, an additional 1 U of analogue or regular insulin for every 50 mg/dL (2.8 mmol/L) above the target blood glucose at the pre-meal measurement is a reasonable starting point. For example, an additional 2 U of regular or analogue insulin would be administered for a

patient with a blood glucose level of 210 mg/dL (11.7 mmol/L) if the target blood glucose is 150 mg/dL (8.3 mmol/L) or less. When administering any prandial or supplemental insulin doses, the duration of action of previous analogue or regular insulin injections must be considered, as the risk of insulin-stacking and subsequent hypoglycemia increases if the dosing is too frequent. Allowing at least 3 to 4 hours between injections can decrease this risk. Premixed insulins containing a fixed percentage of a long-acting and regular or analogue insulin are given twice daily, particularly in patients who are unable to comply with more frequent daily injections, although greater glycemic variability and hypoglycemia are concerns when utilizing a nonphysiologic regimen.

CSII should be considered for select patients with type 1 diabetes if adequate glycemic control is not achieved with adherence to MDI therapy. CSII may be beneficial in several scenarios, including significant early morning hyperglycemia ("dawn phenomenon"), labile plasma glucose values and frequent DKA, frequent severe hypoglycemia or hypoglycemic unawareness, preconception and pregnancy, or active lifestyles/patient preference. If a patient is not adherent with insulin injections and blood glucose monitoring, adherence is unlikely to increase because a pump is prescribed; therefore, pump therapy is not recommended in the nonadherent patient.

Cost of the insulin regimen chosen should be weighed against potential benefits. MDI regimens require more insulin supplies and glucose monitoring. Insulin analogues demonstrate fewer hypoglycemic events, but cost more than regular human insulin. Insulin pens increase both convenience and cost when compared with insulin in vials. Insulin pump supplies are expensive compared with other insulin therapies; however, data from several analyses indicate that overall CSII is a cost-effective treatment modality.

Key Points

- Lifelong insulin therapy is the first-line treatment for type 1 diabetes; physiologic insulin therapy reduces early microvascular disease by 34% to 76% in patients with type 1 diabetes mellitus compared with nonphysiologic regimens.

- Continuous subcutaneous insulin infusion is a cost-effective treatment modality and should be considered for select patients with type 1 diabetes mellitus if adequate glycemic control is not achieved with adherence to multiple daily injection therapy.

Therapy for Type 2 Diabetes Mellitus

Related Question

Question 29

Lifestyle modifications must often be combined with oral pharmacologic agents for optimal glycemic control, particularly as type 2 diabetes progresses with continued loss of pancreatic beta-cell function and insulin production. Multiple oral agents may be required or used in conjunction with noninsulin injectable agents or insulin as glycemic control worsens. There are many options for oral agents, with major differences in cost, timing of administration, mechanism of action, and side-effect profiles (Table 9).

Table 9. OPEN IN NEW WINDOW Pharmacologic Agents Used to Lower Blood Glucose Lev Type 2 Diabetes Mellitus

Class	Mechanism of Action	Effect on Weight	Risks and Concerns	Long-Term Studies on Defi Outcomes
Insulin[a]	Decreases hepatic glucose production, increases peripheral glucose uptake	Increase	Hypoglycemia; insulin allergy (rare)	Decrease in both microvascular ar macrovascular events
Sulfonylureas (tolbutamide, chlorpropamide,	Stimulate insulin secretion	Increase	Hypoglycemia (especially in drugs with long	Decrease in microvascular events possible increase in macrovascula with tolbutamide, chlopropamide,

Table 9. OPEN IN NEW WINDOW Pharmacologic Agents Used to Lower Blood Glucose Levels in Type 2 Diabetes Mellitus

Class	Mechanism of Action	Effect on Weight	Risks and Concerns	Long-Term Studies on Definitive Outcomes
glipizide, glyburide, gliclazide, glimepiride)[b]			half-lives or in older populations); weight gain	glyburide, and glipizide; not seen with gliclazide or glimepiride
Biguanides (metformin)[b]	Decrease hepatic glucose production, increase insulin-mediated uptake of glucose in muscles	Neutral	Diarrhea and abdominal discomfort; lactic acidosis (rare); contraindicated in presence of progressive liver, kidney or cardiac failure	Decrease in both microvascular and macrovascular events
α-Glucosidase inhibitors (acarbose, miglitol, voglibose)[b]	Inhibit polysaccharide absorption	Neutral	Flatulence; abdominal discomfort	May reduce CVD events
Thiazolidinediones (rosiglitazone, pioglitazone)[b]	Increase peripheral uptake of glucose,	Increase	Fluid retention; heart failure; macular edema; osteoporosis	Unclear whether pioglitazone causes net harm or good

Table 9. OPEN IN NEW WINDOW Pharmacologic Agents Used to Lower Blood Glucose Levels in Type 2 Diabetes Mellitus

Class	Mechanism of Action	Effect on Weight	Risks and Concerns	Long-Term Studies on Definitive Outcomes
	decrease hepatic glucose production		(possible increased risk of bladder cancer with pioglitazone)	
Meglitinides (repaglinide, nateglinide)[b]	Stimulate insulin release	Increase	Hypoglycemia	None
Amylinomimetics (pramlintide)[a]	Slow gastric emptying, suppress glucagon secretion, increase satiety	Decrease	Nausea; vomiting; increased hypoglycemic risk with insulin	None
GLP-1 mimetics (exenatide and liraglutide)[a]	Slow gastric emptying, suppress glucagon secretion, increase satiety	Decrease	Hypoglycemia when used in combination with sulfonylureas; nausea and vomiting; possible	None

Table 9. OPEN IN NEW WINDOW Pharmacologic Agents Used to Lower Blood Glucose Levels in Type 2 Diabetes Mellitus

Class	Mechanism of Action	Effect on Weight	Risks and Concerns	Long-Term Studies on Definitive Outcomes
			increased risk of pancreatitis and chronic kidney disease	
DPP-4 inhibitors (sitagliptin, saxagliptin, vildagliptin, linagliptin, alogliptin)[b]	Slow gastric emptying, suppress glucagon secretion	Neutral	Hypoglycemia when used in combination with sulfonylureas; nausea; increased risk of infections; possible increased risk of pancreatitis	No increase in ischemic cardiovascular events; increased rate of hospitalization for heart failure with saxagliptin
SGLT2 inhibitors (dapagliflozin and canagliflozin)[b]	Increases kidney excretion of glucose	Decrease	Hypoglycemia with insulin secretagogues and insulin; hypotension; kidney impairment; hypersensitivity reactions; increased	None

Table 9. OPEN IN NEW WINDOW Pharmacologic Agents Used to Lower Blood Glucose Lev
Type 2 Diabetes Mellitus

Class	Mechanism of Action	Effect on Weight	Risks and Concerns	Long-Term Studies on Defi Outcomes
			candidal genital infections and urinary tract infections	

- CVD = cardiovascular disease; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; SGLT2 = sodium-glucose co-transporter 2.
- [a]Injection.
- [b]Oral.

Metformin is the recommended first-line therapy to be initiated either in conjunction with lifestyle modifications at the time of diagnosis or within 6 weeks of failing to obtain glycemic control with lifestyle changes alone. Metformin has a lower incidence of hypoglycemia and weight gain compared with some of the other oral agents and insulin. Gastrointestinal side effects (such as abdominal cramping or diarrhea) are common with metformin; initial low doses with gradual increases and administration of the tablet following a substantial meal can improve tolerance to the medication. Due to the potential risk of lactic acidosis, contraindications to metformin therapy include serum creatinine greater than 1.5 mg/dL (133 µmol/L) in men and 1.4 mg/dL (124 µmol/L) in women, symptomatic heart failure or liver disease, and illness with hemodynamic instability. Metformin must be withheld for 48 hours in the setting of intravenous contrast dye. In a nonhospitalized patient, metformin should be withheld with any illness that may cause dehydration.

If lifestyle modifications and maximally tolerated doses of metformin fail to adequately control glucose, additional agents should be added every 3 months until glycemic goals have been met. Without strong comparative-effectiveness data to identify the best class of second-line drugs to be implemented, several factors must be considered. Patient preferences and financial resources are key components to developing an individualized

treatment plan. Another important determining factor in selection of the second-line drug class is the patient's weight. Weight-neutral drug classes include α-glucosidase inhibitors and dipeptidyl peptidase-4 (DPP-4) inhibitors. If weight loss is a desired effect, glucagon-like peptide 1 (GLP-1) mimetics, pramlintide, and sodium-glucose transporter-2 (SGLT2) inhibitors are candidates to consider. Weight gain is likely with the use of insulin, sulfonylureas, thiazolidinediones, and meglitinides. The risk of hypoglycemia must be considered with the selection of any therapeutic agent, particularly when it is combined with insulin secretagogues or insulin. Gastrointestinal side effects from GLP-1 mimetics and pramlintide may decrease tolerability for some patients and should not be used in patients with gastroparesis. Patients with frequent candidal genital infections would not be ideal candidates for SGLT2 inhibitor therapy.

Insulin therapy should be strongly considered in the setting of symptomatic hyperglycemia or markedly elevated hemoglobin A_{1c} (>8.5% to 9%) at the time of diagnosis or when lifestyle modifications and/or noninsulin therapies fail to achieve glycemic goals. The American Association of Clinical Endocrinologists (AACE) recommends weight-based initiation of basal insulin at initial doses of 0.1 to 0.3 U/kg. The dose should be increased several units every 2 to 3 days to reach fasting plasma glucose goals, based on the patient's SMBG readings. Reductions of insulin doses by 10% to 40% should be made in the setting of hypoglycemia with insulin titrations. If glycemic goals are not met with basal insulin, then prandial insulin should be added to the regimen with frequent titration of doses for optimal glucose control. When premeal glucose values are not at a patient-specific goal, the preceding prandial insulin dose should be increased or decreased by 10% to 20% in the setting of hyper- or hypoglycemia, respectively. (Also see section on Therapy for Type 1 Diabetes Mellitus.)

Key Points

- For patients with type 2 diabetes mellitus, metformin is recommended first-line therapy and should be initiated in conjunction with lifestyle modifications; it has a lower incidence of hypoglycemia and weight gain compared with some of the other oral agents and insulin.
- In older patients with type 2 diabetes mellitus of longer disease duration, treatment of severe recurrent hypoglycemia should take precedence over controlling hemoglobin A_{1c} values; the increased risks of hypoglycemia outweigh the risks of diabetes complications.

Inpatient Management of Hyperglycemia

Inpatient hyperglycemia, defined as consistently elevated plasma glucose values above 140 mg/dL (7.8 mmol/L), is associated with poor outcomes. Attempts to decrease morbidity and mortality with tight glycemic control (80-110 mg/dL [4.4–6.1 mmol/L]) have not consistently demonstrated improvements in adverse outcomes and, in some settings, have shown increased rates of severe hypoglycemic events and mortality. As a result, revised inpatient glycemic targets are less stringent than outpatient glucose targets to avoid both hypoglycemia and severe hyperglycemia that can lead to volume depletion and electrolyte abnormalities.

Hospitalized Patients with Diabetes Mellitus

Related Question

Question 47

Critically ill patients with type 1 diabetes mellitus will require insulin therapy upon admission to the hospital. For critically ill patients with type 2 diabetes, intravenous insulin infusion therapy should be initiated when plasma glucose levels exceed 180 to 200 mg/dL (10-11.1 mmol/L). Glucose goals on intravenous insulin are 140 to 200 mg/dL (7.8-11.1 mmol/L) with frequent bedside point-of-care (POC) monitoring every 1 to 2 hours for insulin adjustments.

In noncritically ill patients, the ADA and AACE advocate a premeal glucose goal of less than 140 mg/dL (7.8 mmol/L) and random plasma glucose values less than 180 mg/dL (10 mmol/L). Therapy adjustments should be considered when plasma glucose levels are less than 100 mg/dL (5.6 mmol/L) and are necessary when glucose values fall below 70 mg/dL (3.9 mmol/L) to avoid continued hypoglycemia. In contrast, the American College of Physicians (ACP) recommends avoiding glucose levels less than 140 mg/dL (7.8 mmol/L) owing to the increased risk of hypoglycemia with tighter glycemic control.

Insulin is the preferred therapy and likely the safest choice for achieving inpatient glycemic control. Use of sliding scale insulin alone is not recommended, as it is not physiologic and frequently causes large glucose fluctuations owing to the inherent reactive nature of its dosing, coupled with the near universal lag time between measurement of glucose and injection of insulin that occurs in most hospitals. The recommended insulin regimen should incorporate both basal and prandial coverage. In the setting of preprandial hyperglycemia, prandial coverage can be supplemented with additional insulin (correction factor insulin). Prandial coverage should account for the carbohydrates consumed at each meal and be adjusted accordingly. POC glucose monitoring should coincide with insulin administration before meals and at bedtime, with overnight measurements to monitor for hypoglycemia only if fasting readings are elevated or the patient is symptomatic. This glucose monitoring regimen will simulate the patient's home routine after discharge. POC monitoring should occur every 6 hours when a patient is on insulin therapy and receives nothing by mouth.

Outpatient CSII therapy can be continued if the patient is physically and mentally able to safely administer this therapy under proper supervision from health care providers with CSII expertise. POC glucose monitoring, basal rates of insulin, and patient-initiated bolus amounts of insulin should be documented in the medical record.

Oral agents and noninsulin injectable agents do not have safety or efficacy data in the hospital setting. The safest recommendation is to discontinue these agents upon admission to the hospital, although continuation can be considered in a stable patient with glycemic control at goal and no anticipated changes in nutrition or hemodynamic status. These agents can be particularly dangerous in fasting states or when organ perfusion or function is compromised. Resumption of these medications may be considered once a patient is stable with regular activities and nutrition or at the time of hospital discharge.

Key Points

- For critically ill patients with type 2 diabetes mellitus, intravenous insulin infusion therapy should be initiated when plasma glucose levels exceed 180 to 200 mg/dL (10-11.1 mmol/L); glucose goals on intravenous insulin are 140 to 200 mg/dL (7.8-11.1 mmol/L) with frequent bedside point-of-care monitoring every 1 to 2 hours.
- For noncritically ill patients, basal and prandial subcutaneous insulin is the preferred and safest choice for achieving inpatient glycemic control; oral agents and noninsulin injectable agents do not have proven safety or efficacy data in the hospital setting.

Hospitalized Patients Without Diabetes Mellitus

Hyperglycemia as a result of acute stress related to illness, concomitant medications, or enteral/parenteral nutrition can occur in patients without a previous history of glucose abnormalities. The glycemic goals and glucose-management strategies in this population should follow those for hospitalized patients with diabetes. Hyperglycemia in hospitalized patients may also indicate the presence of previously undiagnosed diabetes. Measurement of hemoglobin A_{1c} in hyperglycemic non-hospitalized patients, if feasible, can provide insight into the length of the hyperglycemia. A hemoglobin A_{1c} level greater than 6.5% suggests long-standing hyperglycemia. Follow-up diabetes screening and care should be implemented after discharge from the hospital.

Management of Hypoglycemia

Hypoglycemia in Patients with Diabetes Mellitus

Related Questions

Question 20

Question 35

Hypoglycemia is a common complication of intensive therapeutic regimens in patients with diabetes mellitus, often limiting the ability to safely reach glycemic goals for many patients. Avoidance of hypoglycemia prior to focusing on a patient's hemoglobin A_{1c} goal is of utmost importance because of the significant morbidity and mortality associated with low plasma glucose levels.

Hypoglycemia is defined as a plasma glucose level less than 70 mg/dL (3.9 mmol/L). Insulin secretion ceases when the glucose level falls below 80 mg/dL (4.4 mmol/L). Hyperadrenergic symptoms begin to alert the patient to hypoglycemia through an increase in heart rate, sweating, tremors, hunger, and anxiety when glucose levels decline. Typically, the body responds to hypoglycemia by secreting counterregulatory hormones, such as glucagon, epinephrine, norepinephrine, cortisol, and growth hormone, in succession based on the escalating degree of hypoglycemia. If the counterregulatory measures fail or the hypoglycemia is not corrected, cognitive function begins to decline and can be rapidly followed by loss of consciousness, seizures, and death. Relative hypoglycemia occurs when a patient has symptoms of hypoglycemia but the plasma glucose level is greater than 70 mg/dL (3.9 mmol/L). This can occur with rapid decreases in glucose or with correction of glucose to near-normal glycemic levels in a patient with a history of prolonged hyperglycemia (plasma glucose >200 mg/dL [11.1 mmol/L]). Relative hypoglycemia can be diminished if glucose levels are maintained closer to normal ranges and if treatment to goal glucose level is achieved over a longer period of time in patients with a history of prolonged uncontrolled diabetes.

The etiology of hypoglycemia can be quite variable. Exercise can lead to hypoglycemia if appropriate measures are not taken to avoid it. Prior to exercise, consumption of a snack with 15 to 30 g of carbohydrates can help reduce the risk of hypoglycemia, or a patient can reduce the dose of prandial insulin given at the meal prior to the planned exercise, if on an MDI regimen. A snack with complex carbohydrates is often required after prolonged exercise to replenish glycogen stores since glucose utilization can be prolonged in muscles and the liver. In overweight/obese patients, decreasing the insulin dose instead of ingesting snacks before exercise can avoid additional weight gain. Poor timing or skipping of meals or consumption of smaller amounts of food without an adjustment to insulin doses or oral hypoglycemic agents can cause hypoglycemia. Use of a nonphysiologic sliding scale insulin regimen or use of an aggressive supplemental insulin correction factor regimen is often the etiology of hypoglycemic events. A reduction in kidney function,

particularly in elderly patients, can decrease clearance of insulin or insulin secretagogues and lead to prolonged hypoglycemia. Alcohol consumption can cause delayed hypoglycemia.

Treatment of hypoglycemia is twofold: immediate correction of hypoglycemia and prevention of future events. If a patient is conscious, 15 to 20 g of a carbohydrate with glucose should be consumed. Glucose tablets or glucose gel are ideal treatment regimens. The blood glucose level should be checked again after 15 minutes, and consumption of 15 to 20 g of glucose should occur again if the hypoglycemia does not improve to greater than 70 mg/dL (3.9 mmol/L). Since the effects of the insulin or oral hypoglycemic agents are likely still present, a meal or snack should be consumed after the glucose has been corrected to avoid continued hypoglycemia. Every patient with diabetes on medications associated with hypoglycemia should receive a prescription for a glucagon kit, which should be used when oral consumption of glucose is not possible or safe.

Relaxing the glycemic targets and hemoglobin A_{1c} goals and reducing doses of therapeutic agents will decrease the risk of future hypoglycemia. A review of a patient's diabetes self-management skills can also help identify recurring risk factors for hypoglycemia.

Key Points

- Hypoglycemia is defined as a plasma glucose level less than 70 mg/dL (3.9 mmol/L) and is associated with significant morbidity and mortality.
- Relaxing the glycemic targets and hemoglobin A_{1c} goals and reducing doses of therapeutic agents will decrease the risk of future hypoglycemia.

Hypoglycemia in Patients Without Diabetes Mellitus

Hypoglycemia in patients without diabetes is rare, thus evaluation for pathologic hypoglycemia should only occur when Whipple triad is present: symptomatic hypoglycemia, documented hypoglycemia at 55 mg/dL (3.1 mmol/L) or lower, and prompt symptomatic relief with correction of hypoglycemia. Hypoglycemia should

not be confirmed with POC glucose monitors, but instead with a more accurate established laboratory method. Hypoglycemia in patients without diabetes is usually related to drugs, illness, hormonal deficiency, non–islet cell tumor, endogenous hyperinsulinism/noninsulinoma, pancreatogenous hypoglycemia, depletion of hepatic glycogen stores, or alcohol ingestion. Diagnostic studies should be obtained during a spontaneous hypoglycemic episode or during an attempt to recreate a scenario known to cause hypoglycemia, such as prolonged fasting or after a mixed meal, which consists of the type of food that induces the hypoglycemia, typically a simple carbohydrate-rich meal, such as orange juice, pancakes, and syrup. Hypoglycemia has classically been categorized as occurring in the fasting versus postprandial state, although the etiologies of each of these classifications of hypoglycemia are not mutually exclusive. The differential diagnoses based on the laboratory test results are found in **Table 10**. Imaging studies should not occur unless biochemical evidence of endogenous hyperinsulinism is confirmed and is related to a tumor or pancreatic abnormality.

Table 10. OPEN IN NEW WINDOW Differential Diagnosis of Spontaneous Fasting Hypoglycemia[a] in a Patient Without Diabetes

Diagnosis	Serum Insulin	Plasma C-Peptide	Plasma Proinsulin	Serum β-hydroxybutyrate	Serum Insulin Antibodies	Urine or Blood Metabolites of Sulfonylureas or Meglitinides
Insulinoma	↑	↑	↑	↓	Negative	Negative
Surreptitious use of sulfonylureas of meglitinides	↑	↑	↑	↓	Negative	Positive

Table 10. OPEN IN NEW WINDOW Differential Diagnosis of Spontaneous Fasting Hypoglycemia[a] in a Patient Without Diabetes

Diagnosis	Serum Insulin	Plasma C-Peptide	Plasma Proinsulin	Serum β-hydroxybutyrate	Serum Insulin Antibodies	Urine or Bl Metabolites Sulfonylure Meglitinide
Surreptitious use of insulin	↑	↓	↓	↓	Negative	Nega
Insulin autoimmune hypoglycemia	↑	↑	↑	↓	Positive	Nega

- [a]Symptomatic hypoglycemia, fasting plasma glucose 55 mg/dL (3.1 mmol/L) or lower, and prompt symptomatic relief with correction of hypoglycemia (Whipple triad).
- Data 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. 2009 Mar;94(3):709-28. PMID: 19088155

Fasting Hypoglycemia Related Question

Question 67

Suspected hypoglycemia that is either spontaneous or begins after a fast should be evaluated by the following simultaneous laboratory measurements: glucose, insulin, C-peptide, proinsulin, β-hydroxybutyrate, and insulin secretagogue screen. C-peptide and proinsulin are measures of the endogenous production of insulin. β-Hydroxybutyrate is suppressed by endogenous and exogenous insulin, but would be unsuppressed in a normal physiologic state of hypoglycemia or in a non–insulin-mediated condition. If hypoglycemia is not present at the time of evaluation, a 72-hour fast is indicated, which is typically performed in consultation with an endocrinologist. This test involves measurement of the above-mentioned laboratory

values every 6 hours until the plasma glucose level reaches 60 mg/dL (3.3 mmol/L) and subsequently every 1 to 2 hours until specific plasma glucose, symptom, or time criteria are met. This test also involves measuring the response to glucagon administration. Evaluation for anti-insulin antibodies can detect the rare condition of insulin autoimmune hypoglycemia as the underlying etiology for the hypoglycemia.

Postprandial Hypoglycemia

Postprandial hypoglycemia without a history of a prior bariatric procedure is rare. It typically occurs within 5 hours of food consumption. A mixed meal tolerance test is usually performed in consultation with an endocrinologist and measures the glucose level as symptoms occur. Glucose, insulin, proinsulin, and C-peptide levels are measured prior to the meal and repeated at 30-minute intervals or at the time of symptomatic hypoglycemia (blood glucose level <60 mg/dL [3.3 mmol/L]) within the 5 hours after meal consumption. If symptomatic hypoglycemia occurs, insulin antibodies are measured and an oral hypoglycemic agent screening test is obtained. Treatment, with or without the detection of pathologic hypoglycemia on the mixed meal test, often involves small, frequent complex meals composed of protein, fat, and carbohydrate to avoid the sensation of hypoglycemia.

Acute Complications of Diabetes Mellitus

Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar Syndrome

Related Question

Question 24

Diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar syndrome (HHS) are acute complications of uncontrolled hyperglycemia with life-threatening consequences if not recognized and treated early. DKA typically occurs in the setting of hyperglycemia with relative or absolute insulin deficiency and an increase in counterregulatory hormones. Sufficient amounts of insulin are not present to suppress lipolysis and oxidation of free fatty acids, which results in ketone body production

and subsequent metabolic acidosis. DKA occurs more frequently with type 1 diabetes, although 10% to 30% of cases occur in patients with type 2 diabetes. HHS occurs in the setting of partial insulin deficiency that is more typical of type 2 diabetes. There is sufficient insulin in patients with HHS to suppress lipolysis and production of ketone bodies, but inadequate amounts to prevent the hyperglycemia, dehydration, and hyperosmolality characteristic of HHS.

Several risk factors can precipitate the development of extreme hyperglycemia: infection, intentional or inadvertent insulin therapy nonadherence, myocardial infarction, stress, trauma, and confounding medications, such as glucocorticoids or atypical antipsychotic agents. In addition, DKA may be the initial clinical presentation in some patients with previously undiagnosed type 1 or type 2 diabetes. An illness or event that leads to dehydration will often precipitate the hyperglycemia associated with HHS.

Symptoms of extreme hyperglycemia in DKA and HHS include polyuria, polydipsia, unintentional weight loss, vomiting, weakness, and mentation changes. Dehydration and metabolic abnormalities worsen as hyperglycemia progresses, which can lead to respiratory failure, lethargy, obtundation, coma, and death. DKA can occur within several hours of the inciting event. The development of HHS is less acute than DKA and may take days to weeks to develop. HHS typically presents with more extreme hyperglycemia and mental status changes compared with DKA.

The initial evaluation of severe hyperglycemia includes serologic studies (plasma glucose, serum ketones, blood urea nitrogen, creatinine, electrolytes, calculated anion gap, arterial blood gases, osmolality, complete blood count with differential, blood cultures), urine studies (ketones, urinalysis, urine culture), chest radiograph, and an electrocardiogram.

Urine and serum ketones are elevated in DKA; however, a negative measurement initially does not exclude DKA. β-Hydroxybutyrate is the major ketone body in DKA, but ketone laboratory measurements often use the nitroprusside reaction, which only

estimates acetoacetate and acetone levels that may not be elevated initially. Although hyperglycemia is the typical finding at presentation with DKA, patients can present with a range of plasma glucose values, including those in the normal range (**Figure 1**). The anion gap is elevated. Stress-related mild leukocytosis is often present. Higher levels of leukocytosis may indicate an infectious process as the etiology of the hyperglycemia. Serum sodium levels can be low due to osmotic shifts of water from the intracellular to extracellular spaces. Normal or elevated serum sodium levels are indicative of severe volume depletion. Serum potassium levels may be elevated due to shifts from the intracellular to extracellular spaces due to ketoacidosis and the absence of sufficient insulin. Normal or low potassium levels on presentation indicate low potassium stores in the body with need for correction prior to initiation of insulin therapy to avoid cardiac arrhythmias. Serum amylase and lipase levels also can be elevated in the absence of pancreatitis.

Figure 1. OPEN IN NEW WINDOW

Spectrum of metabolic decompensation that occurs in diabetic ketoacidosis. DKA = diabetic ketoacidosis.

HHS typically presents with normal or small amounts of urine or serum ketones. Plasma glucose values in HHS are typically greater than in DKA and can exceed 1200 mg/dL (66.6 mmol/L). The serum osmolality is elevated greater than 320 mOsm/kg H_2O. The serum bicarbonate level is greater than 18 mEq/L (18 mmol/L), and the pH remains greater than 7.3.

Treatment of DKA and HHS requires correction of hyperglycemia with intravenous insulin infusions, frequent monitoring and replacement of electrolytes, correction of hypovolemia with intravenous fluids, and possible correction of acidosis (**Table 11**). The ICU is the best place for management of severe hyperglycemia because of the frequent monitoring required with intravenous insulin therapy, the need for monitoring for potential electrolyte-induced arrhythmias, and the potential for rapid decompensation. Plasma glucose levels should be monitored initially every hour

while on insulin infusion therapy. Electrolytes should be monitored every 2 to 4 hours, depending on the initial electrolyte deficits and level of acidosis.

Table 11. OPEN IN NEW WINDOW Management of Hyperglycemic Crisis (DKA and HHS)

Fluids	Insulin (Regular)	Potassium	Correction of Acidosis
Assess for volume status, then give 0.9% saline at 1 L/h initially in all patients, and continue if patient is severely hypovolemic. Switch to 0.45% normal saline at 250-500 mL/h if corrected serum sodium level becomes normal or high. When the plasma glucose level reaches 200 mg/dL (11.1	Give regular insulin, 0.1 U/kg, as an intravenous bolus followed by 0.1 U/kg/h as an intravenous infusion; if the plasma glucose level does not decrease by 10% in the first hour, give an additional bolus of 0.14 U/kg and resume previous infusion	Assess for adequate kidney function, with adequate urine output (approximately 50 mL/h). If serum potassium is <3.3 mEq/L (3.3 mmol/L), do not start insulin but instead give intravenous potassium chloride, 20-30 mEq/h, through a central line catheter until the serum potassium level is >3.3 mEq/L (3.3 mmol/L); then	If pH is <6.9, give sodium bicarbonate, 100 mmol in 400 mL of water, and potassium chloride, 20 mEq, infused over 2 hours. If pH is 6.9 or greater, do not give sodium bicarbonate.

Table 11. OPEN IN NEW WINDOW Management of Hyperglycemic Crisis (DKA and HHS)

Fluids	Insulin (Regular)	Potassium	Correction of Acidosis
mmol/L) in patients with DKA or 300 mg/dL (16.7 mmol/L) in HHS, switch to 5% dextrose with 0.45% normal saline at 150-250 mL/h.	rate; when the plasma glucose level reaches 200 mg/dL (11.1 mmol/L) in DKA and 300 mg/dL (16.7 mmol/L) in HHS, reduce to 0.02-0.05 U/kg/h, and maintain the plasma glucose level between 150-200 mg/dL (8.3-11.1 mmol/L) until anion gap acidosis is resolved in DKA.	add 20-30 mEq of potassium chloride to each liter of intravenous fluids to keep the serum potassium level in the 4.0-5.0 mEq/L (4.0-5.0 mmol/L) range. If the serum potassium level is >5.2 mEq/L (5.2 mmol/L), do not give potassium chloride but instead start insulin and intravenous fluids and check the serum potassium level every 2 hours.	

- DKA = diabetic ketoacidosis; HHS = hyperglycemic hyperosmolar syndrome.

Key Points

- The development of hyperglycemic hyperosmolar syndrome is less acute than that of diabetic ketoacidosis and may take days to weeks to develop; however, hyperglycemic hyperosmolar syndrome typically presents with more extreme hyperglycemia and mental status changes compared with diabetic ketoacidosis.
- Treatment of diabetic ketoacidosis and hyperglycemic hyperosmolar syndrome requires correction of hyperglycemia with intravenous insulin infusions, frequent monitoring and replacement of electrolytes, correction of hypovolemia with intravenous fluids, and possible correction of acidosis.

Chronic Complications of Diabetes Mellitus

Cardiovascular Morbidity

Cardiovascular disease (CVD) is a major contributor to morbidity and mortality among patients with diabetes mellitus. Diabetes alone is an independent risk factor for CVD and is considered a CVD equivalent. Concomitant risk factors in patients with diabetes, such as hypertension, obesity, and dyslipidemia, also contribute to the development of CVD and should be identified early through screening (Table 12).

Table 12. OPEN IN NEW WINDOW Screening Recommendations for Chronic Complications of Diabetes Mellitus

Chronic Complication	Clinical Situation	When to Start Screening	Screening Frequency	Preferred Screening Test
Retinopathy	Type 1 diabetes	At 5 years after diagnosis	Annually[a]	Dilated and comprehensive eye examination
	Type 2	At diagnosis	Annually[a]	Dilated and comprehensive eye

Table 12. OPEN IN NEW WINDOW Screening Recommendations for Chronic Complications of Diabetes Mellitus

Chronic Complication	Clinical Situation	When to Start Screening	Screening Frequency	Preferred Screening Test
	diabetes			examination
	In pregnant women with either type of diabetes	First trimester	Every trimester and then closely for 1 year postpartum	Dilated and comprehensive eye examination
	In women with either type of diabetes planning to conceive	During preconception planning	Same as recommendations for pregnant women once conception occurs	Dilated and comprehensive eye examination
Nephropathy	Type 1 diabetes	At 5 years after diagnosis	Annually[b]	Albumin-creatinine ratio on random spot urine
	Type 2 diabetes	At diagnosis	Annually[b]	Albumin-creatinine ratio on random spot urine
Neuropathy (distal symmetric	Type 1 diabetes	At 5 years after diagnosis	Annually	10-g monofilament, 128-Hz tuning fork, ankle reflexes

Table 12. OPEN IN NEW WINDOW Screening Recommendations for Chronic Complications Diabetes Mellitus

Chronic Complication	Clinical Situation	When to Start Screening	Screening Frequency	Preferred Screening Test
polyneuropathy)				
	Type 2 diabetes	At diagnosis	Annually	10-g monofilament, 128-Hz tur ankle reflexes
Cardiovascular disease	Hypertension	At diagnosis	Every visit	Blood pressure measurement
	Dyslipidemia	At diagnosis	Annually[c]	Fasting lipid profile

- [a]It is reasonable to screen every 2 years if no diabetic retinopathy is present and to screen more often than annually if diabetic retinopathy is advanced or progressing rapidly.
- [b]The American Diabetes Association guidelines state that it is reasonable to assess progression of disease and response to therapeutic interventions with continued monitoring of urine albumin excretion.
- [c]It is reasonable to screen every 2 years if lipid parameters are at goal.

The 8th Joint National Committee (JNC-8) recently revised its recommended blood pressure goals for patients with diabetes to 140/90 mm Hg or less, citing a lack of data to support lower targets. In contrast, the American Diabetes Association (ADA) recommends a blood pressure goal of less than 140/80 mm Hg. The ADA advocates for a lower systolic blood pressure (<130 mm Hg) in select patients (young, long life expectancy, increased risk of stroke), if this can be accomplished safely. Although JNC-8 does not specify use of an ACE inhibitor or an angiotensin receptor blocker (ARB) as initial therapy for patients with diabetes and hypertension in the absence of chronic kidney disease, the ADA recommends preferential use of these agents in treating hypertension in these patients.

The most recent American College of Cardiology/American Heart Association guidelines base treatment recommendations for patients with diabetes on age, the presence of atherosclerotic cardiovascular disease (ASCVD), or estimated 10-year ASCVD risk using the Pooled Cohort Equations; a specific goal LDL cholesterol level is no longer used in these guidelines. Treat patients with diabetes and known cardiovascular or other vascular disease with high-intensity statin therapy. In the absence of known cardiovascular or vascular disease, provide high intensity statin therapy to patients with diabetes if the LDL cholesterol level is greater than 190 mg/dL (4.9 mmol/L) or the 10-year ASCVD risk is equal to or greater than 7.5%. Provide moderate-intensity statin therapy for patients with diabetes and a 10-year ASCVD risk less than 7.5%. Consider withholding statin therapy in patients with diabetes younger than 40 years without additional cardiovascular risk factors. In contrast, ADA guidelines continue to recommend an LDL cholesterol goal in patients with diabetes of less than 100 mg/dL (2.6 mmol/L), with the option of LDL cholesterol less than 70 mg/dL (1.8 mmol/L) in patients with clinical ASCVD. Therefore, it is recommended that statin therapy be added to lifestyle modifications in patients with diabetes who have clinical ASCVD, are older than 40 years of age with CVD risk factors, or are younger than 40 years of age with LDL cholesterol not at goal.

Key Points

- High-intensity statin therapy is indicated for patients with diabetes and known cardiovascular or vascular disease; LDH cholesterol greater than 190 mg/dL (4.9 mmol/L), or atherosclerotic cardiovascular disease 10-year risk of equal to or greater than 7.5%.
- Moderate intensity statin therapy is indicated for patients with diabetes 40 years of age and older and an atherosclerotic cardiovascular disease 10-year risk less than 7.5%.

Diabetic Retinopathy

Among adults aged 20 to 74 years, diabetic retinopathy is the leading preventable cause of blindness. Changes associated with nonproliferative retinopathy include retinal thickening from macular edema, infarcts (resulting in “cotton wool” spots or soft exudates), hard exudates, and hemorrhages. With proliferative retinopathy, neovascularization occurs secondary to chronic retinal ischemia. These new vessels may rupture, causing intraocular hemorrhage and subsequent fibrosis and retinal detachment.

Risk factors for diabetic retinopathy include long-term diabetes, poorly controlled diabetes, hypertension, and nephropathy. Retinopathy can be accelerated in pregnant women with type 1 diabetes. Rapid improvements in glycemic levels for pregnant women and nonpregnant patients can temporarily worsen preexisting retinopathy.

Screening guidelines vary depending on the type of diabetes, time of diagnosis, and pregnancy status (see **Table 12**).

Optimal blood glucose and blood pressure control can prevent or delay the progression of diabetic retinopathy. Laser photocoagulation is used to treat retinopathy as severity progresses. Focal laser photocoagulation of the retina can restore some vision and reduce the risk of further vision loss with macular edema. Panretinal laser photocoagulation reduces continued vision loss in proliferative diabetic retinopathy and severe nonproliferative diabetic retinopathy. Laser photocoagulation can also reduce the risk of retinopathy progression associated with pregnancy. Intravitreal injections of antiangiogenic agents, such as vascular endothelial growth factor inhibitors, may also be included in the management of proliferative retinopathy and macular edema.

Key Point

- Optimal blood glucose and blood pressure control can prevent or delay the progression of diabetic retinopathy; however, laser photocoagulation is used to treat diabetic retinopathy as the severity progresses.

Diabetic Nephropathy

Diabetic nephropathy not only increases the risk of progression to end-stage kidney disease, but is also a risk factor for CVD.

Measurement of increased protein excretion can be performed by two methods: albumin-creatinine ratio on a random spot urine collection or a 24-hour urine collection. Persistently elevated levels of urine albumin excretion are defined as greater than or equal to 30 mg/g in a spot urine measurement or 30 to 299 mg/24 h and greater than or equal to 300 mg/24 h. Urine albumin levels should be elevated on multiple samples over 3 to 6 months to diagnose

albuminuria, as false-positive elevations can occur in the setting of illness, menstruation, recent exercise, extreme hyperglycemia or hypertension, and heart failure. Screening timelines for urine albumin excretion are found in **Table 12**. Annual measurements of serum creatinine and an estimated glomerular filtration rate (GFR) can be utilized in conjunction with the urine albumin measurement to determine the stage of chronic kidney disease. When the estimated GFR is less than 30 mL/min/1.73 m^2, a referral to a nephrologist is recommended.

Diabetic nephropathy can be prevented or delayed with optimal plasma glucose and blood pressure control. In nonpregnant normotensive patients with persistently elevated urine albumin excretion, an ACE inhibitor or angiotensin receptor blocker (ARB) is recommended to decrease progression of nephropathy. In nonpregnant hypertensive patients with persistently elevated urine albumin excretion and hypertension, the ACE inhibitor or ARB should be titrated to achieve a blood pressure goal of less than 130/80 mm Hg. Measurement of urine albumin annually after initiation of therapy with an ACE inhibitor or ARB is reasonable to assess disease progression and therapeutic response as evidenced by stabilization or reduction of urine albumin excretion. Data are conflicting regarding the ability of low-protein diets to slow the progression of kidney disease, but these diets may be considered if nephropathy progresses while using an ACE inhibitor or ARB or after achieving target plasma glucose and blood pressure goals. ACE inhibitor/ARB combination treatment is not recommended.

Key Points

- Elevated urinary albumin excretion is defined as greater than or equal to 30 mg/g in a spot urine measurement; annual measurements of serum creatinine and an estimated glomerular filtration rate can be utilized in conjunction with the urine albumin measurement to determine the presence of diabetic nephropathy and, if present, the stage of chronic kidney disease.
- In nonpregnant normotensive patients with persistently increased urine albumin excretion, an ACE inhibitor or angiotensin receptor blocker is recommended to decrease progression of diabetic nephropathy.

Diabetic Neuropathy

Related Question

Question 66

There are several categories of diabetic neuropathy, which may present separately or in combination. Symptoms of diabetic neuropathy depend on the nerve(s) or nerve root that is affected and may present as focal or diffuse disease. Achieving optimal glycemic control early in the course of diabetes can prevent the development of neuropathy, and sustained optimal glucose levels can delay the progression of neuropathy.

Distal symmetric polyneuropathy (DPN) is the most common form of diabetic neuropathy. It is characterized by a “stocking-glove” distribution that ascends proximally. DPN frequently presents as a sensation of numbness, tingling, burning, heaviness, pain, or sensitivity to light touch. The pain may worsen at night and with walking. Muscle weakness may occur in severe cases. DPN is a risk factor for muscle and joint deformities, such as Charcot foot, and foot ulcers. DPN evaluation includes assessment of ankle reflexes, vibration sensation with a 128-Hz tuning fork, and touch with a 10-g monofilament and pinprick. Screening intervals are found in **Table 12**. Management of DPN symptoms may require one or more classes of drugs, including antidepressants (amitriptyline, venlafaxine, duloxetine, paroxetine), anticonvulsants (pregabalin, gabapentin, valproate), or capsaicin cream.

Autonomic neuropathy can affect a single organ or multiple organs. Symptoms may include gastroparesis, diarrhea, constipation, neurogenic bladder, abnormal hidrosis, and erectile dysfunction. Cardiac symptoms include resting sinus tachycardia, orthostatic or postprandial hypotension, exercise intolerance, and silent myocardial infarction. Cardiovascular autonomic neuropathy is an independent risk factor for mortality, which underscores the need to reduce other cardiovascular risk factors in these patients.

Diabetic amyotrophy occurs in older patients or those with type 2 diabetes, and may be due to infarcts in the major nerve trunks of the leg. It can present acutely with severe pain and asymmetric proximal weakness or pain in the leg, weight loss, and autonomic neuropathy.

Partial remission may occur over many months. Without any approved treatments for diabetic amyotrophy, management consists of symptomatic therapy for neuropathic pain and ambulatory aids, if necessary.

Mononeuropathies can occur acutely with a cranial or peripheral distribution. There are no specific treatments for these mononeuropathies, as the symptoms usual resolve within a few months. Nerve compression syndromes, such as carpal tunnel syndrome or peroneal palsy, occur frequently in patients with diabetes. See MKSAP 17 Neurology for more information regarding diabetic neuropathy. Referral to a neurologist for electrodiagnostic testing or evaluation for nondiabetic-related etiologies should occur with severe, rapidly progressive, or atypical neuropathies.

Diabetic Foot Ulcers

Diabetic foot ulcers increase the risk for amputation and subsequent morbidity and disability. The etiology is often multifactorial. Loss of peripheral sensation can result in significant injuries that may be undetected by the patient. Peripheral arterial disease predisposes to the development of lower extremity ischemic ulcers and impairs healing. Altered leukocyte function from hyperglycemia can impede wound healing of injuries.

Clinicians should evaluate the feet at least annually to assess for pedal pulses, sensation, ulcers, skin or nail infections, pain, ankle reflexes, and foot deformities. Patients should inspect their feet daily for early detection of any abnormality and wear appropriate footwear. Although patients with diabetes have different footwear needs, the selection of shoes should take into account several important factors: intended use, plantar protection, shape and fit on the foot, and stability issues (see MKSAP 17 Infectious Disease).

Hypoglycemic Unawareness

Related Question

Question 76

Frequent severe hypoglycemia can diminish the ability to detect life-threatening hypoglycemia. This unawareness is caused by failure of the release of counterregulatory hormones to trigger an autonomic response to decreased glucose levels. Continual avoidance of hypoglycemia for several weeks or longer may help restore the body's ability to detect hypoglycemia. Plasma glucose levels should be kept greater than 150 mg/dL (8.3 mmol/L) during the time period when restoration of hypoglycemic symptoms is the goal to avoid unintended and unexpected hypoglycemia. Continuous glucose monitoring systems can be useful for hypoglycemia management by alerting the patient to rapid decreases in glucose levels to allow prompt correction and avoidance of hypoglycemia (see Self-Monitoring of Blood Glucose).

Key Point

- Distal symmetric polyneuropathy (DPN) is the most common form of diabetic neuropathy, and it presents as a sensation of numbness or burning pain in a stocking-glove distribution; management may require one or more classes of drugs, including antidepressants (amitriptyline, venlafaxine, duloxetine, paroxetine), anticonvulsants (pregabalin, gabapentin, valproate), or capsaicin cream

Disorders of the Pituitary Gland

Hypothalamic and Pituitary Anatomy and Physiology

The anterior pituitary is made up of glandular tissue that receives its blood supply from the hypothalamus through the hypothalamic-pituitary portal plexus, whereas the posterior pituitary consists of direct extension of neurons from the hypothalamus. Both the portal blood system and the hypothalamic neurons transverse from the hypothalamus to the pituitary by way of the pituitary stalk. The hypothalamus regulates anterior pituitary gland function by synthesizing specific stimulating and inhibiting hormones, which are released in the portal blood. Posterior pituitary hormones are synthesized in the hypothalamus and travel through hypothalamic neurons to be secreted by the posterior pituitary gland. The

anterior and posterior lobes are joined by the Rathke pouch. Table 13lists the pituitary hormones and initial testing for suspected pituitary hormone excess or deficiency.

Table 13. OPEN IN NEW WINDOWInitial Testing for Pituitary Hormone Deficiency and Excess

Pituitary Hormone Excess

Pituitary Hormone	Peripheral Hormone	Initial Test(s)
ACTH	Cortisol	24 hour urine free cortisol (×2) OR nocturnal salivary cortisol (×2) OR overnight low dose dexamethasone test
ADH	ADH	Simultaneous serum, urine sodium, and urine osmolality
GH	IGF-1	IGF-1
TSH	Thyroxine, triiodothyronine	TSH, free (or total) thyroxine

Pituitary Hormone Deficiency

Pituitary Hormone	Peripheral Hormone	Initial Test(s)	Confirmatory Test[a]
ACTH	Cortisol	Simultaneous ACTH, cortisol	ACTH stimulation test

Table 13. OPEN IN NEW WINDOW Initial Testing for Pituitary Hormone Deficiency and Exc

Pituitary Hormone Excess

Pituitary Hormone	Peripheral Hormone	Initial Test(s)	
ADH	ADH	Simultaneous serum sodium, urine and serum osmolality	Water d test
LH and FSH[b]	Sex hormones	Simultaneous LH, FSH, testosterone (male), estriol (female)	
TSH	Thyroxine, triiodothyronine	Simultaneous TSH, free (or total) thyroxine	

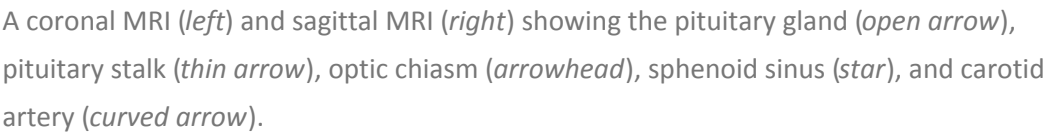
- ACTH = adrenocorticotropic hormone; ADH = antidiuretic hormone; FSH = follicle – stimulating hormone; GH = growth hormone; IGF-1 = insulin-like growth factor 1; LH = luteinizing hormone; TSH = thyroid-stimulating hormone.
- [a]See Table 15 for additional information on confirmatory testing for pituitary dysfunction.
- [b]Routine testing for deficiency is not recommended without specific signs of deficiency such as amenorrhea, gynecomastia, or impotence.

The anterior pituitary gland secretes and releases six hormones: adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), the gonadotropins–luteinizing hormone (LH) and follicle-stimulating hormone (FSH), growth hormone (GH), and prolactin. ACTH is released in response to corticotrophin-releasing hormone (CRH) and acts on the adrenal glands to promote the synthesis and secretion of cortisol. TSH is released in response to thyrotropin-releasing hormone (TRH) and acts on the thyroid to stimulate thyroid hormone production. LH and FSH are differentially released from the pituitary gland in response to pulses of gonadotropin-releasing hormone (GnRH). LH and FSH regulate normal male and female reproductive function. GH production is regulated by somatostatin. Prolactin controls lactation and is inhibited by dopamine.

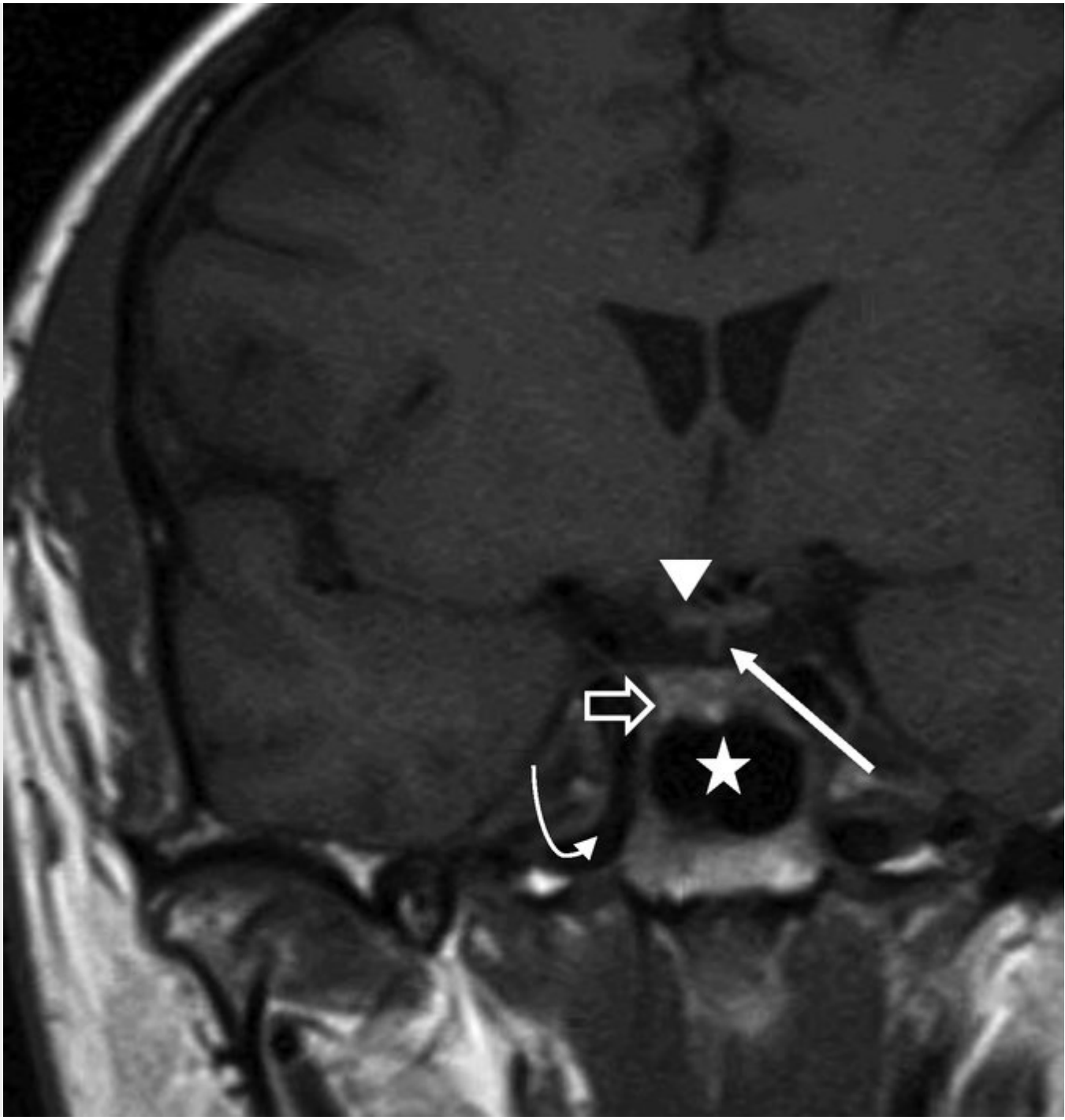
The posterior pituitary gland secretes oxytocin, which is necessary for parturition, and antidiuretic hormone (ADH, also called vasopressin), which regulates water balance.

The pituitary gland is posterior and superior to the sphenoid sinus, which provides surgical access to the gland, and is adjacent to the optic chiasm, the carotid arteries, and the cavernous sinuses(**Figure 2**).

Figure 2.OPEN IN NEW WINDOW



A coronal MRI (*left*) and sagittal MRI (*right*) showing the pituitary gland (*open arrow*), pituitary stalk (*thin arrow*), optic chiasm (*arrowhead*), sphenoid sinus (*star*), and carotid artery (*curved arrow*).



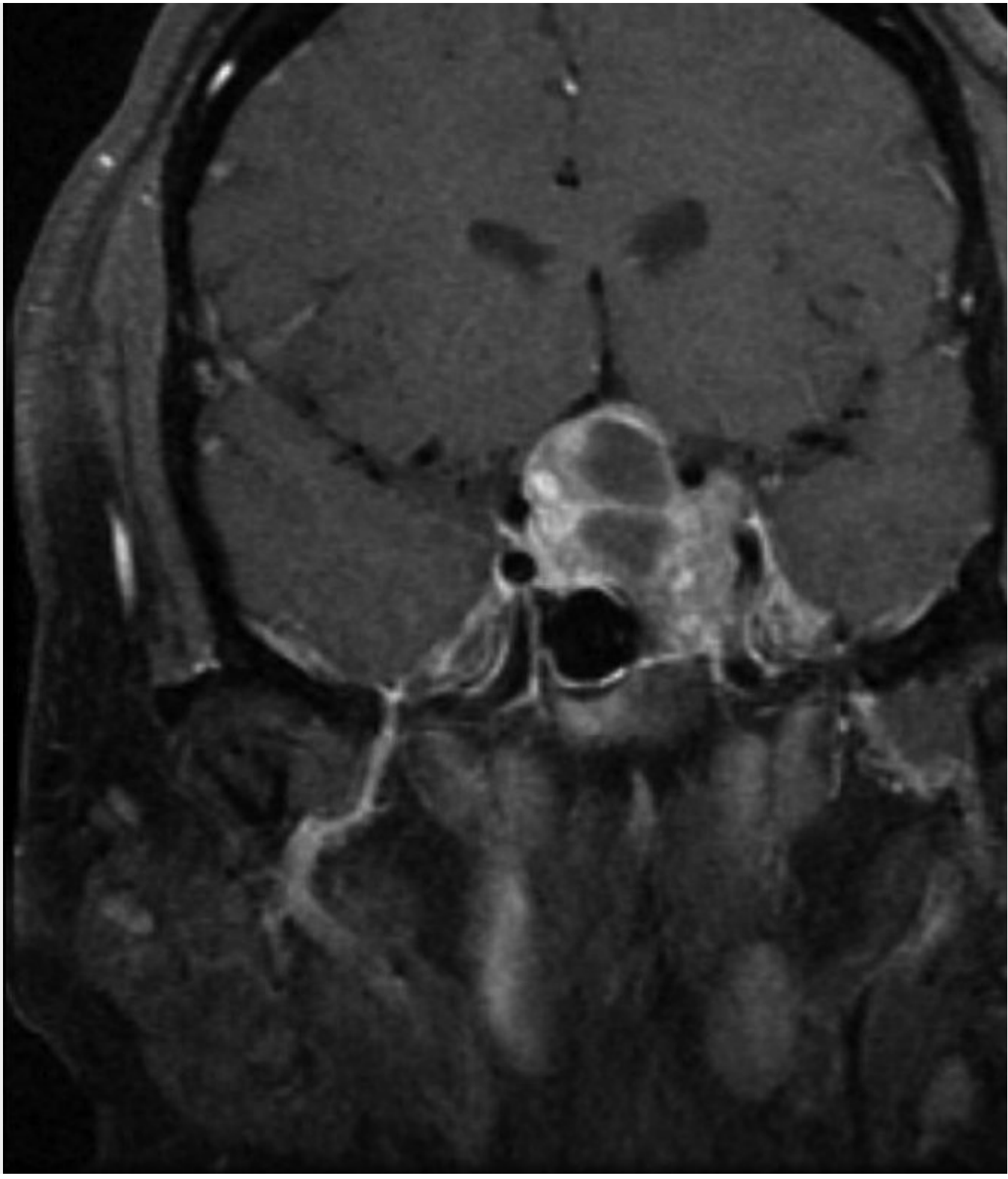
The pituitary gland is best imaged using MRI with gadolinium. Because the normal pituitary is relatively small, a dedicated pituitary protocol that obtains thin MRI slices through the sella is used.

Pituitary Tumors

Pituitary adenomas, which are benign, are the most common tumor of the pituitary gland. A tumor less than 1 cm is defined as a microadenoma, and a tumor 1 cm or larger is termed a macroadenoma(**Figure 3**). Pituitary adenomas are common. Autopsy studies document that 10% of the general population had undiagnosed pituitary adenomas. Frequently, pituitary adenomas are incidental findings on imaging studies completed for other reasons. When patients undergo brain MRI, 10% to 38% are found to have incidental pituitary microadenomas and 0.2% have incidental pituitary macroadenomas. Certain genetic mutations increase the chance of developing a pituitary tumor.

Figure 3. OPEN IN NEW WINDOW

A coronal MRI (*left*) and sagittal MRI (*right*) showing a large pituitary macroadenoma. The normal pituitary gland and the optic chiasm cannot be seen because of compression from the tumor. The tumor is invasive into the left cavernous sinus. Likely, the tumor appears heterogeneous because of internal necrosis.



Approach to a Sellar Mass

When a sellar mass is noted, pituitary adenomas are most likely; however, they need to be distinguished from other pituitary lesions and nonpathologic pituitary enlargement.

The pituitary gland is enlarged diffusely in untreated primary hypothyroidism and during pregnancy. When possible, imaging of the pituitary gland should be avoided or delayed in pregnancy and in untreated primary hypothyroidism because gland enlargement on imaging may prompt an expensive and unnecessary evaluation for pituitary hormone abnormality and tumor.

Pituitary tumors are almost always nonmalignant. Two exceptions are metastatic disease and the very rare pituitary carcinoma. Additional kinds of noncancerous pituitary lesions include craniopharyngiomas, meningiomas, and Rathke cleft cysts. Inflammatory and infiltrative disorders, including lymphocytic hypophysitis, sarcoidosis, hemochromatosis, amyloidosis, Langerhans cell histiocytosis, lymphoma, and tuberculosis, can affect the pituitary gland.

Lymphocytic hypophysitis is an inflammatory pituitary lymphocytic infiltration that most commonly occurs in pregnant and postpartum women. It may cause transient or permanent pituitary insufficiency. Lymphocytic hypophysitis is treated with glucocorticoids.

A sellar mass can compress normal surrounding tissue and impair normal neurologic and pituitary function. Pituitary adenomas may also be functional and secrete excess hormone.

Incidentally Noted Pituitary Masses

When a pituitary tumor is incidentally noted, investigation must determine (1) whether it is causing a mass effect, (2) whether it is secreting excess hormones, and (3) whether it has a propensity to grow and cause problems in the future. After a thorough history and physical examination, biochemical testing can be undertaken in a targeted fashion based on the patient's clinical signs and symptoms. Initial tests could include measurement of 8 AM cortisol, TSH, free (or total) thyroxine (T_4), prolactin, and insulin-like growth factor 1 (IGF-1).

If the tumor is not causing mass effect and there is no evidence of hormone excess, a pituitary MRI should be repeated in 6 months for a macroadenoma and 12 months for a microadenoma to assess for growth. If no growth occurs, MRIs should be repeated

every 1 to 2 years for the next 3 years and then intermittently thereafter. In a patient at risk for cancer or with a history of cancer, metastatic disease must be excluded.

Empty Sella

Empty sella is diagnosed when the normal pituitary gland is not visualized or is excessively small on MRI; it is a radiologic finding and not a distinct clinical condition. The pituitary sella is said to be "empty" because normal tissue is not seen. The finding may be primarily due to increased cerebrospinal fluid entering and enlarging the sella, or it may be secondary to a tumor, previous pituitary surgery, radiation, or infarction. Empty sella can also occur as a congenital abnormality when the sella is normal size, but the pituitary is small. When empty sella is found incidentally on imaging, an evaluation should be completed to determine if there is a known cause for secondary empty sella and if the patient has signs or symptoms of pituitary hormone deficiency. A patient without signs or symptoms should be screened for cortisol deficiency and hypothyroidism with 8 AM cortisol, TSH, and free (or total) T_4. A patient with signs of pituitary hormone deficiency should receive a more complete biochemical evaluation of the pituitary axes, based on the signs and symptoms found.

Repeat imaging is not necessary unless indicated as surveillance for the underlying pathology that resulted in the empty sella.

Key Point s

- Incidentally noted pituitary tumors are common, and biochemical testing is informed by findings on history and physical examination.
- Initial tests for pituitary incidentally noted masses include measurement of 8 AM cortisol, thyroid-stimulating hormone, free (or total) thyroxine (T_4), prolactin, and insulin-like growth factor 1.
- Empty sella is diagnosed when the normal pituitary gland is not visualized or is excessively small on MRI; it is a radiologic finding and not a distinct clinical condition.

Mass Effects of Pituitary Tumors

Pituitary tumors may cause headaches in some but not all patients; the size of the tumor does not always correlate with the presence and severity of headache.

Pituitary masses can compress the normal pituitary gland, causing hormone deficiencies. A large pituitary mass may cause panhypopituitarism in which there is impaired secretion of all pituitary hormones.

Because the optic chiasm is located superior to the pituitary gland, a large pituitary mass may compress the optic chiasm resulting in vision changes. Depending on the size of the tumor and severity of optic nerve damage, a pituitary tumor may cause minimal peripheral vision loss, bitemporal hemianopsia, or complete blindness. Visual field testing is a sensitive measure of optic nerve damage and should be evaluated by an ophthalmologist in patients who report a change in vision, who have a pituitary tumor that abuts or compresses the chiasm on MRI, or who have any evidence of gross peripheral vision loss on physical examination. Change in vision due to optic chiasm compression is an indication for treating a pituitary tumor.

Pituitary tumors can also invade surrounding brain tissue leading to seizures and neurologic manifestations. Pituitary tumors can invade the cavernous sinus, causing damage to cranial nerves III, IV, and VI that pass through the sinus causing diplopia and extraocular muscle palsies/paralysis.

Key Point

- Pituitary masses can compress the normal pituitary gland, causing hormone deficiencies; a large pituitary mass may cause panhypopituitarism in which there is impaired secretion of all pituitary hormones.

Treatment of Clinically Nonfunctioning Pituitary Tumors

Nonfunctioning pituitary tumors that are growing or causing mass effect are treated with neurosurgery. The most common surgical approach is transsphenoidal through the nares or the mouth. A very large or invasive tumor may require craniotomy for decompression. Indications for surgery include mass effect, particularly a visual field defect; tumor that abuts the optic chiasm; tumor growth; or an invasive tumor (invading the brain or cavernous sinus). Surgery should also be considered in a patient with a tumor close to the optic chiasm

who plans to become pregnant (due to the physiologic enlargement of the pituitary associated with pregnancy).

Functional pituitary tumors will be discussed later in this chapter, based on the hormone in excess (seePituitary Hormone Excess).

Key Point

- Nonfunctioning pituitary tumors that are growing or causing mass effect are treated with neurosurgery.

Hypopituitarism

Related Question

Question 7

Hypopituitarism is caused by one or more pituitary hormone deficiencies, usually resulting from damage to the normal pituitary gland by a tumor. Hypopituitarism can also occur as a complication from surgery if the normal gland or the pituitary stalk is damaged during tumor resection or radiation therapy. Additional causes of hypopituitarism are listed in **Table 14**.

Table 14. OPEN IN NEW WINDOWCauses of Hypopituitarism

Pituitary adenoma
Pituitary surgery
Pituitary radiation
Pituitary apoplexy

Pituitary infarction
Craniopharyngioma
Metastatic tumor
Meningioma
Lymphocytic hypophysitis
Sarcoidosis
Langerhans cell histiocytosis
Lymphoma
Hemochromatosis
Congenital deficiencies
Hypothalamic disease

Pituitary apoplexy is acute hemorrhage into the pituitary gland often at the site of a preexisting pituitary adenoma (typically a macroadenoma). Pituitary apoplexy can cause acute pituitary hormone deficiency or mass effect from rapid expansion of the sellar contents due to bleeding. It is an endocrine and neurosurgical emergency. Acute ACTH

deficiency is common and can be life-threatening. If suspected, stress-dose glucocorticoid replacement should be initiated emergently. Patients with vision changes or loss associated with apoplexy require urgent surgical decompression.

Hypopituitarism can occur due to postpartum pituitary infarction (Sheehan syndrome) because of excessive postpartum hemorrhage causing hypotension and hypoperfusion. Patients who may have Sheehan syndrome should be emergently tested and treated for secondary cortisol deficiency. A patient with Sheehan syndrome will not lactate because of prolactin deficiency; no treatment is available to induce lactation. Other hormone deficiencies can be evaluated 6 weeks after delivery.

GH and gonadotropin deficiencies often occur early when the pituitary gland is damaged by tumor, radiation, surgery, or hemorrhage because the cell lines that synthesize GH (somatotrophs) and LH and FSH (gonadotrophs) are most sensitive to injury. Secondary hypothyroidism (TSH deficiency) and secondary cortisol deficiency (ACTH deficiency) often occur later in the disease process. Pituitary adenomas can cause elevation in prolactin due to stalk compression, leading to a decrease in dopaminergic inhibition of prolactin secretion.

Key Points

- Pituitary tumors and surgery for pituitary tumors are the most common causes of hypopituitarism.
- Stress-dose glucocorticoid replacement should be initiated emergently in patients with pituitary apoplexy or infarction, as well as emergent neurosurgical intervention; patients with vision loss associated with apoplexy require urgent surgical decompression.

Adrenocorticotropic Hormone Deficiency (Secondary Cortisol Deficiency)

Although secondary cortisol deficiency may result from damage to the pituitary gland or pituitary stalk that impairs ACTH production, it is most commonly iatrogenic due to exogenous glucocorticoid use that suppresses pituitary ACTH secretion. Patients with secondary cortisol deficiency have only glucocorticoid deficiency. The remainder of the adrenal gland functions normally and the renin-angiotensin system is

intact, so these patients do not have mineralocorticoid deficiency (see Disorders of the Adrenal Glands for a discussion of primary adrenal failure). Although patients with secondary cortisol deficiency do require stress-dose glucocorticoids, they are at less risk for hypotension, hyponatremia, and adrenal crisis than those with primary cortisol deficiency (failure of the adrenal glands) because the production of mineralocorticoid is retained. Also, unlike patients with primary cortisol deficiency, patients with secondary cortisol deficiency do not develop hyperpigmentation or bronzing of the skin because ACTH and its prohormone responsible for these changes, pro-opiomelanocortin (POMC), are not hypersecreted.

Oral, injectable (including joint injections), and even topical glucocorticoids are able to suppress ACTH secretion. Glucocorticoids prescribed at doses above physiologic replacement for longer than 3 weeks should be tapered when discontinued to allow recovery of the pituitary-adrenal axis; if therapy has lasted less than 3 weeks, no taper is required for pituitary-adrenal axis recovery.

When tapering glucocorticoids, the patient can be transitioned to a hydrocortisone dose that is 10% to 20% lower than the equivalent, current glucocorticoid dose. The dose can then be decreased by 2.5 to 5 mg of hydrocortisone every 1 to 2 weeks. When tapering with prednisone, taper large doses by 25% to 50% weekly until the patient is on a dose of 5 mg daily and then taper by 1 mg every 1 to 2 weeks. It is difficult to taper dexamethasone due to the limited mg tablets available. The taper can be slower if symptoms such as lightheadedness persist.

After prolonged glucocorticoid use, recovery of the pituitary-adrenal axis should be tested prior to discontinuing glucocorticoid replacement. Specifically, morning serum cortisol should normalize to greater than 11 µg/dL (303.6 nmol/L) when glucocorticoids are withheld for 36 to 48 hours following the taper. Even after endogenous ACTH production has returned, patients may require more time to mount an adequate ACTH response to stress. After discontinuing the glucocorticoid taper, the patient can undergo an ACTH stimulation test (**Table 15**) to document adequate glucocorticoid response to stress. The diagnosis relies on demonstrating a low basal

serum cortisol level that does not increase appropriately after stimulation with the ACTH analogue cosyntropin. This is done by measuring early morning (8 AM) serum cortisol. A serum cortisol level less than 3 μg/dL (82.8 nmol/L) is consistent with cortisol deficiency. A normal response is a peak serum cortisol greater than 20 μg/dL (552 nmol/L). When the test result is normal, patients no longer require daily cortisol replacement, but should follow "sick day rules" (increasing cortisol replacement dose during illness) for up to a year after cessation of daily cortisol replacement.

Symptoms of secondary cortisol deficiency include weight loss, nausea, vomiting, lightheadedness, hypoglycemia, hypotension, and hyponatremia. Secondary cortisol deficiency is also diagnosed using an ACTH stimulation test. Secondary cortisol deficiency can be life threatening and must be treated with glucocorticoid replacement, often with hydrocortisone, although prednisone or dexamethasone may also be used. Hydrocortisone (15-30 mg/d) should be administered in 2 to 3 divided doses, or hydrocortisone should be dosed 10 to 20 mg in the morning and 5 to 10 mg in the early afternoon.

Patients require stress doses of glucocorticoids when acutely ill, hospitalized, or undergoing the stress of surgery. For moderate physiologic stress (minor or moderate surgery with general anesthesia), hydrocortisone should used (45-75 mg/d orally or intravenously in 3-4 divided doses for 2-3 days). Prednisone (10-20 mg or dexamethasone 2-3 mg/d in 1-2 divided doses) may be used alternatively. For major physiologic stress (major surgery, trauma, critical illness, or childbirth), hydrocortisone (150-200 mg/d intravenously in 3-4 divided doses; 100 mg/d the next day; taper to baseline in 3-5 days) may be used. An alternative would be dexamethasone (6-8 mg/d intravenously in 2-3 divided doses). If the patient has pituitary apoplexy and urgent/emergent neurosurgery is planned with no time for ACTH-stimulation testing, the patient should empirically be treated with glucocorticoids and then receive an ACTH stimulation test 4 to 8 weeks after surgery.

Thyroid-Stimulating Hormone Deficiency

Thyroid-stimulating hormone (TSH) deficiency leads to secondary or central hypothyroidism. Secondary hypothyroidism is clinically identical to primary hypothyroidism (see Disorders of the Thyroid Gland).

Secondary hypothyroidism is diagnosed by demonstrating a simultaneously inappropriately normal or low TSH and low T_4 (free or total). Patients are treated with levothyroxine replacement in the same manner as primary hypothyroidism; however, the serum TSH cannot be used to monitor and assess for adequacy of thyroid hormone replacement dosing. Instead, the levothyroxine dose is adjusted based on free T_4 levels with the goal of obtaining a value within the normal reference range.

Key Points

- Patients with secondary cortisol deficiency have isolated glucocorticoid deficiency without mineralocorticoid deficiency; in addition, they do not develop hyperpigmentation or bronzing of the skin because adrenocorticotropic hormone and pro-opiomelanocortin are not hypersecreted.
- Secondary or central hypothyroidism is diagnosed by demonstrating a simultaneously inappropriately normal or low thyroid-stimulating hormone and low thyroxine (T_4) (free or total) level.

Gonadotropin Deficiency

The pituitary gland normally secretes LH and FSH in response to GnRH from the hypothalamus. LH and FSH stimulate the secretion of normal male and female sex hormones; LH and FSH deficiency causes hypogonadotropic hypogonadism (see Reproductive Disorders).

Hypogonadotropic hypogonadism may be caused by GnRH deficiency. The most common cause of GnRH deficiency in women is hypothalamic amenorrhea, which is associated with excess exercise, illness, or anorexia. Additional causes of GnRH deficiency include congenital GnRH deficiency and Kallmann syndrome, a condition in which hypothalamic neurons

responsible for releasing GnRH fail to migrate into the hypothalamus during embryonic development.

Treatment of hypogonadotropic hypogonadism depends on the goals of therapy and whether the patient desires fertility. Fertility treatment requires replacement of the gonadotropins in men and women. Premenopausal women who do not desire fertility may be treated with estrogen- and progesterone-containing oral contraceptives (after assessment of risk of thromboembolic disease). Treatment of premenopausal hypogonadotropic hypogonadism is recommended to avoid loss of estrogen-dependent bone at a young age, which could lead to osteoporosis. Treatment of postmenopausal hypogonadotropic hypogonadism is not indicated. Men who do not desire fertility may be treated with testosterone replacement therapy (see Reproductive Disorders).

Growth Hormone Deficiency

Growth hormone (GH) is vital for normal linear growth, and deficiency prior to puberty will lead to short stature. At puberty, the epiphyses close, halting linear growth. In adulthood, GH production is necessary for normal physiology but is not as important for growth as during childhood. In adults, GH deficiency causes fatigue, loss of muscle mass, an increased ratio of fatty tissue to lean tissue, and increased risk for osteoporosis.

GH deficiency is often the first hormone deficiency to occur when a patient is developing pituitary insufficiency, but isolated adult-onset GH deficiency is extremely rare, and its clinical significance in adults is debated. Therefore, evaluation for GH deficiency is recommended in patients with at least one known pituitary hormone deficiency. Unfortunately, GH therapy has been used inappropriately as an alternative medication. GH naturally declines with age and does not require replacement. The use of GH does not promote longevity and when used inappropriately can be harmful. Specifically, GH therapy can encourage cancer growth, worsening the disease in a patient with cancer, or promoting growth of an occult, undiagnosed cancer.

Because GH secretion is pulsatile, testing random levels is not diagnostically useful. Therefore, GH deficiency is diagnosed by measurement of IGF-1. A GH deficiency is confirmed by measuring the response of serum GH on a stimulatory test, such as the insulin tolerance test. An insulin tolerance test carries a high risk of severe hypoglycemia, so referral to an endocrinologist for testing is appropriate.

A decision regarding replacement therapy should be made based on that patient's symptoms, goals, and risks in consultation with the patient's endocrinologist. When clinically indicated, GH deficiency is treated with daily subcutaneous GH injections. In an otherwise healthy adult, treatment of GH deficiency can improve quality of life and increase the percentage of lean muscle mass. Also, it can reduce the risk of osteoporosis. However, the risks and benefits of therapy must be carefully considered. Replacement of GH is cost prohibitive for some patients. It is contraindicated in patients with cancer and should not be used in patients with an untreated pituitary tumor due to potential stimulation of tumor growth.

Key Point

- Isolated adult-onset growth hormone deficiency is extremely rare, and its clinical significance is debated; evaluation for growth hormone deficiency should be reserved for adults with at least one known pituitary hormone deficiency.

Central Diabetes Insipidus

Central diabetes insipidus (DI) results from inadequate production of antidiuretic hormone (ADH) by the posterior pituitary gland. In the presence of ADH, aquaporin water channels are inserted in the collecting tubules and allow water to be reabsorbed. In the absence of ADH, excessive water is excreted by the kidneys. Excretion of more than 3 liters of urine per day is considered polyuric.

The severity of DI varies with the completeness of the deficiency. Patients describe mild to extreme polyuria and corresponding thirst; partial DI is common.

Frank hypernatremia is unusual because patients develop extreme thirst and polydipsia, and with free access to water, can maintain serum sodium in the high normal range. When patients do not drink enough to replace the water lost in the urine, due to poor or absent thirst drive or lack of free access to water, they develop hypernatremia.

In the patient with polyuria, DI is diagnosed with simultaneous laboratory evidence of inability to concentrate urine in the face of elevated serum sodium and osmolality, with inappropriately low urine osmolality. If necessary, a water deprivation test can confirm the diagnosis (see **Table 15**).

Table 15. OPEN IN NEW WINDOW Dynamic Testing for Pituitary Dysfunction

Indication	Test	Technique	Interpretation
ACTH (cortisol) deficiency	ACTH stimulation test	Measure baseline serum cortisol level. Administer 250 µg of synthetic ACTH. Measure cortisol levels at 30 and 60 minutes.	Serum cortisol level >18 µg/dL (496.8 nmol/L) indicates a normal response.
ADH deficiency (DI)	Water deprivation test, followed by desmopressin challenge if	Patient empties bladder, and baseline weight is measured. Measure urine volume and	**Water deprivation test interpretation:** Urine osmolality >600 mOsm/kg H_2O is a normal response to water deprivation, indicating ADH production and peripheral effect are intact. Urine osmolality <600 mOsm/kg H_2O, serum osmolality >295

Table 15. OPEN IN NEW WINDOW Dynamic Testing for Pituitary Dysfunction

Indication	Test	Technique	Interpretation
	indicated	osmolality hourly. Measure serum sodium, osmolality, and weight every 2 hours. The test is stopped when one of the following occurs: - Urine osmolality exceeds 600 mOsm/kg H_2O - Patient has lost 5% of body weight - Urine osmolality is stable for 2-3 h while serum osmolality rises - Plasma osmolality >295 mOsm/kg H_2O	mOsm/kg H_2O and/or serum sodium >145 mEq/L (145 mmol/L) are diagnostic of DI. **Desmopressin challenge interpretation:** >100% increase in urine osmolality is diagnostic of complete central DI. 0% increase in urine osmolality is diagnostic of complete nephrogenic DI. >50% increase in urine osmolality is diagnostic of partial central DI. <50% increase in urine osmolality is diagnostic of partial nephrogenic DI.

Table 15. OPEN IN NEW WINDOW Dynamic Testing for Pituitary Dysfunction

Indication	Test	Technique	Interpretation
		- Serum sodium >145 mEq/L (145 mmol/L) Desmopressin challenge if final urine osmolality <600 mOsm/kg H_2O, serum osmolality >295 mOsm/kg H_2O, or serum sodium >145 mEq/L (145 mmol/L): Give desmopressin 1 µg subcutaneously. Measure urine osmolality every 30 minutes for 2 hours.	
Growth hormone excess	Glucose tolerance test	75 g oral glucose tolerance test.	GH <0.2 ng/mL (0.2 µg/L) is a normal response. GH ≥1.0 ng/mL (1.0 µg/L) (or ≥0.3 ng/mL [0.3 µg/L] on an ultrasensitive assay) is diagnostic of acromegaly.

Table 15. OPEN IN NEW WINDOW Dynamic Testing for Pituitary Dysfunction

Indication	Test	Technique	Interpretation
(acromegaly)		Measure glucose and GH at 0, 30, 60, 90, 120, and 150 minutes.	

- ACTH = adrenocorticotropic hormone; ADH = antidiuretic hormone; DI = diabetes insipidus; GH = growth hormone.

Patients with mild partial DI with an adequate thirst drive and access to water may choose to compensate without hormone replacement therapy, but highly symptomatic polyuria and nocturia that interferes with restful sleep and daily function necessitate treatment. In those requiring treatment, hormone replacement is with desmopressin (1-desamino-8-D-arginine vasopressin, or dDAVP) either intranasally, subcutaneously, or orally. Desmopressin is not absorbed well in the gastrointestinal tract, so oral doses are much higher than intranasal or subcutaneous doses. Most patients with DI require either evening dosing to aid in sleep or twice daily dosing of desmopressin. If ADH is overreplaced, patients will develop water intoxication, volume overload, and hyponatremia.

Key Points

- In the patient with polyuria, diabetes insipidus is diagnosed by clinical symptoms with simultaneous laboratory evidence of inability to concentrate urine with elevated serum sodium and osmolality, and inappropriately low urine osmolality; a water deprivation test can confirm the diagnosis.
- Treatment of central diabetes insipidus is once or twice daily hormone replacement with desmopressin.

Panhypopituitarism

Related Question

Question 56

Panhypopituitarism occurs when patients lack all anterior and posterior pituitary hormone production. Panhypopituitarism may be caused by a large or aggressive pituitary tumor or as a complication of surgery. If the pituitary stalk is transected during surgery or as the result of trauma, panhypopituitarism will result acutely. Patients with panhypopituitarism require lifelong replacement of T_4, cortisol, and ADH because these deficiencies can be life-threatening. GH and sex hormones are replaced dependent on each patient's preference, coupled with a discussion of the risks and benefits of therapy. In addition to requiring exogenous gonadotropins to conceive, a reproductive-aged woman with panhypopituitarism will not go into spontaneous labor and will not lactate. These pregnancies are classified as high risk, and obstetric care should be provided by a maternal-fetal specialist.

Patients with panhypopituitarism should wear medical alert identification documenting their panhypopituitarism, specifically noting the need for stress-dose glucocorticoid therapy and desmopressin dosing in emergent situations.

Key Point

- Patients with panhypopituitarism require lifelong replacement of thyroxine (T_4), cortisol, and antidiuretic hormone because these deficiencies can be life-threatening.

Pituitary Hormone Excess

Pituitary tumors are called functional when they secrete excessive amounts of hormone. The most common functional pituitary tumor is a prolactinoma. GH and ACTH overproduction by pituitary tumors is important to recognize because the clinical consequences of oversecretion are potentially severe. TSH-secreting tumors cause hyperthyroidism but are extremely rare.

Occasionally, a pituitary tumor can oversecrete more than one hormone, most commonly GH and prolactin, or less commonly, TSH and GH or prolactin.

Hyperprolactinemia and Prolactinoma

Related Question

Question 84

Causes
Related Questions

Question 11

Question 80

Prolactinomas are pituitary tumors that secrete excessive amounts of prolactin; however, they are not the only cause of hyperprolactinemia (Table 16).

Table 16. OPEN IN NEW WINDOW Causes of Hyperprolactinemia

Physiologic	Medications	Other
Pregnancy	Antipsychotic agents[a]	Prolactinoma
Lactation	Metoclopramide	Pituitary tumor—stalk compression
Nipple stimulation	Cimetidine	Hypothyroidism
	Verapamil	Cirrhosis
	Methyldopa	Chronic kidney disease
	Opiates	
	Cocaine	

- [a]Including risperidone, olanzapine, haloperidol, chlorpromazine, and clomipramine.

The most common cause of hyperprolactinemia is physiologic; prolactin is released during pregnancy and postpartum to cause lactation. Nipple stimulation such as during sex can cause mild hyperprolactinemia (serum prolactin <40 ng/mL [40 µg/L]). Physiologic stress,

coitus, and exercise can also increase prolactin levels up to 40 ng/mL (40 µg/L). Nipple piercing can raise prolactin levels above 200 ng/mL (200 µg/L). Clinical breast examination should not raise prolactin levels above the reference range, unless evaluation for milk production is performed, but if desired, palpation of the breast can be deferred until after a serum prolactin level is measured.

Medications are a common cause of hyperprolactinemia (see **Table 16**). Antipsychotic agents cause hyperprolactinemia due to their antidopaminergic effect that interrupts the inhibition of prolactin by dopamine. Specific agents, such as risperidone or metoclopramide, may raise the prolactin level above 200 ng/mL (200 µg/L). Evaluation for pituitary hypersecretion when a patient is taking a medication known to raise the prolactin level is difficult. When the prolactin level is only mildly elevated (<50 ng/mL [50 µg/L]), it may be reasonable to assume that hyperprolactinemia is a medication side effect. When significantly elevated (>100 ng/mL [100 µg/L]), either the medication needs to be withheld to further assess or a pituitary MRI obtained to evaluate for prolactinoma. Caution is warranted when discontinuation of an antipsychotic agent is being considered, and consultation with a psychiatrist is recommended prior to discontinuation.

Another common cause of hyperprolactinemia is primary hypothyroidism. Hypothyroidism can cause diffuse swelling of the pituitary gland that may resemble enlargement due to a pituitary adenoma on imaging. Therefore, a patient with primary hypothyroidism and hyperprolactinemia should be treated with thyroid hormone replacement with retesting of the prolactin level once the TSH has normalized. Further evaluation is indicated if the hyperprolactinemia does not correct when hypothyroidism is treated. If pituitary imaging has noted pituitary enlargement prior to treatment of hypothyroidism, repeat MRI should be obtained when the TSH is normal.

Nonfunctioning pituitary adenomas can also cause hyperprolactinemia by compressing the pituitary stalk and decreasing dopamine inhibition of prolactin secretion. It is important to distinguish between prolactinomas and nonfunctioning pituitary adenomas as the cause of hyperprolactinemia because of different treatment approaches.

Clinical Features and Diagnosis

Physiologically, prolactin induces and regulates lactation. Hence, elevated levels of prolactin cause galactorrhea. Women are more likely to develop galactorrhea than men.

Hyperprolactinemia also causes hypogonadotropic hypogonadism because of negative feedback on GnRH, LH, and FSH by high levels of prolactin. Both men and women present with hypogonadism. Women of reproductive age often present earlier than men because of amenorrhea. They may also have early menopausal symptoms. Symptoms in men are insidious and may go unrecognized for years. Both men and women with hyperprolactinemia are likely to be infertile and are at risk for osteoporosis. Postmenopausal women are already hypogonadal because of ovarian failure; therefore, hyperprolactinemia may have minimal clinical implications in this population. However, the cause of postmenopausal hyperprolactinemia still requires diagnosis because it may be due to a pituitary tumor.

Diagnostic imaging is indicated in situations in which there is unexplained hyperprolactinemia.

The degree of hyperprolactinemia is useful in differentiating prolactinomas from nonfunctioning macroadenomas. In general, large nonfunctioning tumors cause mild serum prolactin elevations (<100 ng/mL [100 µg/L]) from stalk compression. Macroprolactinomas raise serum prolactin levels to greater than 250 ng/mL (250 µg/L). Very large macroprolactinomas may raise prolactin levels greater than 10,000 ng/mL (10,000 µg/L).

Therapy Related Questions

Question 19

Question 65

Patients with microprolactinomas without symptoms of hypogonadism do not require treatment. Symptomatic women with microadenomas may be treated with either oral contraceptive pills (if fertility is not desired) or dopamine agonists. Postmenopausal women

with microadenomas do not require treatment. Patients with hypogonadism from medication-induced hyperprolactinemia may be treated with hormone replacement.

Unlike other pituitary tumors, medication rather than surgery is first-line therapy for prolactinomas. Even patients with severe mass effect such as vision loss are treated with medical therapy initially. Rarely, very large tumors or more invasive prolactinomas do not shrink with medical therapy and, also rarely, continue to grow. In these patients, surgery should be considered, followed by radiotherapy if growth recurs or continues. After being debulked, the prolactinoma may respond better to medical therapy.

Prolactinomas are treated with dopamine agonists (DA). The two FDA-approved dopamine agonists are bromocriptine and cabergoline. Dopamine agonists typically decrease the size and hormone production of prolactinomas rapidly. Response to therapy can be monitored by checking serum prolactin levels 1 month after initiating therapy and then every 3 to 4 months. Decreasing serum prolactin usually correlates with decreasing size of the tumor. MRI should be repeated in 1 year for microprolactinomas if the prolactin level normalizes on dopamine agonists. After tumor shrinkage is confirmed, additional MRIs are not necessary unless the serum prolactin level rises. An MRI should be repeated after 3 months of medical therapy for macroprolactinomas, or if prolactin levels are rising on therapy with good medication adherence. MRI should be repeated every 6 to 12 months until the macroprolactinoma is stable on serial studies and the prolactin level is not rising.

Bromocriptine is dosed 1 to 3 times daily, so adherence can be challenging. When initiated, it is associated with orthostasis and lightheadedness, and patients can have dizziness, nausea, and headache during treatment. Cabergoline is much better tolerated and more effective at normalizing prolactin and tumor shrinkage, so it is typically the initial therapy chosen. It is dosed once or twice a week, but typically costs more than bromocriptine.

Therapy may be tapered after the prolactin level has been normal for 2 years, and there is no longer a visible tumor on pituitary MRI. After discontinuing the dopamine agonist, prolactin levels should be followed once a month for 3 months, then every 3 months for the

first year, and then annually thereafter; a pituitary MRI should be repeated if the prolactin level rises above normal.

Prolactinomas and Pregnancy Related Question

Question 3

Hyperprolactinemia is a frequent cause of infertility because of the effect on gonadotropin release. DA therapy lowers prolactin, normalizing gonadotropin regulation and allowing normal ovulation. DA therapy should be discontinued when the pregnancy is diagnosed. The pituitary increases in size during normal pregnancy, and prolactinomas can increase in size as well. The risk for significant tumor expansion is negligible in patients with microprolactinomas.

Women with macroprolactinomas are at risk for clinically significant tumor growth or vision compromise during pregnancy. If the tumor is very large or abuts the optic chiasm, patients should be counseled on risk of tumor growth during pregnancy, as well as the risks and benefits of surgical resection of the tumor before pregnancy. DA therapy is sometimes continued during pregnancy if the patient has a history of visual field defect.

Pregnant women with macroprolactinomas should be assessed clinically at least once per trimester and have visual fields tested every trimester or more frequently for vision change. Changes in visual fields or severe headache are indications to proceed with pituitary MRI. If the macroprolactinoma causes mass effect during pregnancy, bromocriptine may be started. If the bromocriptine does not decrease tumor size and reduce symptoms of mass effect, surgical debulking may be necessary.

Normal pregnancy causes hyperprolactinemia, so hyperprolactinemia from prolactinoma does not require treatment during pregnancy. Prolactin levels should not be measured during pregnancy. Postpartum, prolactin levels return to normal within a few months, and lactation becomes non-prolactin mediated.

Key Points

- Prolactinomas, pregnancy and lactation, or medications such as antipsychotic agents are frequent causes of hyperprolactinemia.
- A patient with primary hypothyroidism and hyperprolactinemia should be treated with thyroid hormone replacement with retesting of the prolactin level once the thyroid-stimulating hormone level has normalized.
- Dopamine agonists (bromocriptine and cabergoline) are first-line therapy for symptomatic patients with hyperprolactinemia and prolactinomas.

Acromegaly

Acromegaly is a rare diagnosis that is often missed for years because of the insidious onset and rare presentation in primary care; however, it has very serious implications for a patient's health and longevity and must be diagnosed and treated in as timely a manner as possible.

Causes

Acromegaly is the clinical syndrome that occurs when a pituitary tumor secretes excessive amounts of GH in an adult patient. Prior to puberty, patients with a GH-secreting tumor develop excessive longitudinal growth and gigantism, a term used to indicate excessive growth and height above normal for age. Because epiphyseal growth plates require sex hormones to close, patients with large pituitary tumors causing hypogonadism will not have closure of their growth plates and will continue growth into adulthood.

Clinical Features and Diagnosis in the Adult Patient with Acromegaly

Patients have changes in facial structure such as a prominent brow and jawline, an enlarged skull, a large nose, facial edema, excessive spacing between teeth, and macroglossia. The hands and feet may be disproportionately large. Other manifestations may include arthritis, skin tags, diabetes mellitus, hypertension, colon polyps, thickened skin, and excessive perspiration. Acromegaly can cause severe obstructive sleep apnea because of soft-tissue swelling and macroglossia. Additionally, it can result in heart disease, including left ventricular hypertrophy, cardiomyopathy, valvular heart disease, arrhythmia and diastolic heart failure. Increased rates of cancer are observed in acromegaly, including colon,

esophageal, and gastric adenocarcinomas; thyroid cancer; and melanoma. Acromegaly increases mortality, likely due to cardiovascular disease, diabetes, sleep apnea, and cancer. Age-appropriate testing for these conditions should occur for the lifetime of the patient with acromegaly.

Acromegaly is diagnosed biochemically. Because GH is pulsatile throughout the day, it is not useful for diagnosis, so measurement of serum IGF-1 is used instead. Excess GH is confirmed with an oral glucose tolerance test (see **Table 15**) because glucose normally suppresses GH levels to less than 1 ng/mL (1 µg/L). GH levels greater than 1 ng/mL (1 µg/L) are diagnostic of GH excess. A pituitary MRI should be obtained once GH excess is confirmed biochemically. Consultation with an endocrinologist is recommended if IGF-1 is elevated.

Treatment
Related Question

Question 61

Treatment of acromegaly is transsphenoidal tumor resection; surgery is the only treatment that is potentially curative. In many instances, cure with surgery is not possible and additional therapy is necessary to treat the residual GH excess and tumor.

Remission is achieved when IGF-1 levels are within the normal reference range for age and the response of GH to a glucose tolerance test is normal. Patients not achieving remission require medication to decrease GH levels and the long-term effects of GH excess. The initial therapy of choice is injectable somatostatin analogues to inhibit GH secretion. If a patient fails to benefit from somatostatin analogue treatment, high-dose dopamine agonist therapy is marginally effective when the tumor co-secretes prolactin. If IGF-1 remains elevated, pegvisomant, a GH receptor blocker, is used. Pegvisomant effectively lowers IGF-1 levels, but patients on pegvisomant have risk of tumor growth because the medication works in the peripheral tissues as an antagonist to GH and does not decrease GH production by the tumor.

Stereotactic radiosurgery (gamma knife) may be offered to increase the chance of remission or cure. External beam radiation carries a high risk of causing pituitary insufficiency, but the risk is decreased when stereotactic radiosurgery is used.

When acromegaly is in remission, MRI and hormone testing should be completed annually. When the pituitary tumor is stable but the IGF-1 level is elevated, MRI should be repeated annually and treatment should be altered until the IGF-1 declines.

Key Points

- Acromegaly occurs when a pituitary tumor secretes excessive amounts of growth hormone in an adult patient resulting in changes in facial structure, an enlarged skull, a large nose, facial edema, excessive spacing between teeth, macroglossia, and disproportionately large hands and feet.
- Treatment of acromegaly is transsphenoidal tumor resection; however, in some patients, adjuvant radiation therapy or medical therapy, such as injectable somatostatin analogues, is needed for residual disease.

Gonadotropin-Producing Adenomas

Gonadotropin-producing pituitary adenomas are typically asymptomatic and are treated similarly to nonfunctioning adenomas because they either do not secrete functional gonadotropins or do not secrete enough FSH or LH to produce a clinical syndrome. Often, the diagnosis is made postoperatively, based on histopathologic staining of surgical pathology specimens.

Thyroid-Stimulating Hormone–Secreting Tumors

TSH-secreting tumors are extremely rare. These tumors may co-secrete TSH and prolactin or GH. TSH-secreting tumors cause hyperthyroidism. Patients with TSH-secreting tumors have either an inappropriately normal or a high TSH level with a simultaneous elevation of T_4 and T_3 levels. They present with identical symptoms associated with non-TSH-mediated thyrotoxicosis (see Disorders of the Thyroid Gland). After biochemical proof of TSH excess is obtained, pituitary imaging is recommended to confirm a pituitary mass. Neurosurgery is

first-line therapy, but patients often require additional medical therapy with either somatostatin analogues or dopamine agonists.

Excess Antidiuretic Hormone Secretion

The syndrome of inappropriate ADH secretion (SIADH) causes water retention and hyponatremia. Central nervous system pathology such as stroke, hemorrhage, trauma, or infection can cause SIADH because of the excessive release of hypothalamic and pituitary ADH. Also, transient SIADH is a common complication of pituitary surgery, occurring in about one third of patients approximately 3 to 10 days after surgery (see MKSAP 17 Nephrology).

Cushing Disease

Related Question

Question 43

Cushing disease is the term used to indicate excess cortisol production due to an ACTH-secreting pituitary adenoma. Cushing syndrome refers to hypercortisolism from any cause, exogenous or endogenous, ACTH-dependent or not. The most common cause of endogenous Cushing syndrome is Cushing disease. When undiagnosed, Cushing disease is associated with devastating long-term morbidity such as diabetes, morbid obesity, hypertension, infertility, and osteoporosis.

The initial step in evaluation for Cushing disease is to seek biochemical evidence of hypercortisolism (see Disorders of the Adrenal Glands).

Once ACTH-dependent Cushing syndrome is confirmed biochemically, a pituitary MRI should be obtained. If no pituitary tumor or a tumor less than 6 mm is visualized on MRI, an 8-mg dexamethasone suppression test is used to differentiate Cushing disease from an ectopic source of ACTH. Ectopic ACTH production from a nonpituitary tumor (most often lung, pancreas, or thymus carcinomas) is very uncommon.

Dexamethasone is administered at 11 PM, and cortisol is tested at 8 AM. A pituitary source of ACTH will respond to negative feedback from high doses of dexamethasone, suppressing cortisol to less than 5 μg/dL (138 nmol/L), while an ectopic source of ACTH will not have suppressible cortisol. However, this test has low sensitivity (88%) and specificity (57%) for Cushing disease, so intrapetrosal sinus sampling (IPSS) is often recommended before exploratory pituitary surgery. In IPSS, a catheter is threaded through the petrosal sinus, and ACTH levels in the sinus are compared with those in the periphery after the administration of corticotropin-releasing hormone (CRH). A central to peripheral gradient greater than 2.0 before CRH or greater than 3.0 after CRH is diagnostic of Cushing disease (95% sensitivity, 93% specificity). Imaging of the chest and abdomen is indicated in patients with a suspected ectopic source of ACTH.

Treatment

Cushing disease is treated by transsphenoidal pituitary tumor resection, which may be curative. Endogenous ACTH production in the remaining normal pituitary gland will be suppressed after removal of the tumor due to long-standing hypercortisolism, so patients with successful surgical treatment will have acute ACTH deficiency and require glucocorticoid replacement. It may take up to 1 year for endogenous ACTH production to return to normal, and sometimes the hypothalamic-pituitary-adrenal axis does not recover. After successful resection, Cushing disease can recur, and patients must be monitored annually for several years, and then less frequently, or sooner if symptoms of hypercortisolism recur.

If surgical cure is not achieved, patients may be offered pituitary radiation or medical therapy. Medical options include inhibitors of adrenal enzyme synthesis of cortisol, ketoconazole, or metyrapone; the dopamine agonist, cabergoline; or the somatostatin analogue, pasireotide. Medical cure of Cushing disease has a relatively low success rate, but hypercortisolism symptom control is an achievable goal in all patients with endogenous Cushing syndrome.

In patients who do not benefit from surgical treatment and who have an inadequate response to medical treatment, bilateral adrenalectomy to remove the target of ACTH stimulation is an option. However, these patients will require lifelong glucocorticoid and mineralocorticoid replacement.

Key Points

- Cushing disease refers to excess cortisol production due to an adrenocorticotropic hormone (ACTH)-secreting pituitary adenoma; Cushing syndrome refers to hypercortisolism from any cause, exogenous or endogenous, ACTH-dependent or not.
- Cushing disease is treated by transsphenoidal pituitary tumor resection; after surgery glucocorticoid replacement therapy will be required at least transiently while the hypothalamic-pituitary-adrenal axis recovers endogenous function.

Disorders of the Adrenal Glands

Adrenal Anatomy and Physiology

Located just superior to each kidney, the paired adrenal glands consist of an outer cortex and an inner medulla that are distinct in embryologic origin and endocrine function. The adrenal cortex is composed of three zones: the zona (outer) glomerulosa, zona (middle) fasciculata, and zona (inner) reticularis. Within these zones corticosteroid hormones are synthesized from cholesterol by cytochrome P450 enzymes. Aldosterone, the principal mineralocorticoid hormone, is produced in the zona glomerulosa. Aldosterone production is triggered by an increase in the extracellular potassium concentration and by activation of aldosterone synthase through the renin-angiotensin-aldosterone pathway. Upon binding to type 1 mineralocorticoid receptors (MR) in the kidney, aldosterone promotes potassium wasting and sodium retention, which leads to an increase in intravascular volume and consequently blood pressure.

The zona fasciculata is the main site of glucocorticoid synthesis. Production of cortisol, the principal glucocorticoid, is stimulated by adrenocorticotropic hormone (ACTH) secretion

from the anterior pituitary. Cortisol secretion varies according to the circadian rhythm with relatively little secretion overnight, peak levels in the early morning, and smaller oscillations throughout the day. Cortisol attenuates inflammatory responses and contributes to glucose homeostasis by promoting lipolysis, hepatic gluconeogenesis, and insulin resistance. Physical stress (for example, critical illness) stimulates increased cortisol secretion, which enhances vascular smooth muscle tone and responsiveness to endogenous vasoconstrictors, thereby augmenting blood pressure.

Synthesis of adrenal androgens, dehydroepiandrosterone (DHEA) and its sulfate (DHEAS), and androstenedione, occurs primarily in the zona reticularis and is regulated by ACTH. Although the adrenal androgens themselves have minimal intrinsic androgenic activity, they are converted peripherally to testosterone and dihydrotestosterone. Unlike glucocorticoids and mineralocorticoids, deficiencies of adrenal androgens are not typically recognized due to parallel production of gonadal androgens.

The adrenal medulla and extra-adrenal sites of the sympathetic nervous system consist of chromaffin cells, which synthesize catecholamine hormones from the amino acid tyrosine (**Figure 4**). Catecholamines are stored within chromaffin granules, which release their contents in response to stress. Although catecholamine excess produces disease, hypofunction of the adrenal medulla does not because of redundancy of catecholamine production throughout the sympathetic nervous system. Norepinephrine is synthesized in the adrenal medulla and the extra-adrenal sites of the sympathetic nervous system. It causes vasoconstriction due to preferential binding to α-receptors. Epinephrine is almost exclusively produced in the adrenal medulla. It binds predominantly to β-receptors, and thus has positive effects on cardiac inotropy and chronotropy, produces peripheral vasodilation, and increases plasma glucose levels in response to hypoglycemia.

Figure 4. OPEN IN NEW WINDOW

Catecholamine hormones are produced in the adrenal medulla and sympathetic ganglia. The pathways of synthesis and degradation are shown. Excessive catecholamine secretion can occur with pheochromocytomas and paraganglionomas.

Adrenal Hormone Excess

Cushing Syndrome

Related Questions

Question 5

Question 23

Question 39

Question 48

Cushing syndrome (CS) is a rare disorder affecting two to three persons per million per year that results from elevated levels of cortisol. Poor suppressibility of cortisol with dexamethasone and loss of normal diurnal variation in cortisol secretion are seen. Without treatment, it is associated with high morbidity and mortality.

However, iatrogenic hypercortisolism from the administration of exogenous oral, inhaled, intra-articular, or topical glucocorticoids is often seen in clinical practice and is the most common cause of CS overall. The pharmacokinetics and relative potencies of synthetic oral glucocorticoids are shown in **Table 17**. The sustained administration of any synthetic glucocorticoid above the normal physiologic cortisol requirement can result in iatrogenic CS and hypothalamic-pituitary-adrenal (HPA) axis suppression, but is more likely to occur the longer the half-life of the drug. Doses equivalent to prednisone 5 mg/d or less are unlikely to cause clinically significant HPA axis suppression, while those in excess of 10 to 20 mg/d commonly do after 3 weeks or more of consecutive use.

Table 17. OPEN IN NEW WINDOW Dose Equivalence and Relative Potencies of Common Synthetic Oral Glucocorticoids

Synthetic Glucocorticoid	Equivalent Replacement Dose (mg)[a]	Biologic Half-Life (hours)	Relative Anti-Inflammatory Potency[b]	Relative Mineralocorticoid
Hydrocortisone	20	8-12	1	1/125
Prednisolone/prednisone	5	18-36	4	1/156
Methylprednisolone	4	18-36	5	0
Dexamethasone	0.75	36-54	25-50	0

- [a]Denotes common glucocorticoid dosing for primary adrenal failure equivalent to hydrocortisone, 20 mg.
- [b]Anti-inflammatory potency relative to hydrocortisone.
- [c]Mineralocorticoid potency relative to fludrocortisone.

Endogenous CS can result from ACTH-dependent and ACTH-independent causes. Cushing disease, which results from the autonomous secretion of ACTH by a corticotroph adenoma of the pituitary gland, is the cause of CS in more than two thirds of patients (see Disorders of the Pituitary Gland). Ectopic ACTH secretion by carcinomas and carcinoid tumors (usually bronchial origin) is less common, accounting for 10% to 15% of cases, while ectopic corticotropin-releasing hormone (CRH) production is rare. The most common ACTH-independent etiologies of CS are adrenal adenomas and carcinomas, which collectively account for approximately 20% of CS cases.

CS must be differentiated from other disorders and clinical states that are associated with physiologic hypercortisolism (pseudo-Cushing syndrome). Causes of pseudo-Cushing syndrome include severe obesity, polycystic ovary syndrome, pregnancy, anorexia nervosa, depression, alcoholism, and extreme physical stress, as in the setting of infection.

Clinical manifestations of CS are listed in Table 18. Clinical findings that are highly specific for CS include centripetal obesity, facial plethora, abnormal fat deposition in the supraclavicular or dorsocervical ("buffalo hump") areas, and wide (>1 cm) violaceous striae (Figure 5). It is important to initiate evaluation for CS in patients who have specific signs and symptoms of CS, rather than in patients who are diffusely obese, have nonpathologic striae, and are having trouble losing weight because endogenous CS is such a rare condition with a costly evaluation algorithm.

Table 18. OPEN IN NEW WINDOW Clinical Features of Cushing Syndrome

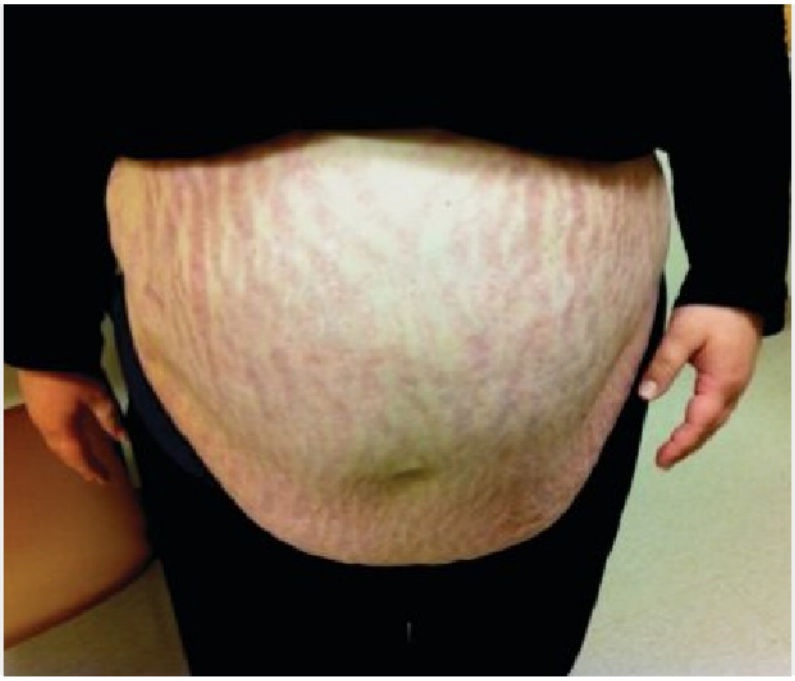
Specific Findings	Less Specific Findings	Associated Conditions[a]
Centripetal obesity	Easy bruising	Osteoporosis
Facial plethora	Excessive skin fragility	Hypertension
Supraclavicular fat pads	Proximal muscle weakness	Diabetes mellitus
Dorsocervical fat pads	Impaired memory	Obesity
Wide violaceous striae	Temporal balding[b]	Depression
	Hirsutism (in women)[b]	Hypokalemia
	Menstrual abnormalities[b]	Nephrolithiasis
		VTE/PE

- PE = pulmonary embolism; VTE = venous thromboembolism.
- [a]Medical disorders that may be seen in association with but are not specific for Cushing syndrome.

- [b]Features of androgen excess seen with pituitary corticotroph adenoma or adrenocortical carcinoma.

Figure 5. OPEN IN NEW WINDOW

Wide violaceous striae are seen on the abdomen of a patient with Cushing syndrome. Striae larger than 1 cm in width are highly specific for hypercortisolism.



Biochemical testing is used to establish the diagnosis of CS. It is critical that the biochemical diagnosis is firmly established prior to any imaging studies due to the relatively high prevalence of clinically insignificant pituitary and adrenal nodules. At least two first-line tests should be diagnostically abnormal before the diagnosis is confirmed. Initial tests include the overnight low-dose dexamethasone suppression test (LDST), 24-hour urine free cortisol (UFC), and late-night (LN) salivary cortisol. All three tests have similar diagnostic utility, but the LDST or LN salivary cortisol tests are more convenient. The 24-hour UFC and LN salivary cortisol tests should be performed at least twice to ensure reproducibility of results. Because the secretion of cortisol is pulsatile, measurement of random serum cortisol is neither sensitive nor specific for the diagnosis of CS. An algorithm to establish the diagnosis of CS is shown in Figure 6. Referral to an endocrinologist is indicated if two initial tests are abnormal.

Figure 6. OPEN IN NEW WINDOW

Algorithm to confirm or rule out the diagnosis of Cushing syndrome. CS = Cushing syndrome; DST = dexamethasone suppression test; LN salivary cortisol = late-night salivary cortisol; UFC = urine free cortisol.

- [a]Must be performed at least twice.

In the standard LDST, dexamethasone (0.5 mg) is administered every 6 hours for 48 hours and serum cortisol is measured at 9 AM. In the overnight LDST, 1 mg of dexamethasone is administered at 11 PM or midnight, and serum cortisol is measured the next morning at 8 AM. With either test, serum cortisol will typically be suppressed to less than 2 µg/dL (55 nmol/L). Standard assays measure total serum cortisol, or that which is bound to cortisol-binding globulin (CBG) and other proteins. Therefore the LDST should not be performed when CBG is likely to be abnormal, such as with malnutrition, cirrhosis, the nephrotic syndrome, and hyperestrogenemia (oral contraceptive pills or pregnancy). There is no clear association between dexamethasone responses and BMI or weight, and therefore the LDST may be used similarly in the obese population. The LDST is best avoided in patients taking medications that could accelerate dexamethasone metabolism, such as antiepileptic drugs (phenytoin, phenobarbital, and carbamazepine), rifampin, or pioglitazone. Concomitant measurement of serum dexamethasone can confirm altered dexamethasone metabolism and patient adherence.

Measuring 24-hour UFC circumvents problems related to cortisol pulsatility and binding protein abnormalities. The test should be performed at least twice to ensure accuracy. To confirm adequate collection, 24-hour urine creatinine is also measured (normal range, 20-25 mg/kg/24 h [177-221 mmol/kg/24 h] in men; 15-20 mg/kg/24 h [133-177 mmol/L/24 h] in women). A test is considered abnormal when UFC exceeds the upper limit of the normal range of the assay (45 µg/24 h [124 nmol/24 h]), while values greater than 3 times normal are diagnostic of CS. Less marked elevations are seen with pseudo-Cushing syndrome and polyuria. A falsely low UFC can occur in chronic kidney disease and when CS is subclinical or mild.

The LN salivary cortisol test is performed between 11 PM and midnight. The normal evening nadir in cortisol secretion is lost in patients with CS, while it is preserved in patients with pseudo-Cushing syndrome. Both emotional and physical stress (for example, exercise) can cause a physiologic increase of salivary cortisol. False-positive results are seen with cigarette smoking or use of chewing tobacco. LN salivary cortisol testing should not be performed in patients with erratic sleep schedules (for example, shift-workers).

After CS has been confirmed biochemically, further testing is required to distinguish ACTH-dependent or -independent causes, and consultation with an endocrinologist is recommended. The first step is to measure plasma ACTH on two separate occasions. With adrenal (ACTH-independent) CS, plasma ACTH is usually less than 5 pg/mL (1.1 pmol/L), whereas values greater than 20 pg/mL (4.4 pmol/L) are typically seen with ACTH-dependent causes. Plasma ACTH values of 5 to 20 pg/mL (1.1-4.4 pmol/L) are nondiagnostic but are more likely to be seen with ACTH-dependent disorders. For a discussion of the evaluation and management of ACTH-dependent CS, see Disorders of the Pituitary Gland.

The next step in the evaluation of ACTH-independent CS is with imaging of the adrenal glands, such as dedicated adrenal imaging with thin-section CT or MRI. Both studies have equal sensitivity; however, MRI is more costly. Adrenal adenomas and carcinomas can usually be distinguished from one another radiographically (**Table 19**). Surgery is considered first-line treatment for adrenal adenomas and nonmetastatic adrenocortical carcinomas (ACCs). When surgery is delayed for patients with overt CS, adrenal enzyme inhibitors (metyrapone, ketoconazole, and etomidate) can be used to reduce cortisol levels and decrease the risk of complications, such as opportunistic infections and cardiovascular events. The management of ACC is discussed elsewhere (see Adrenocortical Carcinoma).

Table 19. OPEN IN NEW WINDOW Typical Imaging Characteristics of Adrenal Masses

Adrenal Mass	Overall	CT	MRI Signal Intensity[a]

Table 19. OPEN IN NEW WINDOW Typical Imaging Characteristics of Adrenal Masses

Adrenal Mass	Overall	CT	MRI Signal Intensity[a]
Adrenal adenoma	Diameter <4 cm Homogeneous enhancement[b] Round, clear margins	Density <10 HU Contrast washout >50% (10 min)	Isointense on T2-weighted images
Adrenocortical carcinoma	Usually >4 cm Heterogeneous enhancement[b] Irregular margins Calcifications, necrosis	Density >10 HU Contrast washout <50% (10 min)	Hyperintense on T2-weighted images
Pheochromocytoma	Variable size Heterogeneous enhancement[b], cystic areas Round, clear margins Can be bilateral	Density >10 HU Contrast washout <50% (10 min)	Hyperintense on T2-weighted images

Table 19. OPEN IN NEW WINDOW Typical Imaging Characteristics of Adrenal Masses

Adrenal Mass	Overall	CT	MRI Signal Intensity[a]
Metastases	Variable margins Can be bilateral	Density >10 HU Contrast washout <50% (10 min)	Hyperintense on T2-weighted images

- HU = Hounsfield units (measure of radiodensity compared with water).
- [a]Signal intensity as compared with liver.
- [b]Enhancement following intravenous contrast administration.

Following adrenalectomy, patients with adrenal CS will often develop acute adrenal insufficiency because of HPA axis suppression and contralateral adrenal atrophy from long-standing elevated cortisol levels. All patients should therefore be treated with stress-dose glucocorticoids during the perioperative period and continued on physiologic replacement until HPA axis recovery has been confirmed. Following successful surgery, the physical changes associated with CS can take up to 1 year to resolve.

Key Points

- Cushing syndrome results from endogenous hypercortisolism or exogenous exposure to glucocorticoids; it is associated with poor suppressibility of endogenous cortisol production with oral dexamethasone.
- The most common cause of Cushing syndrome is the administration of exogenous glucocorticoid therapy for another medical condition.
- Initial tests for Cushing syndrome include the overnight low-dose dexamethasone suppression test, 24-hour urine free cortisol, and late-night salivary cortisol.

Pheochromocytomas and Paragangliomas

Related Questions

Question 2

Question 55

Paragangliomas are tumors composed of chromaffin cells. Approximately 80% are intra-adrenal (pheochromocytomas); the rest originate from extra-adrenal sympathetic or parasympathetic paraganglia. The most common location for extra-adrenal sympathetic paragangliomas is the abdomen, whereas parasympathetic paragangliomas are usually found in the head and neck. Pheochromocytomas and extra-adrenal sympathetic paragangliomas almost always secrete catecholamines (norepinephrine, epinephrine, dopamine); however, head and neck parasympathetic paragangliomas almost never do.

Although catecholamine-secreting tumors are rare overall, they are found in 0.5% of patients with hypertension, and pheochromocytomas account for 5% of adrenal incidentalomas (see Incidentally Noted Adrenal Masses). Most pheochromocytomas secrete norepinephrine, resulting in episodic or sustained hypertension. Orthostatic hypotension can also be seen and likely reflects low plasma volume. In addition to the classic triad of diaphoresis, headache, and tachycardia, common symptoms include palpitations, tremor, pallor, and anxiety. Less common features are papilledema, diabetes mellitus, and cardiomyopathy. Approximately 10% of pheochromocytomas and 20% to 50% of paragangliomas are malignant.

One third of pheochromocytomas and paragangliomas occur in the context of a genetic disorder. Pheochromocytomas are seen with multiple endocrine neoplasia (MEN) syndromes type 2A and 2B(**Table 20**), neurofibromatosis type 1, and von Hippel-Lindau syndrome (VHL). Paragangliomas and, less frequently, pheochromocytomas can occur with familial paraganglioma syndrome mutations, some of which are associated with high rates of malignancy.

Table 20. OPEN IN NEW WINDOW Multiple Endocrine Neoplasm Syndromes

Type	Mutation	Most Common Feature	Associated Features
1	*MEN1* (inheritance of one mutated allele with somatic mutation in other allele leads to neoplasia)	Parathyroid adenoma (often multiple)	Pancreatic islet cell and enteric tumors (gastrinoma, insulinoma most common) Pituitary adenoma Other (carcinoid tumors, adrenocortical adenoma)
2A	*RET* (exon 11, codon 634[a])	Medullary thyroid carcinoma	Pheochromocytoma (often multifocal) Parathyroid hyperplasia
2B	*RET* (exon 16, codon 918[a])	Medullary thyroid carcinoma	Pheochromocytoma (often multifocal) Mucosal neuroma Gastrointestinal ganglioneuroma Marfanoid body habitus

- [a]Most common mutation observed.

The diagnosis of pheochromocytoma and paraganglioma is based on confirmation of the excessive secretion of catecholamines or their metabolites, as measured in the plasma or urine. Evaluation is recommended, if clinically suspected, in the evaluation of an incidentally noted adrenal mass or in the setting of hereditary pheochromocytoma or paraganglioma syndromes. The sensitivity of plasma free metanephrines is the highest of any screening test (96%-100%); however, its specificity is relatively low (85%-89%). Therefore, plasma free metanephrines will reliably exclude a pheochromocytoma when negative, but further testing

is needed to confirm the diagnosis unless the result is markedly abnormal (above 4 times the upper limit of normal). The sensitivity and specificity of 24-hour urine fractionated metanephrines and catecholamines are 91% to 98%. Due to the lower frequency of false-positive results, 24-hour urine measurements are recommended when the pre-test probability of disease is relatively low (adrenal mass without typical radiographic appearance), while measurement of plasma free metanephrines is preferred when clinical suspicion is higher (known hereditary syndrome). Referral to an endocrinologist is recommended when biochemical testing is abnormal.

Many medications and other substances cause falsely high levels of plasma and urine catecholamines or metanephrines (Table 21); therefore, discontinuation of these agents before testing is recommended. If a catecholamine-secreting tumor is strongly suspected in a critically ill hospitalized patient, CT or MRI of the abdomen is the preferred initial test because biochemical testing cannot be interpreted reliably in this setting.

Table 21. OPEN IN NEW WINDOW Substances Associated with False-Positive Biochemical Testing for Pheochromocytoma

Drug Class	Medication/Substance
Analgesics	Acetaminophen
Antiemetics	Prochlorperazine
Antihypertensives	Phenoxybenzamine[a]
Psychiatric medications	Antipsychotics
	Buspirone

Table 21. OPEN IN NEW WINDOW Substances Associated with False-Positive Biochemical Testing for Pheochromocytoma

Drug Class	Medication/Substance
	Monoamine oxidase inhibitors
	Tricyclic antidepressants[a]
Stimulants	Amphetamines
	Cocaine
	Caffeine
Other agents	Levodopa
	Decongestants (pseudoephedrine)
	Reserpine
Withdrawal	Clonidine
	Ethanol
	Illicit drugs

- [a]Most likely to cause false-positive results.

Following the biochemical diagnosis of pheochromocytoma or catecholamine-secreting paraganglioma, radiographic localization is needed. Because most catecholamine-secreting tumors are located in the abdomen, CT or MRI of the abdomen and pelvis is the best initial study. If negative, iodine 123 (^{123}I)-metaiodobenzylguanidine (MIBG) scanning can be performed. Adjunctive diagnostic tests are CT or MRI of the chest or head and neck region.

When multiple tumors or malignant pheochromocytomas or paragangliomas are suspected, MIBG scanning should be performed preoperatively. However, for identification of metastatic disease, fluorine 18 (^{18}F)-fluorodeoxyglucose (FDG) PET scanning is superior to other diagnostic tests.

Preoperative pharmacologic treatment is mandatory for pheochromocytomas and paragangliomas to prevent life-threatening cardiovascular complications related to the massive release of catecholamines during surgery. Preoperative blockade of α-adrenoceptors, usually with phenoxybenzamine, is first-line medical therapy. The dosage is titrated to achieve a blood pressure below 130/80 mm Hg seated and greater than 90 mm Hg (systolic) standing. Commonly used but non-FDA approved alternatives include calcium channel blockers and selective α_1-blockers (terazosin or doxazosin). β-Adrenoceptor blockers (metoprolol or propranolol) are added later to treat reflex tachycardia, but should never be started before adequate α-blockade has been achieved due to the risk of hypertensive crisis from unopposed α-receptor stimulation. A heart rate of 60 to 70/min seated and 70 to 80/min standing can be targeted in most patients.

Because it is associated with fewer surgical complications and shorter postoperative hospital stays, laparoscopic adrenalectomy is preferred for pheochromocytoma except in the case of large or malignant tumors, when open adrenalectomy is required. Following the surgical removal of a catecholamine-secreting tumor, large-volume intravenous crystalloid is administered to counter hypotension. Vasopressors (for example, norepinephrine) are sometimes required. Long-term follow-up is needed for pheochromocytomas and paragangliomas due to difficulty distinguishing benign from malignant tumors. Metastases have been reported up to 20 years after diagnosis. In addition to routine clinical surveillance, annual measurement of plasma or urine metanephrines is indicated to assess for recurrent or metastatic disease. Metastatic disease is managed with additional surgery, iodine 131 (^{131}I)-labeled MIBG therapy, chemotherapy, and/or radiotherapy. Cure is not possible unless all disease can be surgically resected.

Key Points

- Pheochromocytomas are seen with multiple endocrine neoplasia (MEN) syndromes type 2A and 2B, neurofibromatosis type 1, and von Hippel-Lindau syndrome.
- When clinical suspicion of pheochromocytoma or paraganglioma is low, measurement of 24-hour urine fractionated metanephrines and catecholamines are the tests of choice because of their high specificity (low false-positive rates); when clinical suspicion is high, measuring plasma free metanephrines is preferred due to its greater sensitivity.
- Preoperative α-adrenergic blockade is first-line medical therapy for pheochromocytomas and paragangliomas; β-adrenoceptor blockers (metoprolol or propranolol) are added after α-blockade to treat reflex tachycardia.
- Pheochromocytomas and paragangliomas require lifelong surveillance for recurrence with annual plasma free metanephrine measurement.

Primary Hyperaldosteronism

Related Questions

Question 71

Question 79

Primary hyperaldosteronism (PA) results from the autonomous secretion of excessive aldosterone. PA is relatively common, occurring in approximately 10% of patients with hypertension. Additional signs of PA include hypokalemia and metabolic alkalosis. Without treatment, excess cardiovascular morbidity and mortality are seen.

Aldosterone-producing adrenocortical adenomas (APA; aldosteronomas) cause approximately 40% of PA, whereas nearly all other cases are due to bilateral adrenal hyperplasia. Unilateral adrenal hyperplasia and aldosterone-secreting adrenocortical carcinomas (ACCs) are rare. Familial hyperaldosteronism is also uncommon.

Testing for PA should be considered in all patients with difficult to control hypertension. It should also be performed in patients with hypertension and an incidentally noted adrenal mass or spontaneous or diuretic-induced hypokalemia. A number of disorders can mimic PA clinically; however, the results of biochemical testing will differ. Examples include secondary hyperaldosteronism (renal artery

stenosis or renin-secreting tumors), autosomal dominant pseudoaldosteronism (Liddle syndrome), CS, certain forms of congenital adrenal hyperplasia (CAH), and licorice-induced hypermineralocorticoidism.

Initial screening for PA is with the simultaneous measurement of midmorning ambulatory plasma renin activity (PRA) and plasma aldosterone concentration (PAC), in a volume replete normokalemic patient. Testing is positive if PAC is frankly elevated (>15 ng/dL [414 pmol/L]), PRA is suppressed, and PAC/PRA ratio is greater than 20. Many medications, including common antihypertensive agents, can affect measurements of PAC, PRA, or both (**Table 22**). However, because patients undergoing screening often have drug-resistant hypertension, discontinuing all potentially offending medications can be unsafe. Stopping mineralocorticoid receptor antagonists (spironolactone and eplerenone) for 4 to 6 weeks prior to testing is recommended. Diuretics should also be discontinued prior to testing to assure euvolemia. Most other medications can be continued, but results must be interpreted in context. For example, if PRA is suppressed despite treatment with an ACE inhibitor or angiotensin receptor blocker, PA is likely. If results are difficult to interpret, repeat testing after eliminating potential interfering medications is advised. Verapamil, hydralazine, and α-blockers (doxazosin) can be substituted for blood pressure control if necessary. Referral to an endocrinologist is recommended when screening tests are abnormal.

Table 22. OPEN IN NEW WINDOW The Effect of Commonly Prescribed Medications on Measurements of Plasma Renin Activity and Plasma Aldosterone Concentration

Effect on Test Results	Medication Class	PRA	PAC	PAC/PRA
False-Positive	α-Adrenoceptor agonist	↓↓	↓	↑

Table 22. OPEN IN NEW WINDOW The Effect of Commonly Prescribed Medications on Measurements of Plasma Renin Activity and Plasma Aldosterone Concentration

Effect on Test Results	Medication Class	PRA	PAC	PAC/PRA
	β-Adrenoceptor blocker	↓↓	↓	↑
	Direct renin inhibitor	↓	↓	↑
	NSAID	↓↓	↓	↑
False-Negative	ACE inhibitor/ARB	↑↑	↓	↓
	Dihydropyridine CCB	↑	↓	↓
	Diuretic[a]	↑↑	↑	↓
	Mineralocorticoid receptor antagonist	↑↑	↑	↓
	SSRI		↑	↓

- ARB = angiotensin receptor antagonist; CCB = calcium channel blocker; PAC = plasma aldosterone concentration; PRA = plasma renin activity; SSRI = selective serotonin reuptake inhibitor.
- [a]Both potassium-sparing (amiloride) and potassium-wasting (hydrochlorothiazide) diuretics.

Confirmatory testing is performed except when initial testing is diagnostic for PA, as in cases of spontaneous hypokalemia with undetectable PRA and PAC greater than 30 ng/dL (828 pmol/L). Confirmatory tests include oral and intravenous salt loading and the fludrocortisone suppression and captopril challenge tests (Table 23).

Table 23. OPEN IN NEW WINDOW Laboratory Testing Used in the Diagnosis of Hyperaldosteronism

Test	Details	Positive If…
Captopril challenge test	Administer: Captopril 25-50 mg orally after the patient has been seated for 1 hour Measure: PAC, PRA, and cortisol at 0 and 1 or 2 hours while seated	PAC remains elevated and PRA suppressed (Normal response is suppression of PAC by >30%)
Fludrocortisone suppression test	Administer: Fludrocortisone 0.5 mg orally every 6 hours for 4 days along with sodium and potassium	PAC >6 ng/dL (165.6 pmol/L) PRA <1 ng/mL/h (1 µg/L/h) (Cortisol at 10 AM lower than 7 AM)

Table 23. OPEN IN NEW WINDOW Laboratory Testing Used in the Diagnosis of Hyperaldosteronism

Test	Details	Positive If…
	supplementation Measure: Serum cortisol at 7 and 10 AM, and PAC and PRA at 10 AM on day 4	
Oral salt loading test	Administer: Sodium chloride 6 g orally daily (in divided doses) for 3 days Measure: 24-hour urine aldosterone and urine Na on the third day	24-hour urine aldosterone >12 µg (Urine Na >200 mEq [220 mmol/L])
Intravenous salt loading test	Administer: 2 L 0.9% saline intravenously over 4 hours while supine Measure: PAC, PRA, cortisol,	PAC >10 ng/dL (276.0 pmol/L)

Table 23. OPEN IN NEW WINDOW Laboratory Testing Used in the Diagnosis of Hyperaldosteronism

Test	Details	Positive If…
	and serum K at 0 and 4 hours	

- IM = intramuscular; IV = intravenous; K = potassium; Na = sodium; PAC = plasma aldosterone concentration; PRA = plasma renin activity.

Once the diagnosis of PA has been confirmed biochemically, radiographic localization with abdominal CT is indicated. CT is recommended over MRI in most cases due to similar efficacy and lower cost. Adrenal hyperplasia and adenomas can often be visualized and adrenocortical carcinoma can be ruled out. Adrenal vein sampling (AVS) is needed in most patients to determine the source of aldosterone secretion when imaging is unrevealing and to confirm lateralization when imaging demonstrates an adrenal adenoma. AVS is especially important in older patients (40 years and older) because of a higher frequency of nonfunctioning adrenal incidentalomas. AVS should be performed at experienced centers only.

The goals of treatment include improvement in blood pressure (resolution of hypertension is unlikely), normalization of serum potassium (this is very likely), and reduction in plasma aldosterone because hyperaldosteronemia is associated with a blood pressure–independent increase in cardiovascular events. The treatment of choice for PA due to APA or unilateral adrenal hyperplasia is laparoscopic adrenalectomy.

For patients with bilateral adrenal hyperplasia or those with unilateral causes of PA who are not surgical candidates, medical therapy with a mineralocorticoid antagonist is indicated. Spironolactone is the most commonly used medication due to its proven efficacy and cost-effectiveness. Eplerenone is less likely to cause side effects (gynecomastia in men and menstrual irregularities in women) because of greater mineralocorticoid receptor selectivity. Amiloride is a potassium-sparing diuretic that

blocks the aldosterone-sensitive sodium channel. Use of amiloride in PA is second-line therapy because of lower efficacy.

Key Points

- Testing for primary hyperaldosteronism is with the simultaneous measurement of midmorning ambulatory plasma renin activity and plasma aldosterone levels; testing is positive if plasma aldosterone concentration is frankly elevated (>15 ng/dL [414 pmol/L]), plasma renin activity is suppressed, and a ratio of the former over the latter is greater than 20.
- The treatment of choice for primary hyperaldosteronism due to an aldosteronoma or unilateral adrenal hyperplasia is laparoscopic adrenalectomy; for patients with bilateral adrenal hyperplasia or those with unilateral causes of primary hyperaldosteronism who are not candidates for surgery, medical therapy with a mineralocorticoid antagonist such as spironolactone is indicated.

Androgen-Producing Adrenal Tumors

Related Question

Question 52

Pure androgen-secreting adrenal neoplasms are very rare. These tumors usually secrete DHEA and DHEAS and/or androstenedione, which are converted peripherally to testosterone. Approximately half of androgen-producing tumors are benign and half are malignant. Manifestations of androgen-producing adrenal tumors are usually absent in adult men, although decreased testicular volume can occur. In women, rapid onset of hirsutism, menstrual irregularities, and virilization can be seen and, if present, should raise suspicion for tumoral hyperandrogenism. Signs of virilization are deepening of the voice, clitoromegaly, and temporal hair loss. The diagnosis of an androgen-producing adrenal tumor is based on demonstrating elevated levels of DHEA and its sulfate (usually greater than 800 µg/dL [21.6 µmol/L]) and/or androstenedione. Although adrenal androgen excess can be seen in 30% to 40% of women with polycystic ovary syndrome, mild elevation of DHEAS (approximately 300 µg/dL [8.1 µmol/L) is typical. Adrenal imaging with CT or MRI is indicated following biochemical diagnosis of disease to locate the tumor. Treatment is surgical removal of the tumor.

Adrenal Insufficiency

Adrenal insufficiency may be due to failure of the adrenal glands (primary adrenal failure), or there may be inadequate secretion of cortisol from the adrenals due to other causes, including critical illness and pituitary ACTH deficiency (secondary cortisol deficiency). For a discussion of secondary cortisol deficiency, see Disorders of the Pituitary Gland.

Primary Adrenal Failure

Causes and Clinical Features
Related Question

Question 42

Primary adrenal failure is a rare disorder resulting from a failure in production of all the hormones of the adrenal cortex. The overall prevalence is 10 to 15 per 100,000 persons. Autoimmune adrenalitis is the most common etiology accounting for 70% to 80% of cases. Up to two thirds of patients have at least one other autoimmune endocrine disorder, and more than 80% have adrenal autoantibodies (21-hydroxylase antibodies). Infiltration of the adrenal glands by tuberculosis (Addison disease) was formerly the most common etiology of primary adrenal failure; now it is responsible for only 7% to 20%. Replacement of the adrenal glands can also occur with metastatic cancer. Genetic causes include autoimmune polyglandular syndromes (APS) type 1 and 2, congenital adrenal hyperplasia, and X-linked adrenoleukodystrophy. Adrenal crisis resulting from bilateral adrenal hemorrhage can occur with the antiphospholipid syndrome, disseminated intravascular coagulation, or systemic anticoagulation.

The clinical presentation of primary adrenal failure depends on disease chronicity and the presence of physical stressors. In autoimmune adrenalitis, the zona glomerulosa is usually affected first, which is manifest by an increase in PRA. With involvement of the zona fasciculata, a diminished cortisol response to ACTH is seen, followed by an increase in basal plasma ACTH, and lastly a decrease in serum cortisol. Patients typically do not have symptoms until hypocortisolemia occurs. **Table 24**shows the clinical and laboratory manifestations of primary adrenal failure. Hyperpigmentation is a clinical hallmark of this

disorder that is not seen with secondary cortisol deficiency (see Disorders of the Pituitary Gland for discussion of secondary cortisol deficiency).

Table 24. OPEN IN NEW WINDOW Clinical and Laboratory Manifestations of Primary Adrenal Failure

Hormone Deficiency	Symptoms	Signs	Laboratory Findings
Cortisol	Fatigue Weakness Low-grade fever Weight loss Anorexia Nausea/vomiting Abdominal pain Arthralgia Myalgia	Hyperpigmentation[b] (palmar creases, extensor surfaces, buccal mucosa) Decrease in BP	↓ Serum cortisol ↑ Plasma ACTH ↓ Serum sodium[c] ↓ Plasma glucose[d]
Aldosterone	Salt craving Dizziness	Orthostasis Hypotension	↑ PRA ↓ Serum sodium ↑ Serum potassium
DHEAS	Reduced libido[a]	Decreased axillary or pubic hair[a]	↓ Serum DHEAS

- ACTH = adrenocorticotropic hormone; BP = blood pressure; DHEAS = dehydroepiandrosterone sulfate; PRA = plasma renin activity.

- [a]Women only.
- [b]Occurs exclusively in primary adrenal failure.
- [c]Cortisol inhibits the secretion of antidiuretic hormone (ADH), so hypocortisolemia will lead to increased secretion of ADH and hyponatremia.
- [d]Rare in adults.

Adrenal crisis may occur when onset of adrenal failure is abrupt (bilateral adrenal hemorrhage) or when increased stress occurs in the setting of chronic adrenal failure. Manifestations of adrenal crisis include shock, hypotension, fever, nausea, vomiting, abdominal pain, tachycardia, and even death. Aldosterone is critical to the maintenance of intravascular volume and blood pressure, while cortisol contributes to augmentation of blood pressure mostly during times of increased physical stress (see Adrenal Anatomy and Physiology). Aldosterone deficiency is the major impetus for the development of hypotension and shock in patients with untreated primary adrenal failure. Adrenal crisis is rare in the setting of secondary cortisol deficiency because the renin-angiotensin-aldosterone pathway is intact.

Diagnosis

The diagnosis of primary adrenal failure is based on demonstrating inappropriately low serum cortisol levels. Because most assays measure total cortisol, abnormalities in cortisol-binding protein or albumin can trigger spurious results. An early morning (8 AM) serum cortisol of less than 3 µg/dL (82.8 nmol/L) is consistent with cortisol deficiency, whereas values greater than 15 to 18 µg/dL (414.0-496.8 nmol/L) exclude the diagnosis when binding protein abnormalities and synthetic glucocorticoid exposure are excluded. For patients with nondiagnostic basal cortisol values (5-12 µg/dL [138-331.2 nmol/L), stimulation testing with synthetic ACTH (cosyntropin) is indicated (see Disorders of the Pituitary Gland). A normal response is a peak serum cortisol level greater than 20 µg/dL (552 nmol/L). ACTH stimulation testing should not be used for diagnosis in the critical care setting (see Adrenal Function During Critical Illness).

Once the diagnosis of cortisol deficiency has been established, measurement of 8 AM plasma ACTH will differentiate primary and secondary causes. In primary adrenal failure, ACTH is typically greater than 200 pg/mL (44 pmol/L), whereas it will be low or inappropriately normal in secondary cortisol deficiency. Although not specific for the diagnosis,

hyponatremia and hyperkalemia are characteristic of primary adrenal failure and principally result from aldosterone deficiency.

Treatment Related Questions

Question 44

Question 82

Without appropriate treatment, primary adrenal failure is uniformly fatal. Even when treated, the mortality of patients is twice that of the general population. Normal adrenal physiology cannot be reproduced exactly by the administration of exogenous glucocorticoids and mineralocorticoids. Moreover, the administration of doses of glucocorticoid in excess of physiologic replacement can be associated with decreased bone mineral density and features of CS, with increased risk of metabolic syndrome, type 2 diabetes mellitus, hypertension, hyperlipidemia, obesity, and cardiovascular disease. Avoidance of chronic overreplacement is paramount.

Table 25 shows the medical treatment for primary adrenal failure. Most patients require glucocorticoid doses equivalent to 12.5 to 25 mg of hydrocortisone daily. Hydrocortisone is administered 2 to 3 times daily, while once daily dosing of longer-acting glucocorticoids (prednisone or dexamethasone) is acceptable. All patients with cortisol deficiency need to receive instructions for increasing their cortisol replacement dose during illness ("sick day rules"). Patients should always wear a medical alert identification.

Table 25. OPEN IN NEW WINDOW Chronic Medical Treatment of Primary Adrenal Failure

Medication	Basal Dose	Considerations
Glucocorticoid[a]	Hydrocortisone	"Sick Day Rules": patient follows at home

Table 25. OPEN IN NEW WINDOW Chronic Medical Treatment of Primary Adrenal Failure

Medication	Basal Dose	Considerations
Hydrocortisone Prednisone Prednisolone Dexamethasone	Usually 12.5-25 mg/d, divided into 2-3 doses over the day **Alternatives to hydrocortisone:** Prednisone 2.5-5 mg once daily Dexamethasone 0.25-0.75 mg once daily **How to dose:** Titrate to clinical response with goal of no signs or symptoms of cortisol deficiency or excess (increase dose if symptoms of cortisol deficiency remain; decrease if CS signs and symptoms are present)	For minor physiologic stress (upper respiratory infection, fever, minor surgery under local anesthesia) 2-3 times basal dose for 2-3 days Stress Dosing: health care providers follow while patient is in the hospital For moderate physiologic stress (minor or moderate surgery with general anesthesia) Hydrocortisone 45-75 mg/d orally or IV in 3-4 divided doses for 2-3 days Alternatives: Prednisone 10-20 mg or dexamethasone 2-3 mg/d in 1-2 divided doses For major physiologic stress (major surgery, trauma, critical illness, or childbirth) Hydrocortisone 150-200 mg/day IV in 3-4 divided doses; 100 mg/day the next day; taper to baseline in 3-5 days Alternative: Dexamethasone 6-8 mg/d IV in 2-3 divided doses

Table 25. OPEN IN NEW WINDOW Chronic Medical Treatment of Primary Adrenal Failure

Medication	Basal Dose	Considerations
Mineralocorticoid Fludrocortisone	0.05-0.2 mg once daily in the morning **How to dose:** Titrate to 1. Normal BP 2. Normal serum Na, K	Fludrocortisone is not required if hydrocortisone dose >50 mg/d
Adrenal androgen DHEA	25-50 mg once daily	Consider DHEA for women with impaired mood or sense of well-bei glucocorticoid replacement has been optimized.

- BP = blood pressure; CS = Cushing syndrome; DHEA = dehydroepiandrosterone; IV = intravenous; Na = sodium; K = potassium.
- [a]Shorter acting glucocorticoids may be preferred over longer acting agents due to lower risk of glucocorticoid excess. Longer-acting preparations have the advantage of once daily dosing (see **Table 17**).

In contrast to patients with secondary cortisol deficiency (see Disorders of the Pituitary Gland), those with primary adrenal failure also require mineralocorticoid replacement. Usual doses are 0.05 to 0.2 mg per day of fludrocortisone. Measurements of serum sodium and potassium help guide dosing. Replacement of DHEA is controversial. It is not indicated for men but can be considered for some women with primary adrenal failure. However, the objective benefit is minimal, and there are concerns regarding the quality and safety of U.S. preparations where DHEA is considered a supplement rather than a pharmaceutical.

Patients who present emergently with suspected adrenal crisis should be treated empirically prior to confirmation of the diagnosis. A blood sample should be drawn for serum cortisol, plasma ACTH, and routine chemistries. The patient should receive immediate treatment with 100 mg of hydrocortisone intravenously and aggressive fluid resuscitation. Hydrocortisone is continued at 100 to 200 mg per day in divided doses (every 6-8 hours) and then tapered to physiologic replacement if cortisol deficiency is confirmed with the above testing. Other synthetic glucocorticoids can also be used for the treatment of adrenal crisis; however, only hydrocortisone in supraphysiologic doses has clinically relevant mineralocorticoid activity. If present, electrolyte abnormalities and hypoglycemia should be treated, and precipitants of adrenal crisis (for example, infection) should be sought and treated.

It is critical that patients with suspected primary or secondary cortisol deficiency and concomitant hypothyroidism be treated with glucocorticoids first because correcting thyroid hormone deficiency will accelerate the clearance of cortisol and can precipitate acute adrenal crisis.

In the nonmedical literature, the term “adrenal fatigue” has been used to describe a constellation of symptoms, including difficulty sleeping, fatigue, and salt and sugar craving, hypothetically from long-term emotional or physical stress having a deleterious effect on the adrenal glands, resulting in a simultaneous excess and deficiency of cortisol. However, there is no scientific evidence to support this claim, and the term “adrenal fatigue” should not be used. Proponents of adrenal fatigue prescribe synthetic glucocorticoids and supplements containing adrenal, pituitary, or hypothalamic extracts that can cause iatrogenic CS, as well as mineralocorticoid supplements that can lead to hypertension. Patients should receive appropriate evaluation for their symptoms and be educated to avoid taking hormonal replacements for which there has not been a demonstrated biochemical need.

Adrenal Function During Critical Illness

Glucocorticoid deficiency related to critical illness is an entity that has not been well characterized. It has been postulated that critical illness may lead to transient primary or secondary cortisol deficiency (ACTH deficiency) or an increase in tissue resistance to cortisol. The American College of Critical Care Medicine recommends considering this diagnosis in patients with hypotension who have responded insufficiently to fluids and vasopressor therapy. A maximum increase in serum cortisol of 9 µg/dL (248.4 nmol/L) or less following the administration of synthetic ACTH has been associated with increased mortality from septic shock; however, results of testing do not predict benefit from glucocorticoid therapy. In the setting of critical illness, both CBG and albumin concentrations decrease resulting in lower total cortisol. Free cortisol levels, either directly measured or calculated based on total cortisol and CBG, may be more reliable in critically ill patients with hypoalbuminemia. It is not known if free cortisol levels provide useful prognostic information. The administration of glucocorticoids has not been shown to benefit critically ill patients who do not have shock, and the results of placebo-controlled randomized trials in patients with septic shock are conflicting. Further research is needed to clarify if there is a population of critically ill patients who can objectively benefit from glucocorticoid therapy.

Adrenal Masses

Incidentally Noted Adrenal Masses

Related Questions

Question 50

Question 60

Adrenal masses are often discovered incidentally when abdominal imaging is performed for another reason. These adrenal incidentalomas are seen on 4% of all CT scans and 7% of those performed in patients 70 years of age and older. The differential diagnosis includes benign and malignant neoplasia of adrenal cortex or

medulla, adrenal cysts, adrenal hyperplasia, metastatic tumors of nonadrenal origin, and infections and infiltrative disorders. The most common cause of an adrenal mass is an adrenal adenoma, and adrenal metastasis is the next most common. The two main goals in the evaluation of an incidentally noted adrenal mass are to identify adrenal masses that are likely to be malignant and those that are associated with hormonal hypersecretion so that targeted treatment can be undertaken promptly. An algorithm for the evaluation and follow up of an adrenal mass is shown in **Figure 7**.

Figure 7. OPEN IN NEW WINDOW

Algorithm for the initial diagnostic evaluation and follow up of an incidentally noted adrenal mass. CS = Cushing syndrome; DHEAS = dehydroepiandrosterone sulfate; HTN = hypertension; HU = Hounsfield units; K = potassium; LDST = low-dose (1-mg) dexamethasone suppression test; PAC = plasma aldosterone concentration; PRA = plasma renin activity.

- [a]Repeat imaging and hormone testing are indicated for adrenal masses not meeting criteria for surgery at initial diagnosis.
- [b]Refer to **Table 19** for more CT and MRI findings. If imaging is suspicious in a patient with known malignancy, biopsy should be considered to confirm adrenal metastasis after screening for pheochromocytoma is completed.
- [c]CT scan findings.
- [d]Positive screening tests usually require further biochemical evaluation to confirm the diagnosis (see text).
- [e]Measure plasma metanephrines if radiographic appearance is typical for a pheochromocytoma; otherwise measure 24-hour urine metanephrines and catecholamines.
- [f]Hormonal evaluation for an androgen-producing adrenal tumor is indicated only if clinically suspected based on the presence of hirsutism, virilization, or menstrual irregularities in women.
- [g]Adrenalectomy is considered for confirmed cases of subclinical CS associated with recent onset of diabetes, hypertension, obesity, or low bone mass.

The risk of malignancy varies according to size. Only 2% of adrenal masses smaller than 4 cm are cancerous; however, 25% of those larger than 6 cm are malignant. An adrenal mass's risk of malignancy can be clarified based on its appearance on CT or MRI (see **Table 19** for the typical radiographic features of adrenal masses).

Adrenal metastases account for about half of adrenal masses in patients with known nonadrenal malignancies. Cancers that metastasize to the adrenal glands include lymphomas, carcinomas, and melanomas. Percutaneous biopsy is indicated to confirm

the diagnosis of adrenal metastasis; however, this should never be performed prior to ruling out pheochromocytoma biochemically. Biopsy is not recommended when adrenocortical carcinoma (ACC) is suspected because it cannot reliably distinguish benign from malignant adrenocortical neoplasia. The evaluation and management of ACC are covered in the Adrenocortical Carcinoma section.

One quarter of incidentally noted adrenal masses autonomously secrete hormones (cortisol 6%-10%; catecholamines 5%; aldosterone 1%). Excess cortisol secretion is most common; however, the majority of patients have subclinical disease without classic stigmata of CS. Despite this, important complications may be seen, including osteoporosis, hypertension, diabetes mellitus, and cardiovascular events. The LDST is the initial screening test of choice. A serum cortisol value greater than 5 µg/dL (138 nmol/L) is considered positive; however, some advocate using a cut-off of 1.8 µg/dL (49.7 nmol/L) to increase diagnostic sensitivity if CS is suggested by history or physical examination. Because the specificity of the LDST is only approximately 90%, the diagnosis of subclinical CS should be confirmed with additional testing. For a review, see the Cushing Syndrome section.

Aldosteronomas are usually smaller than 2 cm. Case detection for PA is performed in all patients with hypertension or those on antihypertensive medications. Testing for autonomous secretion of adrenal androgens is performed if clinically suspected following careful history and physical examination. All patients with an incidental adrenal mass should be tested for pheochromocytoma. Measurement of 24-hour urine metanephrines and catecholamines is the preferred first test in most asymptomatic patients, due to the lower incidence of false-positive test results. However, if the radiographic appearance of the adrenal mass is suspicious for a pheochromocytoma (see **Table 19**) or the patient is symptomatic, then plasma free metanephrines should be measured (see Primary Hyperaldosteronism, Androgen-Producing Adrenal Tumors, and Pheochromocytomas and Paragangliomas).

Adrenal masses that are larger than 4 cm, those with worrisome radiographic findings, and pheochromocytomas should be removed surgically. Surgery is also indicated for

unilateral aldosteronomas and is considered for patients with subclinical CS associated with the recent onset of diabetes, hypertension, obesity, or low bone mass. For nonfunctioning adrenal masses, if imaging favors a benign lesion, repeat radiographic evaluation is recommended in 3 to 6 months, and then annually for 1 to 2 years. Adenomas usually will not grow more than 1 cm over 12 months. More rapid growth should prompt adrenalectomy. Screening for hormonal hypersecretion is repeated annually for 4 years, as in the rare instance that the mass becomes functional, it is likely to occur in the first 4 years following its discovery. A recent study documented subclinical CS on follow-up testing in approximately 8% of patients who were thought to have nonfunctioning adenomas at initial screening.

Key Points

- The two main goals of evaluation of adrenal incidentalomas are to identify adrenal masses that are likely to be malignant and those that are associated with hormonal hypersecretion so that targeted treatment can be undertaken promptly.
- Adrenal masses that are larger than 4 cm, those with worrisome radiographic findings, and pheochromocytomas should be removed surgically.

Adrenocortical Carcinoma

Related Question

Question 27

ACC is a rare malignancy affecting 0.5 to 2 persons per million per year that is often associated with the excessive production of adrenal hormones. Patients with ACC most frequently present with signs and symptoms related to hormonal excess. They may also experience symptoms related to local tumor growth (abdominal fullness, nausea, or back pain) or metastasis. ACC is sometimes detected incidentally when abdominal imaging is performed for another reason (see Incidentally Noted Adrenal Masses).

Autonomous secretion of adrenal hormones or their biologically inactive precursors is seen in more than 80% of patients with ACC (cortisol 50%; multiple hormones 20%; androgens 5% to 10%; aldosterone rarely). The pathologic diagnosis of ACC is challenging, such that with

low-risk pathology but large tumor size or concerning imaging findings (see **Table 19**) close interval radiographic follow up is needed after surgery.

The prognosis of ACC is very poor with an overall mortality rate of 67% to 94%. Management depends on the extent of disease at presentation. Open surgical resection is first-line treatment for early disease. Adjuvant radiotherapy to the tumor bed is used when resection is incomplete. Adjuvant medical therapy with mitotane, an adrenolytic drug, is recommended for patients with known or suspected residual or metastatic disease. Cytotoxic chemotherapy has poor efficacy. In addition to mitotane, inhibitors of adrenal steroidogenesis (metyrapone, ketoconazole, and etomidate) are used to treat CS, if present. Surgery for metastatic ACC is indicated if symptoms related to hormonal hypersecretion cannot be controlled with medical therapy alone. Percutaneous radiofrequency ablation may also be used to treat unresectable primary tumors or metastases when needed.

Key Point

- Adrenocortical carcinoma is marked by signs and symptoms related to hormonal excess as well as symptoms related to local tumor growth (abdominal fullness, nausea, or back pain) or metastasis.

Disorders of the Thyroid Gland

Thyroid Anatomy and Physiology

In healthy adults in the United States, each thyroid lobe normally measures up to 5 cm in length, 2 cm in width, and 2 cm in depth; the entire gland weighs 10 to 20 grams. The isthmus, a thin band of thyroid tissue that connects the two lobes, is 1 to 4 mm in thickness and is typically not palpable. Diffuse thyroid disorders, such as lymphocytic thyroiditis, may result in enlargement of the isthmus to 5 mm or more, which may be palpable and give the clinician the false sense that the entire thyroid is enlarged.

There are two forms of active thyroid hormone: thyroxine (T_4) and triiodothyronine (T_3). Iodine is necessary for the formation of thyroid hormone. Deficiency may result in

hypothyroidism. The hypothalamic-pituitary-thyroid axis responds to the subsequent hormone deficiency by increasing thyroid-stimulating hormone (TSH) secretion, resulting in development of a goiter. Iodine is typically obtained through diet; it is present in seafood, dairy products, and iodized salt. Although iodine deficiency is a worldwide health problem, it is relatively rare in the United States with the incorporation of iodine into salt.

Thyroid hormone production is controlled by two main forces: secretion of TSH (thyrotropin) and regulation of peripheral conversion of T_4 to T_3. TSH release from the anterior pituitary is stimulated by decreases in concentrations of serum T_4 and T_3 and secretion of thyrotropin-releasing hormone (TRH) from the hypothalamus. The T_3 and T_4, in turn, decrease secretion of TSH from the anterior pituitary as part of a negative feedback loop. Additionally, T_3 inhibits further secretion of TRH from the hypothalamus.

Although the thyroid gland produces both T_3 and T_4, the ratio of T_4 to T_3 secretion is nearly 20:1, with most T_3 (80%) resulting from 5'-deiodination of T_4 in peripheral tissues.

The vast majority of both hormones are bound to circulating proteins, including thyroxine-binding globulin, transthyretin, albumin, and lipoproteins. The function of these proteins is to increase the circulating pool of hormone by delaying clearance and maintaining a reservoir of hormone available for use. Only a small percentage of total circulating thyroid hormone is free (unbound); this fraction is readily available for cellular uptake and determines the biologic activity of the hormone.

Key Point

- Thyroid hormone production is controlled by two main forces: secretion of thyroid-stimulating hormone (thyrotropin) and regulation of peripheral conversion of thyroxine (T_4) to triiodothyronine (T_3).

Evaluation of Thyroid Function

Related Questions

Question 21

Question 36

Question 59

In patients with an intact hypothalamic-pituitary axis, the initial laboratory test of thyroid activity is TSH measurement, which is exquisitely sensitive for detection of disorders of thyroid dysfunction. In patients for whom there is a high suspicion of thyroid or pituitary dysfunction, a concomitant thyroid hormone (T_4) level should be assessed with the TSH level to evaluate for central hypothyroidism. The TSH level may reflect hypofunction (high TSH), hyperfunction (low TSH), or a normal range.

The normal reference range for TSH is variable among laboratories but is generally between 0.5 and 5 µU/mL (0.5-5 mU/L), and determinations of normal TSH levels should be made based on the reference range of the laboratory being used. There are three very important exceptions to this general range. During pregnancy, the range shifts lower and varies by trimester (see Thyroid Function and Disease in Pregnancy). The second important exception is in the elderly. With aging, the reference range shifts higher; the upper limit of normal extends to 7 µU/mL (7 mU/L) in patients older than 70 years. The third exception is in patients with known pituitary dysfunction or a risk of pituitary dysfunction (history of cranial irradiation, pituitary surgery, or massive head trauma).

If the serum TSH level is frankly abnormal, additional evaluation of thyroid function should be considered to determine the extent of the dysfunction. This is accomplished by measuring T_4 when the TSH is elevated and by measuring T_4 and T_3 when the TSH is suppressed.

When indicated by an abnormal TSH, the circulating level of thyroid hormone should be assessed using total or free T_4 levels. Total T_4 is a reflection of the bound and unbound fractions of the hormone and is a reasonable method of assessing overall thyroid hormone levels in most patients. However, in patients with disorders of protein metabolism, such as kidney or liver disease, measurement of free T_4ensures a more accurate representation of the hormone concentrations. Additionally, conditions that raise serum total protein level,

such as in patients taking estrogen or during pregnancy, may result in a higher total T_4 concentration, and measuring the free T_4 is indicated. The same rules apply to T_3 as to T_4 regarding protein levels, but free T_3 has a very short half-life and levels fluctuate more and are less reliable; therefore, it is controversial whether total or free T_3 should be measured in patients at risk for protein abnormalities.

Measurement of serum T_3 is necessary if the patient has a suppressed TSH level because, in some patients with thyrotoxicosis, T_3 may be preferentially secreted over T_4 (T_3 toxicosis). In patients with an elevated TSH level, indicating hypothyroidism, measurement of serum T_3 is not helpful because it will be maintained in the normal range even in those with significant disease.

Thyroid autoantibody measurement may be helpful under certain clinical circumstances. In patients with a personal history of autoimmune disease (such as type 1 diabetes mellitus, systemic lupus erythematosus, or celiac disease) or a strong family history of thyroid dysfunction, measuring thyroid autoantibodies may indicate the cause of the thyroid dysfunction or whether a patient is at risk for developing thyroid autoimmune disease if the TSH is normal. There is no clinical indication for serial measurement of thyroid antibody titers to determine the need for or to guide therapy. There are three forms of thyroid autoantibodies: thyroid peroxidase (TPO), thyrotropin receptor (TRAb), and thyroglobulin (TgAb). Elevated titers of TPO antibodies are associated with autoimmune hypothyroidism, or Hashimoto disease. Patients with TPO antibodies and normal thyroid function tests are at an increased risk of developing overt thyroid failure (2%-4% per year). Thyrotropin receptor antibodies (TRAb) are divided into three types: blocking (also called thyrotropin-binding inhibitory immunoglobulins), stimulating (also called thyroid-stimulating immunoglobulins or TSI), and neutral. The presence of TSI autoantibodies is responsible for the development of Graves disease. TSI autoantibodies should be measured if autoimmune hyperthyroidism is suspected. Thyroglobulin (Tg) is a glycoprotein located within the colloid on which thyroid hormones are synthesized and stored. Serum Tg and TgAb measurements are used to monitor patients with thyroid cancer; serum Tg is a highly sensitive and specific marker of residual thyroid tissue. After total thyroidectomy and radioactive iodine ablation, the

persistence of a detectable serum Tg is a possible indicator of residual or recurrent disease. Thyroglobulin antibodies are present in up to 30% of patients. Their presence in the serum is only significant in patients with thyroid cancer, as they can falsely lower the serum Tg. Therefore, TgAb titers should always be assessed simultaneously with the Tg; if antibodies are present, the Tg level may not be reliable.

Calcitonin, secreted by the C cells of the thyroid, is most frequently used as a tumor marker in patients with a history of medullary thyroid carcinoma. Serum calcitonin levels can help increase the sensitivity of detection of medullary thyroid carcinoma when used in conjunction with fine-needle aspiration (FNA). However, it is not recommended as a screening test in all patients with thyroid nodules because it lacks the requisite specificity. Instead, measurement of calcitonin should be considered if a patient with thyroid nodular disease has a history of hyperparathyroidism or a family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2, or if there is clinical suspicion for these disorders.

Radioactive iodine uptake (RAIU) is a measure of iodine uptake by the thyroid over a pre-specified time frame, typically 24 hours. RAIU is used to evaluate the cause of hyperthyroidism; it is not indicated in patients with normal or elevated TSH levels. The degree of uptake is useful for distinguishing the various causes of hyperthyroidism. RAIU percentage is typically very high in patients with Graves disease (diffusely increased uptake) and only moderately elevated in those with toxic multinodular goiter (patchy uptake in areas of nodules with relative suppression of normal tissue). In contrast, the RAIU is very low in those with thyroiditis or exposure to exogenous thyroid hormone. The presence of a “cold” nodule on isotope scanning is an indication for ultrasonography to help determine if FNA is indicated. RAIU is contraindicated during pregnancy and while breastfeeding.

Key Points

- The initial laboratory test of thyroid activity is thyroid-stimulating hormone measurement; in patients with an intact anterior pituitary, measurement of thyroid-stimulating hormone is exquisitely sensitive for detection of disorders of thyroid hypofunction (high thyroid-stimulating hormone) and hyperfunction (low thyroid-stimulating hormone).

- If central hypothyroidism is suspected, a concomitant thyroid hormone (thyroxine [T_4]) level should be assessed in conjunction with the thyroid-stimulating hormone level.
- If the thyroid-stimulating hormone level is frankly abnormal, additional evaluation of thyroid function should be considered to determine the extent of the dysfunction; measure thyroxine (T_4) when the thyroid-stimulating hormone is elevated and measure both thyroxine (T_4) and triiodothyronine (T_3) when the thyroid-stimulating hormone is suppressed.
- There is no clinical indication for serial measurement of thyroid antibody titers to determine the need for or to guide therapy except to monitor for residual disease in patients treated for thyroid cancer.
- Radioactive iodine uptake is a measure of iodine uptake by the thyroid over 24 hours; it is used to evaluate the cause of hyperthyroidism and is not indicated in patients with normal or elevated thyroid-stimulating hormone levels.

Functional Thyroid Disorders

Thyrotoxicosis

Related Question

Question 10

Evaluation

Thyrotoxicosis is a term used to describe thyroid hormone excess from all sources, whereas hyperthyroidism is the more specific term to describe thyroid gland overactivity. Thyrotoxicosis may result from endogenous thyroid disorders, pituitary tumors, and exogenous levothyroxine. The most common causes of hyperthyroidism are Graves disease and toxic adenoma(s).

The symptoms of thyrotoxicosis include heat intolerance, palpitations, dyspnea, tremulousness, menstrual irregularities, hyperdefecation, weight loss, increased appetite, proximal muscle weakness, fatigue, insomnia, and mood disturbances. The severity of symptoms may not correlate with the level of thyroid hormone derangement. In older patients, many of the classic symptoms of thyroid hormone excess may be absent, and the only presenting symptom may be atrial fibrillation or heart failure; this is known as apathetic hyperthyroidism.

The initial evaluation based on clinical signs and/or symptoms of thyrotoxicosis should be measurement of serum TSH alone, followed by measurement of T_4 and T_3 levels if TSH is suppressed. The typical pattern of hyperthyroidism is TSH suppression with an elevated T_4 and/or T_3. A normal serum TSH in the setting of an elevated T_4 and/or T_3 concentration suggests the presence of a TSH-secreting pituitary adenoma; these tumors are extremely rare and are managed differently from other causes of thyrotoxicosis (see later discussion).

Key Point

- The typical pattern of laboratory studies in hyperthyroidism is thyroid-stimulating hormone suppression with an elevated thyroxine (T_4) and/or triiodothyronine (T_3) level.

Management

Although the specific intervention used is usually determined by the underlying cause and patient and physician preference, control of the thyrotoxic state may be achieved by one of three treatment modalities: thionamides, radioactive iodine ablation, or surgery.

Rapid control of adrenergic symptoms with a β-blocker is indicated in most patients with thyrotoxicosis. Although propranolol is frequently used for its added effect of inhibition of peripheral conversion of T_4 to T_3, cardioselective β-blockers, such as atenolol, are preferred owing to the additional benefits of decreased central nervous system side effects and improved adherence with once-daily dosing.

Methimazole and propylthiouracil (PTU) are the two thionamides available in the United States. Methimazole is the preferred agent because it has a higher intrathyroidal retention (potency), a preferable dosing regimen (typically once daily), and a reduced side-effect profile. Antithyroid medications reduce T_3 and T_4 levels within a few days of initiation, but the full effect may take several weeks. Normalization of a previously suppressed TSH level may take several months. It is critical, therefore, to monitor T_4 and T_3 levels during treatment of hyperthyroidism because the TSH may not be an accurate reflection of the thyroidal status.

Thionamides may be used to prepare patients for thyroidectomy or radioiodine treatment, or they may be used as the primary therapy. Thionamides may be used for 1 to 2 years in patients with Graves disease in the hope of achieving remission; more definitive therapy with radioactive iodine or surgery may then be sought after that timeframe if hyperthyroidism persists. Although thionamides are generally well tolerated, it is important to be familiar with their side-effect profile. The most common reaction to antithyroid medications is a rash, seen in up to 10% of patients. Additionally, PTU may cause elevations of aminotransferase levels. Rare cases of fatal hepatotoxicity have been described with PTU. Therefore, its use is reserved for patients who cannot tolerate methimazole and during the first trimester of pregnancy, when methimazole has a possible teratogenic effect. A cholestatic pattern of liver test abnormalities may also be seen with methimazole, but it is typically temporary and milder than that seen with PTU. Both drugs may be associated with reversible agranulocytosis in approximately 1 in 500 patients. Baseline liver chemistry studies and complete blood count with differential are recommended before initiation of antithyroid medications, with serial monitoring of the complete blood count during therapy. If patients taking a thionamide develop a fever, rash, severe sore throat, jaundice, or other symptoms of serious illness, they should be assessed promptly for an adverse reaction to the medication.

The goal of radioactive iodine ablation is to render the patient hypothyroid, which can typically be accomplished in 90% of patients with the first treatment. Although a minority of patients may develop acute anterior neck pain from radiation thyroiditis, radioactive iodine ablation is typically well tolerated. It may take several months for the development of hypothyroidism, so it is important to monitor thyroid function tests monthly after therapy. In a patient with severe thyrotoxicosis, radioactive iodine may provide additional substrate to the hyperfunctioning gland, resulting in exacerbation of the hyperthyroid state. Consequently, it may be reasonable to initiate a thionamide prior to ablation to lower the thyroid hormone levels.

Surgery is rarely first-line therapy, given the inherent risks with any surgery. Patients in whom control cannot be achieved with thionamides and those who are not comfortable with radioiodine therapy are typically referred for surgery. Because of the increased intrathyroidal vascularity, the procedure can be technically more difficult than a typical thyroidectomy. Additionally, restoration of the euthyroid state before surgery with thionamides is important to improve hemodynamics during general anesthesia and decrease the patient's risk of thyroid storm.

Key Point

- Control of hyperthyroidism may be achieved by one of three treatment modalities: thionamides, radioactive iodine ablation, or surgery; modality choice depends on the underlying cause and patient preference.

Graves Disease Related Question

Question 70

Graves disease is a multiorgan system autoimmune disorder that can affect the thyroid, eyes, and skin. It is frequently seen in women between the ages of 20 and 50 years and is the most common cause of hyperthyroidism in the United States. Antibodies against the TSH receptor (TSI or TRAb) stimulate autonomous production of T_4 and T_3. Patients frequently report a family history of Graves disease, Hashimoto thyroiditis, or other autoimmune conditions.

On physical examination, patients have elevated systolic blood pressure with a widened pulse pressure, tachycardia, and a diffusely enlarged thyroid. Further inspection of the thyroid may reveal a bruit. Careful examination of the skin may reveal pretibial myxedema, an infiltrative process that is typically patchy with a peau d'orange appearance to the skin.

Diagnosis of Graves disease is made clinically in most instances, and measurement of TSI antibodies is reserved for patients who are not markedly thyrotoxic on examination and do not have a classic smooth, rubbery, diffuse goiter. In those patients, TSI antibodies may help

determine the cause of the hyperthyroidism. RAIU and scan will show markedly increased uptake with diffuse activity on the scan.

If ophthalmopathy is present, the patient may exhibit lid retraction (lid lag), whereby contraction of the levator palpebrae muscles of the eyelids results in immobility of the upper eyelid with downward rotation of the eye. Additionally, patients may have proptosis, scleral injection, and periorbital edema.

Because thionamide drugs also have an immunomodulatory effect that reduces autoantibody titers, antithyroid drugs are often first-line treatment for Graves disease. Up to 50% of patients may go into remission within 24 months, and some may maintain a euthyroid state without further therapy after an initial treatment with thionamides. If the patient does not go into remission or if disease recurs, definitive therapy with radioactive iodine ablation or surgery is recommended. However, in patients with Graves ophthalmopathy, there is an acute escalation of thyroid autoantibody titers following radioiodine therapy that may exacerbate ocular symptoms. Such patients may be better treated with thionamides and/or surgery.

Toxic Adenoma and Multinodular Goiter Related Questions

Question 18

Question 72

Activating mutations in the TSH receptor gene are responsible for the autonomous production of thyroid hormone in a toxic nodule (adenoma) or in multiple hyperfunctioning nodules in a toxic multinodular goiter. Because of this loss of normal regulation of thyroid hormone production, patients are at risk for developing acute thyrotoxicosis when exposed to iodine excess, particularly after a contrast load for medical testing (Jod-Basedow phenomenon), such as in cardiac catheterization and contrast-enhanced CT scans. Although patients with a toxic adenoma or multinodular goiter may exhibit the typical symptoms of thyrotoxicosis, they can be relatively asymptomatic. On physical examination, a nodule may

be palpable or there may be a diffusely enlarged goiter with a nodular contour but no discrete palpable nodules.

If a patient is suspected of having a toxic nodule, thyroid scintigraphy should be performed to determine if the nodule is autonomous. The thyroid uptake scan will reveal increased activity in the “hot” nodule with relative suppression of the remaining thyroid tissue. These results should then be correlated with the ultrasonographic findings to determine if any additional nodules exist, which will require further investigation with FNA.

Radioactive iodine ablation or surgery is the most common treatment for toxic nodules. Thionamides can be used to decrease hormone production in the short term, but unlike Graves disease, this condition has no chance of spontaneous remission and would require lifelong medical therapy, which is not recommended. Radioiodine therapy will ideally ablate only the autonomous areas. In elderly patients, those with coronary disease, those who are highly symptomatic, and those with severe thyrotoxicosis, thionamides are recommended to normalize thyroid hormone levels prior to radioactive iodine; this is done to avoid exacerbation of the thyrotoxicosis due to release of preformed hormone from the gland acutely after radioactive iodine ablation. Thionamides should be withheld for 5 to 7 days before the administration of radioactive iodine therapy. If a patient has a particularly large goiter with compressive symptoms or if there is concern for malignancy, surgery is recommended as first-line therapy.

Key Point

- Radioactive iodine ablation or surgery is the most common treatment for toxic thyroid nodules; indications for surgery include a large goiter with compression symptoms or concern for malignancy.

Destructive Thyroiditis

Thyroiditis is a self-limited inflammatory condition of the thyroid resulting in the release of preformed thyroid hormone into the circulation. The duration of the thyrotoxic phase is typically 2 to 6 weeks, during which patients may exhibit classic symptoms of thyrotoxicosis. Following the release of preformed hormone, the damaged thyroid ceases production of T_3 and T_4 during the recovery phase; consequently, administration of thionamides will not be

effective in treating elevated hormone levels. The patient may then become clinically hypothyroid, a condition that may require temporary levothyroxine therapy. The length of the hypothyroid phase can vary but classically is 6 to 12 weeks.

There are two categories of thyroiditis: painful and painless. The causes of painful thyroiditis are inflammatory (de Quervain or subacute granulomatous thyroiditis), infectious (suppurative), and radiation-induced. The pain, typically only present during the thyrotoxic phase, can be quite intense. Treatment is aimed at controlling inflammation with NSAIDs or systemic glucocorticoids if severe. Subacute thyroiditis is the most common form and is presumably caused by a postviral inflammatory process; many patients report a recent history of upper respiratory illness preceding the thyroiditis. Radiation thyroiditis may occur 5 to 10 days after treatment with radioactive iodine. This may be associated with transient exacerbation of the hyperthyroidism. The accompanying pain is usually mild and lasts for up to 1 week. Infectious thyroiditis is rare but may be seen in an immunocompromised patient; the most common causative organisms are *Staphylococcus* and *Streptococcus* species.

Painless thyroiditis is more commonly seen than painful thyroiditis and has several causes, including postpartum thyroiditis, silent thyroiditis, and drug-induced thyroiditis. Postpartum thyroiditis may occur up to 1 year after delivery; the frequency is variably reported but may occur in up to 10% of pregnancies. The presence of TPO antibodies is nearly universal, and the likelihood of subsequent permanent hypothyroidism is very high. Thyroiditis is also likely to recur in later pregnancies.

Key Point

- Thyroiditis is a self-limited inflammatory condition of the thyroid resulting in the release of preformed thyroid hormone into the circulation; the duration of the thyrotoxic phase is typically 2 to 6 weeks, which is followed by a hypothyroid phase typically lasting 6 to 12 weeks.

Central Hyperthyroidism

TSH-secreting pituitary adenomas are extremely rare. In this condition, serum TSH is detectable or normal in the setting of an elevated T_4 and/or T_3 concentration. A dedicated

pituitary MRI will demonstrate an adenoma. Treatment should focus on removal of the pituitary tumor; thyroid-targeted therapy is ineffective (see Disorders of the Pituitary Gland).

Subclinical Hyperthyroidism

Subclinical hyperthyroidism is a laboratory-based diagnosis, defined as the presence of a suppressed TSH level with normal T_3 and T_4 levels. Repeat assessment of thyroid function should be performed 6 to 12 weeks after the initial tests, as the values will normalize in up to 30% of patients. Symptoms of thyrotoxicosis are typically mild; most patients are asymptomatic.

Which patients will benefit most from normalization of the TSH level is not universally agreed on, but consensus opinion recommends treatment for patients with a TSH level below 0.1 µU/mL (0.1 mU/L). The benefits of treatment for asymptomatic patients with a TSH level between 0.1 µU/mL (0.1 mU/L) and the lower limit of the normal reference range are less clear. Emerging data suggest that chronic subclinical hyperthyroidism has a negative effect on cardiac function, the central nervous system, and bone mass. The risk of atrial fibrillation is significantly increased when the TSH level is below 0.3 µU/mL (0.3 mU/L), so patients over the age of 65 years and those with a history of coronary artery disease or tachyarrhythmias, as well as patients with osteoporosis, may benefit from normalization of the TSH level. Radioiodine is the preferred treatment, but often the gland does not have sufficient iodine avidity and methimazole must be used.

Key Points

- In patients with subclinical hyperthyroidism, repeat assessment of thyroid function should be performed 6 to 12 weeks after the initial tests, as the values will normalize in up to 30% of patients.
- Treatment for subclinical hyperthyroidism is recommended when the thyroid-stimulating hormone level is less than 0.1 µU/mL (0.1 mU/L).

Thyroid Hormone Deficiency

Hypothyroidism

Evaluation

Hypothyroidism refers to low circulating thyroid hormone levels. Hypothyroidism is more prevalent in women than men (2% versus 0.2%) and in those with other autoimmune diseases. The most frequent cause is Hashimoto thyroiditis, also known as chronic lymphocytic thyroiditis. Iatrogenic causes include surgery, radioiodine therapy, and external beam radiation therapy to the neck. Hypothyroidism may also be medication induced; the most common causative agents include lithium, amiodarone, interferons, interleukin-2, and tyrosine kinase inhibitors. Rarely, pituitary tumors, severe head trauma, pituitary surgery, or cranial radiation can cause central hypothyroidism.

The clinical manifestations of hypothyroidism include fatigue, cold intolerance, constipation, heavy menses, weight gain, impaired concentration, dry skin, edema, depression, mood changes, muscle cramps, myalgia, and reduced fertility. The physical examination findings may include reduction in basal temperature, diastolic hypertension, bradycardia, dry skin, brittle hair, hoarseness, delayed relaxation phase of the deep tendon reflexes, and an enlarged thyroid.

An elevated serum TSH level indicates the diagnosis of primary hypothyroidism. In patients with an elevated TSH that is less than 10 µU/mL (10 mU/L), a low serum T_4 measurement is helpful, as a frankly low value indicates that thyroid hormone replacement is necessary. The presence of TPO antibodies suggests that Hashimoto thyroiditis is the underlying cause. Thyroid imaging is not indicated unless there is concern for a nodule on physical examination.

Key Points

- An elevated serum thyroid-stimulating hormone level indicates the diagnosis of primary hypothyroidism; thyroid imaging is not indicated unless there is concern for a nodule on physical examination.

- The most frequent cause of primary hypothyroidism is Hashimoto thyroiditis (chronic lymphocytic thyroiditis); the presence of TPO antibodies is suggestive of Hashimoto thyroiditis.

Management

In patients with a TSH level greater than 10 µU/mL (10 mU/L), daily thyroid hormone replacement is recommended.

Thyroid hormone replacement with levothyroxine alone is recommended. The goal of thyroid hormone replacement therapy is normalization of the TSH. The starting dose can be weight-based at 1.67 µg/kg/d, using ideal body weight. In patients with prevalent cardiac disease, tachyarrhythmias, or multiple comorbidities, or in those who are older than 65 years, the dose should not be based on weight but rather should be 25 to 50 µg/d. The dose should be titrated based on TSH levels measured 6 to 8 weeks after any dose change. To improve gastrointestinal absorption, levothyroxine should be taken on an empty stomach, 1 hour before or 2 to 3 hours after ingestion of food or medications that would interfere with absorption, such as calcium- or iron-containing supplements. Patients with celiac disease may require higher levothyroxine doses because of impaired absorption.

There has been significant debate regarding the need for supplementation of T_3 (liothyronine) in patients with hypothyroidism. The short half-life of T_3 triggers acute spikes in serum T_3 levels, which are of significant concern for elderly patients or those with preexisting cardiac issues. Additionally, numerous studies have failed to show a clear benefit of a T_4/T_3 combination over T_4 alone; therefore, this is not generally recommended.

Key Point

- In patients with a thyroid-stimulating hormone level greater than 10 µU/mL (10 mU/L), daily thyroid hormone replacement is recommended and should be taken on an empty stomach; the dose should be titrated based on thyroid-stimulating hormone levels measures 6 to 8 weeks after any dose change.

Subclinical Hypothyroidism Related Question

Question 16

Subclinical hypothyroidism is defined as an elevated serum TSH level with a normal T_4 level. The potential causes are the same as for overt hypothyroidism. Repeat measurement of the TSH level is recommended, particularly in an asymptomatic patient, as it will normalize in up to 30% of patients by 6 weeks.

Patients typically have mild or no symptoms of hypothyroidism. Subclinical hypothyroidism may be associated with several laboratory abnormalities including elevated total cholesterol, LDL cholesterol, and C-reactive protein levels. Large studies suggest that these laboratory abnormalities translate into an increased risk of atherosclerosis and cardiac events. However, supplementation with levothyroxine has not been shown to mitigate this risk. Treatment is generally recommended for those with a TSH level greater than 10 µU/mL (10 mU/L), but levothyroxine treatment should be considered in patients who have positive TPO antibodies or a large goiter, as these patients are at risk for progression to overt hypothyroidism at rates of 3% to 8% per year. A goal TSH level less than or equal to 2.5 µU/mL (2.5 mU/L) is recommended for women with subclinical hypothyroidism and positive TPO antibody status who are planning to conceive.

Key Point

- In patients with suspected subclinical hypothyroidism, repeat measurement of the thyroid-stimulating hormone level is recommended, as it will normalize in up to 30% of patients by 6 weeks.

Drug-Induced Thyroid Dysfunction

Various medications can affect thyroid function and are listed in **Table 26** based on their mechanism of action.

Amiodarone may have a potentially toxic effect on the thyroid. The iodine content of amiodarone is 37% by weight. It is stored in fat, myocardium, liver, lung, and thyroid tissues, with a half-life exceeding 50 days. This long half-life, coupled with the high iodine content, renders it a potentially toxic compound to the thyroid. The two types of amiodarone thyroid toxicity are changes in thyroid function studies seen in all patients (obligatory effects), and those seen in only a subset of patients (facultative effects).

The obligatory effects result from the increased circulating iodine after initiation of the drug. Adaptation to the acute iodine excess causes a reduction in organification of iodine and reduced production of thyroid hormone (Wolff-Chaikoff effect). The result is a temporary reduction in circulating T_3 and T_4 levels with a minor rise in the TSH level; these changes typically reverse within the first 3 months of treatment and require no intervention.

Facultative effects, seen in up to 15% of patients, may cause either hypo- or hyperthyroidism. In areas of iodine sufficiency, hypothyroidism is the more common toxicity. Those at highest risk are women with preexisting TPO antibody positivity. Amiodarone-induced thyrotoxicosis (AIT) is more commonly seen in males and in those living in iodine-deficient areas. Type 1 AIT is the result of exposure to excess iodine and occurs in those with preexisting thyroid conditions, such as latent Graves disease or nodular goiter, in which the iodine increases unregulated thyroid hormone production. Type 2 AIT is the result of the cytotoxic effects of amiodarone on thyroid tissue, producing a clinical picture of painless thyroiditis, with abnormal release of thyroid hormone. The treatments differ with each type, but distinguishing between the two forms of AIT often can be challenging and may require the aid of an endocrinologist. The time to recovery of normal thyroid function may be several months, even with prompt diagnosis and treatment. Discontinuation of amiodarone is typically necessary, particularly in those patients with type 1 AIT.

Key Points

- In the majority of patients, amiodarone causes a temporary reduction in circulating triiodothyronine (T_3) and thyroxine (T_4) and levels with a minor rise in the thyroid-stimulating hormone that reverses within first 3 months of treatment and requires no intervention.
- In 15% of patients, amiodarone may cause either hypo- or hyperthyroidism; those at highest risk for amiodarone-induced hypothyroidism are women with preexisting thyroid peroxidase antibody positivity.

Thyroid Function and Disease in Pregnancy

Related Questions

Question 1

Question 41

Significant changes in thyroid function occur during pregnancy; understanding the normal physiology during gestation is critical for a correct interpretation of thyroid laboratory studies. Abnormalities of thyroid function can have a dramatic effect on the health of the mother and the fetus. A diagram of the physiologic changes in thyroid function during each trimester is shown in **Figure 8**.

Figure 8. OPEN IN NEW WINDOW

Thyroid function in pregnancy. HCG = human chorionic gonadotropin; T_4 = thyroxine; TBG = thyroid-binding globulin; TSH = thyroid-stimulating hormone.

Increased estrogen levels cause a rise in thyroxine-binding globulin. To maintain a stable free T_4 and T_3, thyroid hormone production is increased and TSH remains within the normal reference range for the patient's trimester (see later discussion for trimester-specific ranges). Routine screening of TSH is not indicated for every pregnant woman. TSH screening is indicated in women with a risk of thyroid gland dysfunction, including those already on thyroid hormone replacement therapy; those with autoimmune disorders, goiter, previous head/neck irradiation, previous thyroid surgery, known positive TPO antibodies or positive TSI antibodies, or a strong family history of thyroid dysfunction; those who live in iodine-deficient areas; or those older than 30 years. In patients on levothyroxine replacement, the dose of the medication may need to be increased, on average by 30% to 50%, and patients should have their TSH level checked as soon as a pregnancy test is positive.

Fetal thyroid tissue is not functional until 10 to 12 weeks' gestation, necessitating maternal thyroid hormone transfer through the placenta. Thyroid hormone deficiency can negatively affect fetal neurocognitive development. It is critical to maintain a euthyroid state during pregnancy in these patients. TSH testing should be performed every 6 weeks throughout pregnancy, with adjustments in thyroid hormone replacement dosing as needed to maintain the TSH within the trimester-specific normal range. The largest dose escalations typically occur in the first trimester, with more dose stability later in pregnancy.

Diagnosing possible hyperthyroidism during pregnancy may be challenging because some physiologic changes during gestation may overlap with symptoms of thyrotoxicosis, such as tachycardia, fatigue, and heat intolerance. Serum TSH and human chorionic gonadotropin have a common α-subunit, allowing cross-reactivity at the TSH receptor. Consequently, TSH declines during the first trimester; the reference range shifts down to 0.03 to 2.5 µU/mL (0.03-2.5 mU/L). During the second and third trimesters the upper limit of TSH rises to 3.0 µU/mL (3.0 mU/L). An additional complicating factor is that radioiodine scanning is contraindicated during pregnancy because of the risk for fetal thyroid exposure to radiation. Instead, several clinical clues may be used to help determine if the patient has thyrotoxicosis, including the presence of a goiter, ophthalmopathy, or TSI antibodies, all of which are suggestive of Graves disease.

The use of thionamides is considered safe during pregnancy, but PTU is preferred during the first trimester because of potential teratogenic effects from methimazole during organogenesis. Although rarely indicated, surgery may be performed during the second trimester. It should be reserved for those who are unable to tolerate thionamides or who have inadequate control on medical therapy. Radioiodine therapy is contraindicated during pregnancy and while breastfeeding. Treatment goals with thionamides are a detectable TSH in the lower end of the pregnancy reference range and a free T_4 in the upper end of the reference range.

Key Point

- In pregnant patients on levothyroxine replacement, the dose may need to be increased, on average by 30% to 50%; patients should have their thyroid-stimulating hormone level checked as soon as a pregnancy test is positive.

Euthyroid Sick Syndrome

Related Question

Question 13

Euthyroid sick syndrome (ESS), nonthyroidal illness syndrome, or low T_3 syndrome are various names that have been assigned to the changes seen in thyroid function test

results during critical illness. Although not a true syndrome, there are significant perturbations of the hypothalamic-pituitary-thyroid (HPT) axis that occur in up to 75% of hospitalized patients. The underlying cause of the critical illness may influence the pattern of thyroid function abnormalities. Drugs that are frequently used in critically ill patients can have a significant effect on the HPT axis (see **Table 26**). The typical pattern is initially a low T_3 level, followed by a decline in the T_4 level. As the patient becomes more critically ill, the TSH level may also decline, creating a clinical picture that is difficult to discern from central hypothyroidism. Rarely, TSH can be elevated in ESS.

Table 26. OPEN IN NEW WINDOW Medications that Affect Thyroid Function

Mechanism of Action	Drugs	Comments
Decreased absorption or enterohepatic circulation	Calcium Proton pump inhibitors Iron Cholestyramine Aluminum hydroxide Soybean oil Sucralfate Psyllium	It is recommended that levothyroxine ingestion be separated from these medications by several hours
Increased metabolism	Phenytoin	Higher levothyroxine doses may be required to maintain levothyroxine in the normal range

Table 26. OPEN IN NEW WINDOW Medications that Affect Thyroid Function

Mechanism of Action	Drugs	Comments
of levothyroxine	Carbamazepine Rifampin Phenobarbital Sertraline	
Thyroiditis	Amiodarone Lithium Interferon alfa Interleukin-2 Tyrosine kinase inhibitors	May cause hypo- or hyperthyroidism
De novo development of antithyroid antibodies	Interferon alfa	May develop Hashimoto thyroiditis, Graves disease, or painless thyroiditis
Inhibition of TSH synthesis or release	Glucocorticoids Dopamine Dobutamine Octreotide	

Table 26. OPEN IN NEW WINDOW Medications that Affect Thyroid Function

Mechanism of Action	Drugs	Comments
Increased thyroxine-binding globulin	Estrogen Tamoxifen Methadone	False elevation of total T_3, total T_4 levels; free T_3, T_4 may be more accurate reflection of hormone levels
Decreased thyroxine-binding globulin	Androgen therapy Glucocorticoids Niacin	False lowering of total T_3, total T_4 levels; free T_3, T_4 may be more accurate reflection of hormone levels

- T_3 = triiodothyronine; T_4 = thyroxine; TSH = thyroid-stimulating hormone.

Two general guidelines are important in evaluating a critically ill patient. First, measurement of TSH alone should be obtained only if there is a high clinical suspicion of thyroid dysfunction. If TSH is abnormal, the previously described recommendations for additional laboratory studies should be followed. If the TSH is greater than 20 µU/mL (20 mU/L) or is undetectable, ESS is less likely to be the cause and overt thyroid dysfunction should be strongly considered. If the TSH falls between these two values, historical clues and examination findings are very important for identifying patients with true thyroid dysfunction.

After discharge from the hospital, thyroid function abnormalities may persist for several weeks. The typical pattern is a mildly elevated TSH level and slightly low T_4 and T_3 levels. In a clinically euthyroid patient, thyroid function tests should be repeated 6 weeks after hospitalization to confirm overt thyroid dysfunction with persistent TSH abnormality or confirm ESS with normalization of TSH.

Key Points

- Critical illness can cause changes in thyroid function tests in up to 75% of hospitalized patients, known as euthyroid sick syndrome; measurement of TSH should only be obtained in the hospital when there is a high clinical suspicion of thyroid dysfunction.
- The typical pattern of euthyroid sick syndrome, nonthyroidal illness syndrome, or low triiodothyronine (T_3) syndrome is a mildly elevated thyroid-stimulating hormone level and slightly low thyroxine (T_4) and triiodothyronine (T_3) levels.
- After patients with euthyroid sick syndrome are discharged from the hospital, thyroid function abnormalities may persist for several weeks so follow-up thyroid function tests should not be repeated until 6 weeks after discharge.

Thyroid Emergencies

Although most thyroid conditions are not urgent, thyroid storm and myxedema coma represent true medical emergencies requiring critical care. Failure to make a timely diagnosis and institute treatment is associated with a high mortality rate.

Thyroid Storm

Related Question

Question 33

Thyroid storm is a severe manifestation of thyrotoxicosis with life-threatening secondary systemic decompensation (shock). The cardinal features for diagnosis include elevated temperature, significant tachycardia, heart failure, gastrointestinal dysfunction (nausea, vomiting, diarrhea, and/or jaundice), and neurologic disturbances. The range of central nervous system manifestations includes increasing agitation, emotional lability, confusion, paranoia, psychosis, or coma. Although thyroid storm has been reported with many causes of thyrotoxicosis, it occurs most commonly with Graves disease. Thyroid storm may be precipitated by another event such as infection, surgery, myocardial infarction, trauma, or parturition. Administration of radioactive iodine therapy to a patient with untreated or uncontrolled hyperthyroidism can trigger thyroid storm.

The diagnosis is based on clinical presentation but can generally be ruled out if T_4 and T_3 levels are within normal limits.

Treatment of thyroid storm should be directed toward reduction of thyroid hormone production, decreasing peripheral conversion of T_4 to T_3, addressing adrenergic symptoms and thermoregulatory changes, searching for and treating precipitating factors, and reversing systemic decompensation. Thionamides and β-blockers are the mainstay of treatment to reduce thyroid hormone production and control adrenergic symptoms. PTU and propranolol are the preferred agents because they have the added benefit of blocking peripheral conversion of T_4 to T_3. Additionally, high-dose glucocorticoids reduce T_4 conversion to bioactive T_3. At least 1 hour after the first dose of a thionamide, iodine drops should be administered to inhibit further release of thyroid hormone from the gland. Acetaminophen and cooling blankets may be used to control the hyperthermia. However, even with aggressive therapy and supportive measures, mortality rates are as high as 15% to 20%.

Key Points

- Thyroid storm is a severe manifestation of thyrotoxicosis with life-threatening secondary systemic decompensation (shock); it occurs most commonly with underlying Graves disease coupled with a precipitating factor such as infection, surgery, myocardial infarction, or parturition and mortality is 15% to 20%.
- In addition to supportive care and treating the participating cause, thionamides and β-blockers are the mainstay of treatment to reduce thyroid hormone production and are often combined with iodine drops and high-dose glucocorticoids to treat thyroid storm.

Myxedema Coma

Myxedema coma is an extreme but rare manifestation of hypothyroidism, resulting in life-threatening secondary systemic decompensation. Without a frankly low T_4 level, myxedema coma is unlikely, regardless of the degree of TSH elevation. It has a very high mortality rate if there is a delay in treatment. Myxedema coma is more common in elderly women; it may occur in those with a history of hypothyroidism or no antecedent illness. Precipitating events are frequent, such as myocardial infarction, infection, stroke, trauma, gastrointestinal bleeding, or metabolic derangements. Cold

exposure appears to be a risk factor, as this condition is more commonly seen in the winter months.

Mental status changes and hypothermia are the most common clinical manifestations. The spectrum of mental status changes includes lethargy, stupor, coma, depression, or even psychosis. Hypothermia (temperature less than 34.4 °C [94.0 °F]) is present in nearly all patients; lower temperatures are associated with a worse prognosis. Ventilatory drive is decreased, resulting in hypoxemia and hypercapnia. Additional signs include bradycardia, hypoglycemia, hyponatremia, and/or hypotension. A significant percentage of patients experience seizures, which may be related to the coexisting metabolic derangements.

If myxedema coma is suspected, the serum TSH and T_4 levels should be tested immediately. Diagnosis is made based on the clinical presentation and the coexisting metabolic abnormalities. The serum cortisol level should be checked as soon as possible to evaluate for concomitant adrenal insufficiency prior to initiation of thyroid hormone replacement. While awaiting the results of the serum cortisol measurement, it is generally advisable to empirically initiate high-dose glucocorticoid therapy. This therapy may be discontinued if the serum cortisol level is found to be normal or high.

The treatment of myxedema coma is aimed at restoration of the euthyroid state with thyroid hormone therapy, supportive care (mechanical ventilation, vasopressors, and glucocorticoids), warmed intravenous fluids, warming blankets, and management of the underlying precipitating event. The exact dose and preparation of thyroid hormone to administer is controversial; minimal clinical trial information is available to ascertain the optimal treatment regimen. It is important to balance the need for rapid reinstatement of a euthyroid state with the risk of precipitating a fatal cardiac event due to increased cardiac work with administration of thyroid hormone. Generally, intravenous levothyroxine therapy is administered, initially as an intravenous bolus of 200 to 500 μg, followed by daily doses of 50 to 100 μg intravenously until transition to an oral formulation is feasible. Treatment with T_3 is not recommended.

Even with aggressive therapy, the mortality rate for myxedema coma is 20% to 25%.

Key Points

- Myxedema coma is an extreme but rare manifestation of hypothyroidism, resulting in life-threatening secondary systemic decompensation and a mortality rate of 20% to 25%.
- The treatment of myxedema coma is aimed at restoration of the euthyroid state with thyroid hormone therapy, supportive care (mechanical ventilation, vasopressors, and glucocorticoids), warmed intravenous fluids, warming blankets, and management of the underlying precipitating event.

Structural Disorders of the Thyroid Gland

Thyroid Nodules

Related Question

Question 8

Nodularity of the thyroid is extremely common; large population studies suggest that up to 5% of women and 1% of men have a clinically evident nodule. The prevalence increases with age. In autopsy series and screening ultrasound studies, nodules may be seen in up to 60%.

The differential diagnosis for a nodule in the thyroid is varied and includes both primary thyroid disorders and metastatic spread from other primary malignancies (Table 27). Most thyroid nodules are benign, with only approximately 10% harboring a malignancy. Ultrasonography is an inexpensive and highly effective method for stratification of malignancy risk. All patients with a suspected thyroid nodule should have a neck ultrasound that includes evaluation of the thyroid and cervical lymph nodes.

Table 27. OPEN IN NEW WINDOW Types of Thyroid Nodules

Benign	Malignant
Multinodular	Papillary thyroid cancer

Table 27. OPEN IN NEW WINDOW Types of Thyroid Nodules

Benign	Malignant
goiter (colloid adenoma)	
Hashimoto (chronic lymphocytic) thyroiditis	Follicular thyroid cancer
Colloid cyst	Medullary thyroid cancer
Hemorrhagic cyst	Anaplastic thyroid cancer
Follicular adenoma	Primary thyroid lymphoma
Hürthle cell adenoma	Metastatic cancer Breast Melanoma Renal cell

Nodules are frequently detected incidentally on imaging studies performed for other reasons. The diagnostic evaluation of incidentally discovered thyroid nodules is identical to those that are clinically detected, with the same rate of malignancy. Nodules incidentally

identified on fluorodeoxyglucose-PET (FDG-PET) scanning, however, have a malignancy rate of 30% to 50%. Consequently, FDG-avid nodules found on PET scans require heightened suspicion and a lower threshold for intervention or diagnostic evaluation.

A careful history should be performed in patients with a thyroid nodule. Increased risk of malignancy is found in patients with history of radiation exposure to the head or neck, a family history of thyroid cancer, or a personal history of thyroid cancer. Additional factors that increase the risk for malignancy in a nodule include male sex, extremes of age (<20 or >60 years), rapid nodule growth, and hoarseness. On physical examination, the nodule should be assessed for texture, mobility, and associated lymphadenopathy. If the nodule is hard, fixed to surrounding tissue (nonmobile with swallowing), and/or there is associated cervical lymphadenopathy, the risk of malignancy is greater. Pain is an uncommon finding with thyroid nodules, but when present it is usually associated with benign conditions.

A serum TSH measurement is the initial laboratory test in a patient with a thyroid nodule. If the TSH is suppressed, measurement of T_4 and T_3 should be performed, and a radionuclide scan should be considered (**Figure 9**). The objective of the scan is to identify "hot" or functioning nodules, which have a very low likelihood of malignancy and typically do not require FNA. In contrast, if the TSH is high or normal, the radionuclide scan is unnecessary as it is unlikely to reveal a hot nodule; the evaluation should proceed with an ultrasound and possible FNA. As thyroid nodular disease can be altered by normalization of the TSH, ultrasound and FNA should be postponed in patients with elevated TSH until TSH is normal, unless there is marked concern for malignancy. One-time measurement of thyroid antibodies may be appropriate if autoimmune thyroid disease is suspected or if multinodular goiter is identified by ultrasound to stratify the patient's future risk of developing overt thyroid failure. Serum thyroglobulin measurement is not useful and is not recommended.

Figure 9. OPEN IN NEW WINDOW

Initial evaluation of a thyroid nodule. There are size thresholds for FNA based on US appearance. A less suspicious lesion may not need FNA until it is larger than 2 cm, suspicious nodules if larger than 1 cm. FNA = fine-needle aspiration; FT_3 = free triiodothyronine; FT_4 = free thyroxine; TSH = thyroid-stimulating hormone; US = ultrasound.

FNA, performed under ultrasound guidance, is the optimal test to determine whether a nodule is malignant. When performed by an experienced clinician, FNA is safe and relatively simple to perform. The sensitivity of FNA cytology is 90% to 95%, and the false-negative rate is 3% to 5%. FNA of a nodule is generally recommended for those nodules larger than 1 cm that are solid and hypoechoic. The threshold for FNA of nodules that are partially cystic and lacking suspicious ultrasound features is 2 cm in size or greater. Aspirating a nodule of 5 mm or more may be considered if a patient has risk factors such as a personal or family history of thyroid cancer or prior radiation exposure.

The sonographic appearance of a nodule may be used to assess the risk of malignancy and thereby guide the decision of which nodules require biopsy. Features concerning for malignancy include microcalcifications, marked hypoechogenicity, irregular borders, and taller-than-wide shape. Such findings are nearly 70% specific for cancer, but their poor sensitivity cannot exclude the presence of malignancy.

The various diagnoses obtained on FNA and the associated risks of malignancy are listed in Table 28.

Table 28. OPEN IN NEW WINDOW Diagnoses Obtained by Fine-Needle Aspiration of Thyro Nodules and Risk for Malignancy

FNA Diagnosis	Risk for Malignancy	Management
Benign	<3%	Serial ultrasound examinations for growth
Atypia of uncertain significance/follicular lesion of uncertain	5%-10%	Repeat FNA

Table 28. OPEN IN NEW WINDOW Diagnoses Obtained by Fine-Needle Aspiration of Thyro Nodules and Risk for Malignancy

FNA Diagnosis	Risk for Malignancy	Management
significance		
Suspicious for follicular lesion	20%-30%	Hemithyroidectomy
Suspicious for malignancy	50%-75%	Hemithyroidectomy or total thyroidectomy
Malignant	97%-100%	Total thyroidectomy
Nondiagnostic	0%-50%	Repeat FNA; if two nondiagnostic FNAs, surgery

- Modified from: Cibas ES, Ali SZ; NCI Thyroid FNA State of the Science Conference. The Bethesda System For Reporting Thyroid Cytopathology. Am J Clin Pathol. 2009 Nov;132(5):658-65. PMID: 19846805
- FNA = fine-needle aspiration.

Nodules that are benign by FNA should be followed with repeat ultrasound examination in 6 to 18 months to assess for significant changes. If the nodule is stable on repeat imaging and lacks suspicious features, clinical examination and repeat ultrasound can be extended to longer intervals, such as 3 to 5 years. Greater than 50% change in nodule volume or interval development of concerning ultrasound characteristics should prompt a repeat FNA to evaluate for a false-negative initial biopsy.

Malignant nodules and those that are suspicious for malignancy require prompt excision; this is typically done with total thyroidectomy, but hemithyroidectomy may be preferable for patients younger than 45 years of age with a tumor smaller than 4 cm. A nondiagnostic

FNA warrants a repeat attempt. In a solid nodule with two unsatisfactory biopsies, diagnostic hemithyroidectomy is indicated. Surgical complications include hypoparathyroidism and recurrent laryngeal nerve paresis; although typically temporary, either complication may be permanent in up to 3% of patients.

Key Points

- Thyroid nodules are found in 1% to 5% of the population; most thyroid nodules are benign, with only approximately 10% harboring a malignancy.
- A serum thyroid-stimulating hormone measurement is the initial laboratory test in a patient with a thyroid nodule; if the thyroid-stimulating hormone is suppressed, then measurement of thyroxine (T_4) and triiodothyronine (T_3) should be performed, and a radionuclide scan should be considered to identify "hot" or functioning nodules, which have a very low likelihood of malignancy and typically do not require fine-needle aspiration.
- If the thyroid-stimulating hormone level is high or normal, the radionuclide scan is unnecessary as it is unlikely to reveal a hot nodule and ultrasonography is an inexpensive and highly effective method for stratification of malignancy risk for nonfunctioning thyroid nodules.
- Fine-needle aspiration of a nodule is generally recommended for those nodules larger than 1 cm (0.4 in) that are solid and hypoechoic and is the optimal test to determine whether a nodule is malignant.

Goiters

Multinodular Goiter

Multinodular goiters occur more frequently with advancing age, low iodine intake, or Hashimoto disease. The risk for malignancy is the same for multiple nodules as it is for a solitary nodule; therefore, the evaluation and management are identical. Biopsy should be performed on the three or four nodules (larger than 1 cm) with the most suspicious ultrasound features. In the absence of suspicious features, the largest nodules should be chosen for aspiration.

A large multinodular goiter may be associated with compressive symptoms such as dysphagia, hoarseness, or positional dyspnea. To assess the extent of mass effect, additional testing and imaging, including noncontrast CT of the neck/chest, barium swallow, direct laryngoscopy, and/or spirometry with flow-volume loops, may be indicated. Levothyroxine therapy to suppress TSH secretion and reduce goiter size is generally not helpful, poses a risk

of thyrotoxicosis, and is not recommended. Radioactive iodine ablation is not an option for euthyroid and hypothyroid patients. Surgical removal is the treatment of choice if the compressive symptoms are significant, if malignancy is suspected, or if the patient desires cosmetic intervention.

Key Points

- In patients with a multinodular goiter, the risk for malignancy is the same for multiple nodules as it is for a solitary nodule; therefore, the evaluation and management are identical.
- Surgical removal of a large multinodular goiter is the treatment of choice if the compressive symptoms are significant, if malignancy is suspected, or if the patient desires cosmetic intervention.

Simple Goiter
Related Question

Question 45

A simple goiter is defined as an enlargement of the thyroid gland without the presence of nodules. It may be seen in conditions of dyshormonogenesis, autoimmune thyroid disease, or primary thyroid lymphoma. Primary thyroid lymphoma is a rare condition that typically occurs in elderly women with a history of Hashimoto thyroiditis. The clinical presentation is a symptomatic, rapidly enlarging goiter with a very firm texture. Patients may also have systemic lymphoma symptoms and lateral cervical lymphadenopathy. The diagnosis can be made by FNA. Treatment typically involves chemotherapy and/or radiation therapy. Surgery generally is not indicated, but it can be used to aid in diagnosis when FNA is not informative.

Thyroid Cancer

Related Questions

Question 62

Question 74

The incidence of thyroid cancer is rising at a faster rate than any other type of malignancy; the incidence has more than doubled in the last 30 years. This increase is due solely to papillary cancers, with the highest rate of rise occurring in tumors measuring less than 2 cm. Meanwhile, the survival rate for thyroid cancer has remained stable or slightly improved. Autopsy series reveal that occult thyroid cancers measuring less than 1 cm may be identified in as many as 20% of dissected specimens. This finding, coupled with the improving survival rate, has led some investigators to conclude that the change in incidence of thyroid cancer is due solely to increased incidental detection of indolent tumors because of greater use of imaging modalities. Although there is little doubt that escalated detection of otherwise occult tumors has contributed to the trend, there is evidence that larger tumors are increasingly being discovered.

The vast majority of patients with thyroid cancer have well-differentiated thyroid cancer, with excellent long-term survival. The major forms and their relative frequency are listed in **Figure 10**. The most common well-differentiated thyroid cancers are papillary, papillary-follicular variant, and follicular. There are rare, less well-differentiated variants of papillary thyroid cancer (columnar, tall cell, insular, oxyphilic, clear cell, diffuse sclerosing) that are more aggressive and carry a worse prognosis. Anaplastic thyroid cancer is undifferentiated and is the most aggressive form of thyroid cancer; 1-year survival rates range from 20% to 30%.

Figure 10. OPEN IN NEW WINDOW

Relative frequency of the types of thyroid cancer.

- Data from Hundahl SA, Fleming ID, Fremgen AM, Menck HR. A National Cancer Data Base report on 53,856 cases of thyroid carcinoma treated in the U.S., 1985-1995. Cancer. 1998 Dec 15;83(12):2638-48. PMID: 9874472

Staging and prognosis of well-differentiated thyroid cancers (papillary and follicular) are based on the American Joint Committee on Cancer criteria, which include age (<45 or ≥45 years), primary tumor size, local and distant metastases, and capsular and lymphovascular invasion. However, because the majority of patients have excellent survival, T (tumor) N (node) M (metastasis) staging plays a minimal role in the management of thyroid cancers.

Instead, decisions regarding treatment are aimed at lowering the likelihood of recurrent disease.

Treatment of well-differentiated thyroid cancer includes a combination of surgery, radioactive iodine, and levothyroxine suppression. The extent of surgery is largely based on the tumor size; solitary tumors smaller than 1 cm may be sufficiently managed with lobectomy alone. Patients with larger tumors, multifocal disease, nodal metastases, or a history of irradiation are best treated with total or near-total thyroidectomy. For patients younger than 45 years of age with a tumor smaller than 4 cm and no evidence of nodal or distant metastases, hemithyroidectomy may be a reasonable alternative to total thyroidectomy. The decision to administer radioactive iodine is based on two factors: improvement in mortality rates and/or reduction in recurrence risk. Patients with distant metastases have improved survival with successful radioiodine therapy, whereas administration of radioactive iodine may decrease the likelihood of recurrent disease in those patients with nodal metastases. Suppression of TSH with levothyroxine therapy may also be used to improve morbidity and reduce mortality, particularly in patients with persistent disease or distant metastases. The necessary degree of TSH suppression varies according to the risk of cancer progression and comorbidities of the patient. Patients with persistent disease typically require lowering of their TSH level to less than 0.1 μU/mL (0.1 mU/L), whereas those who are free of disease but have a high risk for recurrence should have a target TSH level of 0.1 to 0.5 μU/mL (0.1-0.5 mU/L) for 5 to 10 years. Those patients who are disease-free with a low risk of recurrence should maintain a TSH level of 0.3 to 2.0 μU/mL (0.3-2.0 mU/L).

Medullary thyroid cancer represents less than 10% of all thyroid cancers. Approximately 25% of medullary thyroid cancers are hereditary; all patients with medullary thyroid cancer should be screened with *RET* proto-oncogene sequencing. Medullary thyroid cancer may be associated with several syndromes, including multiple endocrine neoplasia type 2A (MEN2A) (which may include pheochromocytoma and hyperparathyroidism), MEN2B (marfanoid habitus and mucosal ganglioneuromas), or familial medullary thyroid cancer (medullary thyroid cancer alone). Biochemical screening for pheochromocytoma with measurement of

plasma fractionated metanephrine levels should be done in all patients with an *RET* mutation prior to thyroidectomy.

Key Points

- The vast majority of patients with well-differentiated thyroid cancer have excellent long-term survival.
- Treatment of well-differentiated thyroid cancer includes a combination of surgery, radioactive iodine, and levothyroxine suppression of thyroid-stimulating hormone for patients with persistent disease or high risk of recurrence.

Reproductive Disorders

Physiology of Fe male Reproduction

A regular, predictable menstrual cycle requires coordination of inhibition and stimulation between the hypothalamus (secreting gonadotropin-releasing hormone [GnRH]), the pituitary (secreting follicle-stimulating hormone [FSH] and luteinizing hormone [LH]), and the ovaries (secreting estradiol and progesterone). The coordination of these signals is referred to as the hypothalamic-pituitary-ovarian axis. The GnRH pulse frequency varies throughout the menstrual cycle to promote follicular development and ovulation (**Figure 11**). The phases of the menstrual cycle are referred to in reference to the activity of the ovary (follicular and luteal phases).

Figure 11. OPEN IN NEW WINDOW

Female reproductive axis. Pulses of GnRH drive LH and FSH production. LH acts on theca cells to stimulate androgen (principally androstenedione) production. Androstenedione is metabolized to estradiol in granulosa cells. FSH acts on granulosa cells to enhance follicle maturation. Granulosa cells produce inhibin B as a feedback regulator of FSH production. FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; LH = luteinizing hormone; – (circled) = negative feedback.

FSH, under control of pulsatile GnRH secretion, rises in the early menstrual cycle to promote recruitment and growth of a follicle containing a microscopic oocyte (follicular phase).

Granulosa cells lining the follicle secrete estradiol, which contributes to negative feedback inhibition of FSH secretion and resultant monofollicular development in the majority of women. Estradiol also stimulates endometrial proliferation. Further into the follicular phase, estradiol levels peak and exert acute positive feedback on the pituitary gland, which elicits an LH surge. This LH surge results in ovulation and initiates the luteal phase of the menstrual cycle. LH stimulates androgen production by the theca cells, which also line the follicle; androgen is subsequently aromatized to estrogen in the granulosa cells via aromatase enzyme. After the LH surge and ovulation, the follicle develops into the corpus luteum, which secretes both estradiol and progesterone and causes the secretory phase of the endometrium in preparation for implantation of a fertilized oocyte. With implantation, the early embryo produces human chorionic gonadotropin, which maintains the corpus luteum. However, when a fertilized embryo is not present, progesterone levels decline, leading to the menstrual phase of the endometrium and menstrual bleeding.

An average menstrual cycle ranges from 25 to 35 days in length. The follicular phase may vary in each woman but is typically from 14 to 21 days. Variability in a menstrual cycle is typically the result of a shortened or lengthened follicular phase, more commonly seen during the first 5 years of menstruation. A decrease in follicular phase length occurs commonly in perimenopause. The luteal phase is usually 14 days and is constant. In women younger than 40 years of age, menstrual cycles less than 25 days or greater than 35 days are likely anovulatory.

Key Point

- In women younger than 40 years of age, menstrual cycles less than 25 days or greater than 35 days are likely anovulatory.

Amenorrhea

Clinical Features

Related Question

Question 9

Primary Amenorrhea

Primary amenorrhea is the absence of menses by age 16 years accompanied by normal sexual hair pattern and normal breast development. Primary amenorrhea with absence of thelarche (breast development at the beginning of puberty) and/or adrenarche (androgen production increase that typically occurs at age 8 or 9 years) prior to 14 years of age should be evaluated. Pregnancy must be ruled out in any patient with primary amenorrhea before additional evaluation occurs. Causes of primary amenorrhea may be genetic, hormonal, or structural. Fifty percent of patients with primary amenorrhea have a chromosomal abnormality, such as Turner syndrome (45,XO) (gonadal dysgenesis), although some patients with Turner mosaicism may have secondary amenorrhea (see Secondary Amenorrhea).

Turner syndrome is commonly characterized by other clinical manifestations such as short stature, neck webbing, recurrent otitis media with hearing loss, aortic coarctation, and bicuspid aortic valve. The diagnosis of Turner syndrome may be made with a karyotype.

Approximately 15% of patients presenting with primary amenorrhea may have an anatomic abnormality of the uterus, cervix, or vagina such as müllerian agenesis, transverse vaginal septum, or imperforate hymen. Digital vaginal examination, transvaginal ultrasound, or MRI may help to identify outflow tract anomalies.

Key Point

- Fifty percent of patients with primary amenorrhea have a chromosomal abnormality, such as Turner syndrome (45,XO) (gonadal dysgenesis); 15% of patients presenting with primary amenorrhea may have an anatomic abnormality of the uterus, cervix, or vagina.

Secondary Amenorrhea Related Question

Question 68

Secondary amenorrhea is the absence of a menstrual cycle for three cycles or 6 months in previously menstruating women. The most common cause of secondary amenorrhea is pregnancy. A potential structural cause of secondary amenorrhea, such as Asherman syndrome, should be considered. Asherman syndrome is an uncommon complication of

dilation and curettage, intrauterine device placement, or surgical procedures such as hysteroscopic myomectomy; it is caused by lack of basal endometrium proliferation and formation of adhesions (synechiae). Diagnosis should be considered in any woman with amenorrhea and past exposure to uterine instrumentation. The classic presentation is amenorrhea or scant bleeding during periods (hypomenorrhea) with ovulatory symptoms (cervical mucous changes, adnexal tenderness associated with follicle formation) or premenstrual symptoms (mood changes or breast tenderness). Some patients will maintain small functional pockets of active endometrium with outflow obstruction by synechia closer to the cervix, resulting in cyclic pain and hematometrium identifiable on ultrasound.

After structural causes and pregnancy are excluded, the hormonal status should be assessed. Low estradiol and inappropriately normal FSH and LH levels indicate hypogonadotropic hypogonadism and point to a central cause (hypothalamic-pituitary). Low estradiol in the setting of elevated FSH and LH levels indicates hypergonadotropic hypogonadism and points to ovarian insufficiency.

The most common hormonal cause of secondary amenorrhea is polycystic ovary syndrome (PCOS) (see Hirsutism and Polycystic Ovary Syndrome), which accounts for 40% of cases. Additional hormonal causes of secondary amenorrhea include hypothalamic amenorrhea (hypogonadotropic hypogonadism), hyperprolactinemia, thyroid disease, and premature ovarian insufficiency (POI) (hypergonadotropic hypogonadism).

Hypogonadotropic hypogonadism caused by hypothalamic amenorrhea (HA) or functional hypothalamic amenorrhea (FHA) affects 3% of women between the ages of 18 and 40 years. Risk factors include low BMI and low body fat percentage, rapid and substantial weight loss or weight gain, eating disorders, excessive exercise, severe emotional stress, or acute and chronic illness. FSH and LH levels are inappropriately low in HA but may be inappropriately normal in FHA. Estradiol levels are typically low, and patients may experience vasomotor symptoms and sleep disturbance. If left untreated, patients are at increased risk for osteoporosis owing to this low-estrogen state. Recovery of menses may occur if BMI returns to normal. Cognitive-behavioral therapy for cases caused by emotional stress has been shown to be effective.

Hyperprolactinemia causes secondary amenorrhea through direct inhibition of GnRH secretion. Treatment of the cause of hyperprolactinemia typically results in restoration of menses. Hypothyroidism may cause secondary amenorrhea through increased thyrotropin-releasing hormone levels, which causes stimulation of prolactin secretion.

Hypergonadotropic hypogonadism as a result of POI is defined as amenorrhea before age 40 years in the setting of two elevated FSH levels (>40 mU/mL [40 U/L]) more than 1 month apart. Possible causes include Turner mosaicism (in which secondary amenorrhea may occur due to POI), fragile X premutation, chemotherapy or radiation, and autoimmune oophoritis. In patients in whom an autoimmune cause is diagnosed, evaluation of other endocrine organs (thyroid, parathyroid, pancreas, and adrenal) is recommended at the time of diagnosis and annually thereafter.

Estrogen replacement is necessary in patients with hypergonadotropic hypogonadism to prevent bone mass loss until the average age of natural menopause (50-51 years). Estrogen replacement preparations are available in oral, transdermal, subcutaneous, and vaginal routes of administration. The dose of estrogen required by young women is titrated to prevent vasomotor symptoms and vaginal dryness and may be higher than that used in an older age group. Because spontaneous ovulation may occur (although it is infrequent), counseling on contraceptive options should also be provided for sexually active women not desiring pregnancy. Cyclic progesterone exposure should be considered in patients with an intact uterus to prevent excessive unopposed endometrial proliferation. Oocyte donation may be considered for fertility options for this patient population.

Key Point

- The most common causes of secondary amenorrhea are pregnancy, structural abnormalities, and polycystic ovary syndrome.

Evaluation of Amenorrhea

A thorough history and physical examination, including a pelvic examination, are needed to evaluate both primary (no history of menstruation) and secondary amenorrhea (cessation of

menstruation after menarche). Urine or serum human chorionic gonadotropin (HCG) testing should be done first to exclude pregnancy, as this is the most common cause of amenorrhea. In patients with primary amenorrhea, a karyotype is recommended if a pregnancy test is negative. Serum levels of prolactin, FSH, LH, estradiol, and thyroid-stimulating hormone (TSH) should then be obtained in the evaluation of primary and secondary amenorrhea. Abnormal levels of prolactin and/or TSH support a nonovarian cause of amenorrhea. Elevations of FSH and LH levels in the presence of a low estradiol level support the diagnosis of POI.

If no elevations in these hormones are found, a progesterone challenge test (oral medroxyprogesterone acetate, 10 mg for 7-10 days) may be used to determine if the amenorrhea is due to estrogen deficiency. If the patient has menstrual bleeding within 1 week of completing 7 to 10 days of medroxyprogesterone, estrogen deficiency is not the cause. In this case PCOS (or a similar diagnosis) should be considered. If no menstrual bleeding occurs, the patient has a low-estrogen state, and hypogonadotropic hypogonadism is the diagnosis (see Disorders of the Pituitary Gland).

Pelvic ultrasound is helpful to identify structural causes of amenorrhea such as müllerian agenesis and intrauterine synechiae. Saline-infusion sonohysterogram can identify intrauterine synechiae, and transvaginal or transabdominal ultrasound can identify absence of a uterus in patients with müllerian agenesis. Endocrinology consultation for further evaluation and testing of patients with findings suspicious for a genetic cause of amenorrhea may be appropriate. A pituitary MRI may be indicated to exclude other intracranial causes of hypogonadotropic hypogonadism when diagnosing HA or FHA, and consultation with an endocrinologist is recommended before imaging is pursued.

Key Points

- After excluding pregnancy, the laboratory evaluation of primary and secondary amenorrhea includes measurements of prolactin, follicle-stimulating hormone, luteinizing hormone, estradiol, and thyroid-stimulating hormone.

- If hormonal evaluation for amenorrhea is negative, the next step is a progesterone challenge test; if the patient bleeds within 1 week of completing 7 to 10 days of progesterone, estrogen deficiency is not the cause and PCOS should be considered

Hyperandrogenism Syndromes

Hirsutism and Polycystic Ovary Syndrome

Related Questions

Question 26

Question 54

Question 64

Question 77

When hirsutism is present, the patient should be assessed for virilization, or development of male characteristics. Rapid onset and progression of deepening of the voice, severe acne, clitoromegaly, and male pattern balding are signs of virilization and are concerning for an ovarian or adrenal tumor. Age of onset after 30 years is also a risk factor for an androgen-secreting tumor.

In patients with hirsutism or virilization, recommended initial laboratory tests include measurement of plasma dehydroepiandrosterone sulfate (DHEAS) level and serum levels of TSH, prolactin, total testosterone, and follicular-phase 17-hydroxyprogesterone. Normal levels exclude adrenal tumors, hypothyroidism, hyperprolactinemia, and ovarian tumor. Common forms of late-onset congenital adrenal hyperplasia, often mistaken for PCOS, can be excluded with a normal 17-hydroxyprogesterone level. Pelvic ultrasound and adrenal CT should be performed to exclude an ovarian or adrenal neoplasm if the serum total testosterone level is greater than 200 ng/dL (6.9 nmol/L). Adrenal CT is necessary to exclude an adrenal cortisol-secreting and/or androgen-secreting neoplasm if the plasma DHEAS level is greater than 7.0 µg/mL (18.9 µmol/L). Hirsutism is typically a benign condition, most

commonly from PCOS. A marked elevation of total testosterone or DHEAS is not compatible with a diagnosis of PCOS.

PCOS has a prevalence of 7% to 10% and is one of the most common endocrine disorders in young women. Two sets of diagnostic criteria are commonly used. The 2003 American Society for Reproductive Medicine and the European Society of Human Reproduction criteria for PCOS require two of the following three findings in the absence of other endocrine disorders: (1) oligo-ovulation or anovulation, (2) clinical or biochemical evidence of hyperandrogenism (such as hirsutism or acne), or (3) ultrasound findings of polycystic ovarian morphology in at least one ovary. The 1990 criteria from the National Institutes of Health and the National Institute of Child Health and Human Development require all of the following for diagnosis of PCOS: oligo-ovulation, signs of androgen excess (clinical or biochemical), exclusion of other disorders that can result in menstrual irregularity, and hyperandrogenism.

A constant stagnant follicular stage is seen in PCOS, resulting in unopposed estradiol secretion from small ovarian follicles. Owing to disordered secretion of LH by the anterior pituitary, intraovarian androgen production is also increased in PCOS, resulting in the hyperandrogenism associated with the disorder. Women with PCOS typically have elevated resting LH levels. In patients trying to conceive, this can lead to false-positive indication of the ovulatory LH surge on home urinary LH kits for ovulation.

Estradiol secretion results in proliferation of the endometrium in the absence of progesterone secretion from a corpus luteum. This predisposes patients to endometrial hyperplasia and heavy menstrual bleeding as a result of anovulatory bleeding. Oligo-ovulation and anovulation result in infertility but are typically correctable with clomiphene citrate or letrozole for ovulation induction if fertility is desired. If fertility is not desired, oral contraceptives should be considered if not contraindicated. Addition of oral contraceptives will increase secretion of sex hormone–binding globulin (SHBG) and decrease circulating levels of free testosterone. If a patient has a contraindication to oral contraceptives, a progestin-secreting intrauterine device or cyclic oral or vaginal progesterone should be given to prevent prolonged unopposed estrogen exposure.

Hyperandrogenism may present as hirsutism, acne, or androgenic alopecia. In patients with hirsutism desiring treatment, existing terminal hairs will need to be removed with depilatory methods, but the rate of hair growth while on treatment will decrease. Spironolactone, an aldosterone and androgen inhibitor, may be added after 6 months if acne and hirsutism are still cosmetically bothersome. Before initiation of therapy, the patient should be counseled about teratogenic effects on a male fetus, and contraceptive counseling should be provided.

Both obese and lean women with PCOS also have insulin resistance, and studies have identified an increased incidence of metabolic syndrome, obesity, impaired glucose tolerance, and type 2 diabetes mellitus in these women. Although insulin resistance may improve with weight loss, the use of insulin-sensitizing agents such as metformin is associated with a decrease in serum androgens; however, it is not very effective as a single agent for ovulation induction.

Evaluation of patients with PCOS should include assessment for signs of sleep apnea, hypercholesterolemia, and fatty liver. In women with a thickened endometrium or menometrorrhagia, endometrial sampling with endometrial biopsy should be considered to evaluate for endometrial hyperplasia. Weight loss and exercise should be emphasized.

Key Points

- Polycystic ovary syndrome has a prevalence of 7% to 10% and is one of the most common endocrine disorders in young women; it is often associated with insulin resistance, metabolic syndrome, obesity and type 2 diabetes mellitus.
- Polycystic ovary syndrome can be diagnosed if two of the following three findings are present: (1) oligo-ovulation or anovulation, (2) clinical or biochemical evidence of hyperandrogenism (such as hirsutism or acne), or (3) ultrasound findings of polycystic ovarian morphology in at least one ovary.
- The 1990 criteria from the National Institutes of Health and the National Institute of Child Health and Human Development require all of the following for diagnosis of PCOS: oligo-ovulation, signs of androgen excess (clinical or biochemical), exclusion of other disorders that can result in menstrual irregularity, and hyperandrogenism.

Androgen Abuse in Women

Anabolic steroids may be abused by some women to enhance their athletic performance or physique. Such exogenous administration may result in absence of GnRH pulsatility and resultant hypogonadotropic hypogonadism and amenorrhea. Adverse effects may include hirsutism, acne, deepening of the voice, decreased breast size, and clitoromegaly. Withdrawal of exogenous androgens does not result in severe hypogonadism as it does in men, and most women return to regular menstrual cycles.

Female Infertility

Related Question

Question 73

Infertility is defined as the absence of conception after 1 year of unprotected intercourse (on average twice weekly) in a woman younger than 35 years of age. Investigation should begin after 6 months if no conception has occurred in a woman 35 years of age or older. Infertility evaluation should include a careful medical history of both partners with special focus on menstrual history, previous exposure to sexually transmitted infections, pelvic surgery, and previous obstetric complications such as miscarriage or cesarean delivery. If a report of oligomenorrhea is elicited, measurement of serum TSH and prolactin levels is appropriate to exclude thyroid disease and hyperprolactinemia as causes of oligo-ovulation.

Further evaluation of infertility causes typically includes semen analysis of the male partner, confirmation of ovulation with measurement of midluteal progesterone level (>3 ng/mL [9.5 nmol/L]), and because Fallopian tubes may be obstructed due to infection such as pelvic inflammatory disease, tubal patency evaluation with hysterosalpingogram. A common cause of tubal occlusion and resultant infertility is past pelvic inflammatory disease. Laparoscopy for evaluation of pelvic adhesions or mild endometriosis may be warranted in patients with dysmenorrhea, previous exposure to sexually transmitted infections, or previous pelvic surgery.

If no abnormalities are found, treatment to enhance endogenous gonadotropin release and increase the numbers of oocytes ovulated monthly may be warranted. Some studies support moving directly to in vitro fertilization treatment for women with infertility at age 40 years. In women treated with ovarian stimulation, oral medications such as clomiphene citrate or letrozole are typically used. This therapy is not appropriate in patients with POI. Patients should be counseled about the 5% to 8% risk of multiple gestation with these therapies. Referral to a reproductive endocrinologist is recommended.

Key Point

- Infertility evaluation in women should include a medical history of both partners with special focus on menstrual history, previous exposure to sexually transmitted infections, pelvic surgery, and previous obstetric complications such as miscarriage or cesarean delivery.

Physiology of Male Reproduction

Control of spermatogenesis and testosterone production depends on the pulsatile secretion of GnRH from the hypothalamus as well as subsequent downstream stimulation of the anterior pituitary and male gonads. In the testicle, FSH stimulates Sertoli cell spermatogenesis, and LH stimulates Leydig cell testosterone production. Negative feedback from testosterone production inhibits FSH and LH secretion at the level of the anterior pituitary as well as pulsatile hypothalamic GnRH secretion. Inhibin B, produced by the Sertoli cells, also inhibits FSH (**Figure 12**).

Figure 12. OPEN IN NEW WINDOW

Male reproductive axis. Pulses of GnRH elicit pulses of LH and FSH. FSH acts on Sertoli cells, which assist sperm maturation and produce inhibin B, the major negative regulator of basal FSH production. The Leydig cells produce testosterone, which feeds back to inhibit GnRH and LH release. Some testosterone is irreversibly converted to dihydrotestosterone or estradiol, which are both more potent than testosterone in suppressing GnRH and LH. FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; LH = luteinizing hormone; – (circled) = negative feedback.

Leydig cell production of testosterone occurs in a diurnal pattern, with the highest concentration observed in the morning. A large percentage of circulating testosterone is bound either to SHBG or albumin. A serum total testosterone level measured in the early morning is generally considered to be an accurate measurement of a patient's androgen status, but it does not account for decreased SHBG as seen in obesity (see Evaluation of Male Hypogonadism).

Hypogonadism

Primary Hypogonadism

Related Question

Question 58

Primary hypogonadism, or testicular failure, represents a decrease in testosterone or sperm production. Primary hypogonadism is uncommon and may have congenital or acquired causes. Klinefelter syndrome is the most common cause of congenital primary hypogonadism. Klinefelter syndrome is a common cause of hypergonadotropic hypogonadism and azoospermia, resulting in infertility. A 47,XXY karyotype is diagnostic of Klinefelter syndrome. Mosaic variants of this condition exist but typically present with oligoasthenospermia, testicular failure or hypogonadism. Concomitant symptoms often include sexual dysfunction and generalized fatigue. Tall stature is a common finding. Patients with Klinefelter syndrome may fail to achieve puberty or may present after sexual maturation with azoospermia. Exposure to chemotherapy or radiation may also result in primary testicular failure. Local injury as a result of torsion, orchitis, or trauma may result in ischemia and necrosis of testicular tissues.

Secondary Hypogonadism

Typically secondary hypogonadism is a result of insufficient GnRH production by the hypothalamus or deficient LH/FSH secretion by the anterior pituitary. Causes may be congenital or acquired. Idiopathic hypogonadotropic hypogonadism, with anosmia (Kallmann syndrome) or without anosmia, is the most common cause of congenital

secondary hypogonadism. Acquired secondary hypogonadism is most commonly iatrogenic due to exogenous testosterone administration. Untreated sleep apnea and obesity are other common causes. Other acquired causes include hyperprolactinemia, chronic opioid use, glucocorticoid use, or infiltrative disease (lymphoma or hemochromatosis).

Androgen Deficiency in the Aging Male

The natural progression of male aging involves testosterone level decline. Most men will not become hypogonadal, and the decline in testosterone production is highly variable with each person. “Low T” has become a part of the popular vernacular, owing to aggressive direct-to-consumer marketing, and describes many symptoms that may or may not be associated with a low serum testosterone level in men. Both prescription and over-the-counter testosterone and derivative sales have surged in the United States and many other countries. With the increased sales of testosterone formulations to treat aging men, questions have emerged about the potential adverse effects of exogenous testosterone therapy, particularly in men who have no biochemical evidence of testosterone deficiency. Potential adverse effects include increased risk of cardiovascular disease and death, venous thromboembolism, and prostate cancer.

Evaluation of Male Hypogonadism

Related Question

Question 30

A thorough history and physical examination are essential in the evaluation of hypogonadism. A sleep history is especially helpful. A large constellation of nonspecific symptoms is associated with male hypogonadism, which makes diagnosis and treatment based on symptoms alone not advisable. Nonspecific symptoms include fatigue, decreased muscle strength, decreased libido, amotivational state, or decreased robustness or frequency of erections. Testosterone measurements are not recommended if only nonspecific symptoms are present; rather, investigation of other causes of the patient's symptoms is appropriate. More specific symptoms include gynecomastia, diminished testicular volumes, and absence of morning erections. Measurement of testosterone levels

is not recommended if a patient is having regular morning erections, does not have true gynecomastia on examination, and has a normal testicular examination, as it is highly unlikely that he has testosterone deficiency.

Testosterone deficiency is diagnosed with two early morning serum total testosterone levels below the reference range. Because illness and strenuous activity can falsely lower testosterone levels, measurement should occur in healthy men who have avoided strenuous activity for several days. Measurements of the testosterone level occurring later in the morning or in the afternoon are not useful for interpretation. Consultation with an endocrinologist should be considered if two early morning total testosterone levels are low. In certain clinical scenarios, such as morbid obesity, total testosterone may be low but free testosterone may be normal. Free testosterone assays can be unreliable, and routine measurement of free testosterone is not recommended. Free testosterone by equilibrium dialysis is the gold-standard assay.

Once confirmed, the cause of hypogonadism (primary or secondary) should be further investigated prior to initiation of testosterone replacement. Serum LH, FSH, prolactin, and TSH levels should be measured. Primary testosterone deficiency (hypergonadotropic hypogonadism) is diagnosed when FSH and LH levels are frankly elevated in the presence of a simultaneously low testosterone level. Low or inappropriately normal FSH and LH levels in the presence of simultaneous low testosterone levels are diagnostic of secondary hypogonadism (hypogonadotropic hypogonadism).

A hypergonadotropic state (elevated LH and FSH levels) should be further investigated with a karyotype if no history of gonadotoxic therapy or testicular insult is elicited. If a hypogonadotropic state is revealed, transferrin saturation and ferritin levels should be evaluated to exclude hemochromatosis. MRI of the pituitary should be performed to evaluate for hypothalamic or pituitary masses as the cause of the hypogonadotropic state if no confounding medications or reversible secondary causes are discovered. **Figure 13** shows an algorithm for evaluating male hypogonadism.

Figure 13.OPEN IN NEW WINDOW

Algorithm for evaluating male hypogonadism. FSH = follicle-stimulating hormone; LH = luteinizing hormone; PRL = prolactin; SHBG = sex hormone–binding globulin; ×2 = two separate measurements.

Key Points

- Measurement of testosterone levels is not recommended if a patient is having regular morning erections, does not have true gynecomastia on examination, and has a normal testicular examination, as it is highly unlikely that he has testosterone deficiency.
- Testosterone deficiency is diagnosed with two early morning total testosterone levels below the reference range.
- Once testosterone deficiency is confirmed, the cause should be further investigated prior to initiation of testosterone replacement.

Testosterone Replacement Therapy

Related Question

Question 32

Testosterone replacement therapy is a widely used treatment for men with hypogonadism. Possible benefits seen with testosterone replacement therapy, such as improved libido, energy level, and bone density, have been described but remain controversial. Testosterone therapy has been associated with increased hemoglobin and hematocrit levels, worsened obstructive sleep apnea, and a decrease in HDL cholesterol levels. LDL cholesterol levels do not appear to be affected.

Although hypogonadism remains an independent risk factor for mortality, recent studies have examined the association between testosterone therapy and cardiovascular risk. The association between testosterone therapy and mortality has remained controversial. Physicians prescribing testosterone therapy to elderly men with biochemically proven testosterone deficiency and comorbidities should use it prudently with close follow-up. Cardiovascular disease risk as well as risk for thrombosis should be discussed with patients before pursuing therapy. Prescribing testosterone therapy in the absence of biochemically

proven testosterone deficiency puts the patient at risk for iatrogenic hyperandrogenism with subsequent increased risk of myocardial infarction, stroke, death, venous thromboembolism, polycythemia, and obstructive sleep apnea. Prescribing testosterone therapy in the absence of a full evaluation may delay treatment for secondary causes such as prolactinoma, hemochromatosis, or intracranial mass.

Although implantable pellets and injectable testosterone preparations are available, the most popular testosterone preparations currently are topical (most commonly hydroalcoholic gels). They require daily use and may incur significant cost to the patient, but the steady level of testosterone achieved within 30 minutes of application is an appealing feature. Inadvertent absorption by patient contacts may occur; users should be informed that virilization of contacts is not uncommon and premature puberty can occur in exposed children. The patient should also be counseled that decline in endogenous testosterone production and spermatogenesis may occur. If fertility is desired, testosterone therapy should be avoided, and consultation with a reproductive endocrinologist is recommended.

Patients requiring testosterone replacement therapy should have testosterone levels monitored at 3 and 6 months after initiation and annually thereafter; the goal total testosterone level should be in the mid-normal range. Monitoring of the prostate specific antigen and hematocrit level should follow Endocrine Society guidelines (Table 29).

Table 29. OPEN IN NEW WINDOW Endocrine Society Clinical Guidelines for Monitoring Adverse Effects of Testosterone Replacement Therapy

Parameter	Recommended Screening Schedule	Alerts
Hematocrit	Value obtained at baseline and then at 3	Value >54%

Table 29. OPEN IN NEW WINDOW Endocrine Society Clinical Guidelines for Monitoring Ac
Effects of Testosterone Replacement Therapy

Parameter	Recommended Screening Schedule	Alerts
	months and 6 months after therapy initiation, followed by yearly measurements	
PSA level	For patients >40 years of age with a baseline value >0.6 ng/mL (0.6 µg/L), DRE and PSA level (determined at 3 and 6 months after therapy initiation followed by regular screening)	Increase >1.4 ng/mL (1.4 µg/L) in 1 year or >0.4 ng/mL (0.4 µg/L) after 6 m use; abnormal results on DRE; AUA prostate symptoms score/IPSS >19

- AUA = American Urological Association; DRE = digital rectal examination; IPSS = International Prostate Symptom Score; PSA = prostate-specific antigen.
- Data from Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2010;95(6):2550. PMID: 20525905

Key Points

- Testosterone deficiency should be diagnosed biochemically, and its cause should be definitively determined before initiation of testosterone replacement therapy.
- Patients requiring testosterone replacement therapy should have testosterone, prostate specific antigen, and hematocrit levels monitored.
- Goal total testosterone level should be in the mid-normal range for patients requiring testosterone therapy.

Anabolic Steroid Abuse in Men

Testicular testosterone production is suppressed in the presence of exogenous testosterone administration. Many elite athletes abuse androgens in injectable form, and herbal preparations of oral testosterone are readily available. Commonly used androgens include injectable testosterone esters and oral alkylated testosterone preparations. HCG injections mimic LH stimulation to the Leydig cells and result in elevated testosterone levels. Although this therapy is appropriate in men with hypogonadotropic hypogonadism, it may also be abused. Aromatase inhibitors are frequently used concurrently with exogenous testosterone preparations to prevent adipose conversion of androgens to estrogens and development of gynecomastia. Androstenedione supplements are commonly abused.

Excessive muscle bulk, acne, gynecomastia, and decreased testicular volume may be found on physical examination in patients using anabolic steroids. Irreversible hypogonadism may result and often presents as male infertility with oligospermia or azoospermia on sperm analysis. Permanent inability to produce endogenous testosterone may occur. Extratesticular effects may also be noted, including low HDL cholesterol level, hepatotoxicity, erythrocytosis, and increased risk of obstructive sleep apnea. Mood disorders are common in anabolic steroid users.

Laboratory studies showing low or normal gonadotropin levels and a low testosterone level with clinical evidence of hyperandrogenism are consistent with use of a non–testosterone-containing product, such as one containing androstenedione, or cessation of long-standing (typically greater than 1 year) anabolic steroid use, with failure to recover endogenous testosterone function.

Key Points

- Excessive muscle bulk, acne, gynecomastia, and decreased testicular volume may be seen on physical examination in male patients using anabolic steroids.
- Exogenous testosterone use may result in irreversible decline in spermatogenesis and resultant infertility, as well as permanent inability to produce endogenous testosterone.

Male Infertility

Related Question

Question 81

Physical examination should include assessment for the presence or absence of the vas deferens, evaluation for congenital bilateral absence of the vas deferens (as seen in cystic fibrosis), assessment of testicular volume, and evaluation for the presence of hernia, varicocele, or tumor. Semen analysis obtained after 48 to 72 hours of abstinence from sexual activity is the best test to assess male fertility. For accurate results, analysis of the sample should occur within 1 hour of ejaculation. Extended abstinence periods may diminish fructose in the ejaculate and artificially lower sperm motility. If the physical examination is abnormal, evaluation by a urologist may be appropriate. If semen analysis results are abnormal, the test should be repeated, and referral, if abnormal, to a reproductive endocrinologist is warranted.

Key Point

- Semen analysis obtained after 48 to 72 hours of abstinence from sexual activity is the best test to assess male fertility; if abnormal, the test should be repeated for confirmation.

Gynecomastia

Gynecomastia is glandular breast tissue enlargement in men due to imbalance in the levels or activity of testosterone and estrogen. This imbalance results in an increased estrogen-to-testosterone ratio, which in turn results in decreased inhibitory action of testosterone on the breast tissue. The less testosterone and/or more estrogen the breast tissue is exposed to, the more likely gynecomastia will develop. Although abnormal in the postpubertal man, it is usually benign. It is typically bilateral but not always symmetric. Unilateral gynecomastia

is uncommon and should be evaluated with mammogram as soon as possible owing to risk of breast cancer.

There are many causes of gynecomastia, ranging from drug-induced (marijuana, alcohol, 5α-reductase inhibitors, H_2-receptor antagonists, spironolactone, digoxin, ketoconazole, calcium channel blockers, ACE inhibitors, antiretroviral agents, tricyclic antidepressants, selective serotonin reuptake inhibitors) and hypogonadism (primary, secondary) to chronic illness (hepatic cirrhosis, chronic kidney disease) and endocrine disorders (hyperprolactinemia, acromegaly, hyperthyroidism, Cushing syndrome). Obesity and aging are associated with gynecomastia owing to increased aromatase activity in the periphery. Estrogen-secreting tumors (such as Leydig or Sertoli cell tumors or adrenal cortical carcinoma) and HCG-secreting tumors (such as germ cell tumors and hepatic carcinomas) are associated with gynecomastia.

A thorough history should be obtained. The breasts should be examined for glandular enlargement, which typically extends concentrically from under the areolae, and is firm, mobile, and rubbery. The breasts may be tender if the time course is acute. Pseudogynecomastia is subareolar adipose tissue, without glandular proliferation, that is associated with obesity. True gynecomastia typically distorts the normally flat contour of the male nipple, causing it to protrude owing to the mass of glandular tissue beneath it. In pseudogynecomastia, the nipple is typically still flat but soft, and nondescript subcutaneous fat tissue is present in the breast area.

Mild, chronic, asymptomatic gynecomastia does not warrant evaluation. Evaluation of gynecomastia that is asymmetric or concerning for malignancy (bloody nipple discharge, hard and fixed, associated with regional lymphadenopathy), of rapid and recent onset, or larger than 2 cm (>5 cm in obese men owing to the known increase in aromatase activity in obesity), should include measurement of total testosterone, LH, FSH, and TSH levels, as well as assessment of liver and kidney function. If indicated by findings on history and/or physical examination, measurement of prolactin, estradiol, and HCG may also be indicated. If the biochemical evaluation demonstrates abnormalities, further evaluation with testicular

ultrasound, adrenal CT, or pituitary MRI may be indicated; consultation with an endocrinologist is recommended before imaging is ordered.

Key Points

- Unilateral gynecomastia in the male patient is concerning for malignancy and warrants immediate evaluation with a mammogram.
- Mild, chronic, asymptomatic gynecomastia in the male patient does not warrant evaluation.

Calcium and Bone Disorders

Calcium Homeostasis and Bone Physiology

Related Question

Question 31

Serum calcium levels are tightly regulated on a moment-to-moment basis by the actions of vitamin D and parathyroid hormone (PTH). The amount of calcium that is albumin bound can be affected by hydration and nutritional status. If albumin levels decrease, total serum calcium levels may appear low (pseudohypocalcemia). Conversely, if albumin levels increase, total calcium levels will appear elevated (pseudohypercalcemia). In both cases, ionized calcium should be measured. It will usually be normal, indicating normal circulating free levels of calcium. There are also instances of artificially increased calcium levels due to high protein states as in multiple myeloma (elevated monoclonal immunoglobulins), hyperalbuminemia, Waldenström macroglobulinemia, and thrombocytosis. In these patients, ionized calcium would be normal with elevated total serum calcium.

Vitamin D is a fat-soluble vitamin, and body sources include de novo production from the skin, through forms found in food, and through supplementation (**Table 30**). There are two forms of vitamin D supplementation: vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol). Although both forms are useful in raising vitamin D levels, vitamin D_3 may be more beneficial because of tighter bonding to vitamin D receptors, longer shelf

life, greater potency than vitamin D_2, and being identical to the vitamin D that naturally occurs in humans after ultraviolet light exposure.

Table 30. OPEN IN NEW WINDOW Sources of Vitamin D

Sources	Type of Vitamin D	Amount of Vitamin D
Food Sources		
Cod liver oil	Cholecalciferol	400-1000 U/teaspoon
Salmon, wild caught	Cholecalciferol	600-1000 U/4 oz
Salmon, canned	Cholecalciferol	300 U/4 oz
Mackerel, canned	Cholecalciferol	250 U/4 oz
Sundried shitake mushrooms	Ergocalciferol	1600 U/4 oz
Egg yolk	Ergocalciferol	20 U/yolk

Table 30. OPEN IN NEW WINDOW Sources of Vitamin D

Sources	Type of Vitamin D	Amount of Vitamin D
Sunlight (one minimal erythermal dose)		20,000 U in bathing suit
Fortified Foods		
Milk	Cholecalciferol	
Orange juice	Cholecalciferol	
Infant formula	Cholecalciferol	
Pharmaceutical Sources		
Vitamin D_2	Ergocalciferol	50,000 U/capsule
Liquid vitamin D_2	Ergocalciferol	8000 U/capsule

Table 30. OPEN IN NEW WINDOW Sources of Vitamin D

Sources	Type of Vitamin D	Amount of Vitamin D
Multivitamin	Ergocalciferol and cholecalciferol	400, 500, or 1000 U/capsule
Vitamin D_3	Cholecalciferol	400, 800, 1000, 2000, 5000, 10,000, 50,000 U/capsule

Regardless of the method of ingestion, vitamin D_3 and D_2 are both inactive forms that must be hydroxylated twice before becoming active. The first occurs in the liver and converts vitamin D to 25-hydroxyvitamin D [25(OH)D], also known as calcidiol. The second occurs primarily in the kidney and forms the physiologically active 1,25-dihydroxyvitamin D [$1,25(OH)_2D$], also known as calcitriol (**Figure 14**).

Figure 14. OPEN IN NEW WINDOW

Production of vitamin D. PTH = parathyroid hormone; UVB = ultraviolet B.

Because 25-hydroxyvitamin D has a relatively long half-life of several weeks, it is the best indicator of whole body vitamin D status. Active vitamin D acts on three organ systems to achieve and maintain normal serum calcium: bone, intestine, and kidney. With adequate vitamin D, bone resorption is increased, intestinal uptake of dietary calcium is increased, and excretion of calcium through the kidney is decreased. PTH is secreted to increase the calcium in the blood in response to even the slightest degree of hypocalcemia; it acts on the kidney to increase production of active vitamin D and promote calcium reabsorption in the distal convoluted tubule and loop of Henle, and increased resorption in bones, thereby increasing release of calcium into the blood.

Hypercalcemia

Clinical Features of Hypercalcemia

Hypercalcemia is marked by serum calcium levels above the normal range, usually greater than 10.5 mg/dL (2.6 mmol/L). Most patients are asymptomatic, and hypercalcemia may be noted incidentally on laboratory tests obtained for other reasons. Symptoms may occur with any degree of hypercalcemia but are more likely when serum calcium levels exceed 12 mg/dL (3 mmol/L). Classic symptoms of polyuria, polydipsia, and nocturia sometimes occur with elevated calcium levels of 11 mg/dL (2.8 mmol/L) or less. Other symptoms such as anorexia, nausea, abdominal pain, constipation, increased creatinine levels, and mild mental status changes are more likely to occur with levels greater than 11 mg/dL (2.8 mmol/L). As serum calcium levels continue to increase beyond 12 mg/dL (3 mmol/L), symptoms become more severe such as profound mental status changes, obtundation, acute kidney injury due to profound dehydration, and increased creatinine concentration.

Key Points

- Classic symptoms of hypercalcemia are polyuria, polydipsia, anorexia, nausea, abdominal pain, constipation, and mental status changes; as serum calcium levels increase and/or the rate of change increases, symptoms become more severe, with profound mental status changes, obtundation, and acute kidney injury.
- 25-Hydroxyvitamin D has a relatively long half-life of several weeks, is the best indicator of whole body vitamin D status, and is the recommended test for vitamin D deficiency.

Diagnosis and Causes of Hypercalcemia

When serum calcium elevation is incidentally noted, repeat measurement of serum calcium is indicated, and if a second hypercalcemic level is noted, further evaluation is warranted to determine the cause (**Table 31**). The next step is determining if the hypercalcemia is PTH- or non-PTH–mediated by simultaneous measurement of serum calcium and intact PTH levels (**Figure 15**). Ionized calcium may be used in evaluating hypercalcemia, but it is rarely helpful in diagnosing hypercalcemia in patients with normal albumin levels or no acid-base disturbances.

Table 31. OPEN IN NEW WINDOW Causes of Hypercalcemia

Parathyroid Hormone-Mediated Hypercalcemia
Primary hyperparathyroidism (adenoma, hyperplasia)
Parathyroid cancer
Tertiary hyperparathyroidism
Familial hypocalciuric hypercalcemia
Normocalcemic primary hyperparathyroidism
Non-Parathyroid-Mediated Hypercalcemia
Hypercalcemia of malignancy (humoral and local osteolytic)
Vitamin D toxicity
Vitamin A toxicity
Milk alkali syndrome
Thyrotoxicosis

Table 31. OPEN IN NEW WINDOW Causes of Hypercalcemia

Parathyroid Hormone-Mediated Hypercalcemia
Prolonged immobilization
Granulomatous diseases (sarcoidosis, tuberculosis)
Lymphomas
Total parenteral nutrition

Figure 15. OPEN IN NEW WINDOW

Relationship of calcium, PTH, and vitamin D status in normal conditions and in several diseases. PTH = parathyroid hormone.

Parathyroid Hormone–Mediated Hypercalcemia

Primary Hyperparathyroidism

Related Questions

Question 17

Question 46

Primary hyperparathyroidism is the most common cause of PTH-mediated hypercalcemia, and is diagnosed with a simultaneously elevated serum calcium level, with an inappropriately normal or elevated intact PTH level. The incidence peaks in the seventh decade and affects mostly women (75%). Before the age of 45 years, rates are similar in men and women. Approximately 80% of patients will have elevated PTH levels with simultaneously elevated calcium levels. Most commonly, primary hyperparathyroidism is

due to a single parathyroid adenoma; however, rarely it may be attributed to multigland hyperplasia (typical in patients with end-stage kidney disease or multiple endocrine neoplasia syndromes) or parathyroid gland carcinoma (calcium is typically >14 mg/dL [3.5 mmol/L] and intact PTH levels >250 pg/mL [250 ng/L] on presentation; diagnosis is made histopathologically given the overlap with benign primary hyperparathyroidism).

Once diagnosed, measurement of serum phosphorus, 24-hour urine calcium, and serum 25-hydroxyvitamin D levels may facilitate management. Serum phosphorus levels are typically low or low-normal in these patients. In contrast, phosphorus levels will be elevated in patients with vitamin D toxicity. Approximately 50% of patients with primary hyperparathyroidism will have elevated urine calcium levels, and the other 50% will have normal levels. Occasionally, urine calcium can be low in those patients with concomitant primary hyperparathyroidism and vitamin D deficiency. Additionally, patients with vitamin D deficiency convert more 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D so they may have elevated levels of 1,25-dihydroxyvitamin D.

Parathyroidectomy is the treatment for primary hyperparathyroidism. Surgical management is curative in roughly 90% of patients, but evidence that the benefit outweighs the risk of the surgical procedure is present under only certain circumstances. There have been several long-term observational studies that found stability in biochemical markers and bone density in patients who do not meet the surgical intervention criteria listed in **Table 32**. When one or more of these criteria are met, surgery is recommended. Surgery can be considered when surgical criteria are not met, but patients should be cautioned that there are no robust data to support that intervention.

Table 32. OPEN IN NEW WINDOW Indications for Surgical Intervention in Patients with Primary Hyperparathyroidism

Increase in serum calcium level ≥1 mg/dL (0.25 mmol/L) above upper limit of normal[a]

Creatinine clearance must be <60 mL/min (0.06 L/min)[a]
T-score (on DEXA scan) of −2.5 or worse at the lumbar spine, total hip, femoral neck, or distal radius[a]
Age 50 years or younger[a]
Surgery also indicated in patients in whom medical surveillance is neither desired nor possible, including those wit significant bone, kidney, gastrointestinal, or neuromuscular symptoms typical of primary hyperparathyroidism

- DEXA = dual-energy x-ray absorptiometry.
- [a]In otherwise asymptomatic patients.
- Recommendations from Bilezikian JP, Khan AA, Potts JT Jr. Third International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Third International Workshop. J Clin Endocrinol Metab. 2009 Feb;94(2):335-9. PMID: 19193908

It is critical that an experienced surgeon perform the surgery to avoid increased risk of postoperative hypoparathyroidism and damage to the recurrent laryngeal nerve. Historically, a bilateral neck dissection was done to identify parathyroid glands that appeared to have irregular appearance or increased size. With the increased use of sestamibi scans, high-definition ultrasound, and intraoperative measurement of PTH levels, the minimally invasive technique is now preferred. Minimally invasive surgery allows for a smaller incision and a shortened surgical duration.

In patients with osteoporosis who are poor surgical candidates or refuse surgery, intravenous bisphosphonate therapy will slow bone resorption and temporarily decrease serum calcium levels. Intravenous bisphosphonate should be redosed when hypercalcemia recurs.

In patients who do not meet the criteria for surgery, surveillance is recommended. Patients should have annual measurement of serum calcium and creatinine levels. A three-site dual-energy x-ray absorptiometry (DEXA) scan should be performed every 1 to 2 years to evaluate

bone mineral density of the lumbar spine, hip, and distal radius. The frequency of DEXA scanning should increase to yearly when any treatment has been initiated for bone health or other medications have been added that may affect bone health (antiandrogen, antiestrogen, antiseizure medications, or glucocorticoids).

In patients with asymptomatic primary hyperparathyroidism, other precautions can be taken to prevent disease-related complications. These patients should maintain adequate vitamin D (400-600 U daily) intake to prevent further PTH stimulation. In patients with concomitant vitamin D deficiency, repletion is recommended to replete patients whose levels are below 30 ng/dL (75 nmol/L) with careful attention to urine calcium excretion and serum calcium once values are greater than 30 ng/dL (75 nmol/L). A large study did not show worsening calcium levels when repleting vitamin D in patients with levels less than 30 ng/dL (75 nmol/L). Adequate physical activity to prevent bone resorption and adequate hydration to prevent kidney damage are imperative.

Parathyroid Carcinoma

Parathyroid carcinoma is very rare, accounting for less than 1% of all persons with primary hyperparathyroidism. Mutations in the *HRPT2* gene are thought to be the major genetic link in parathyroid carcinoma, and inactivation of this gene leads to familial hyperparathyroidism as well. When compared with benign primary hyperparathyroidism, parathyroid carcinoma is equally prevalent in both sexes, more commonly presents with kidney and bone involvement and a neck mass, and frequently is associated with a total serum calcium level greater than 14 mg/dL (3.5 mmol/L) and very high parathyroid hormone levels, typically greater than four times the upper limit of normal. Most patients present with single gland involvement. Because parathyroid carcinomas may not appear histologically different from benign adenomas, local spread from the capsule, distant metastasis, or lymph node involvement must be present for carcinoma diagnosis. In these patients, surgical resection is the treatment of choice with calcimimetics used for residual disease or in patients who are poor surgical candidates. Any patient found to have parathyroid carcinoma should be screened for the *HRPT2* gene, and if positive, family members should be screened as well.

Tertiary Hyperparathyroidism

Tertiary hyperparathyroidism is the result of the prolonged PTH stimulation needed to maintain normocalcemia resulting from decreased 1,25-dihydroxyvitamin D levels from kidney impairment. This prolonged stimulation results in increased calcium levels and severe hyperparathyroid hyperplasia and elevated PTH levels that do not respond to phosphate binders and calcitriol therapy. Severe bone loss and other symptoms make surgical resection the treatment of choice.

Normocalcemic Primary Hyperparathyroidism

Normocalcemic primary hyperparathyroidism is defined as increased PTH levels in the absence of elevated calcium levels. This is a diagnosis of exclusion used in patients being evaluated for low bone density in which all secondary causes have been ruled out, including vitamin D deficiency. Approximately 20% of these patients will develop hypercalcemia within 3 years, so they should be monitored closely.

Familial Hypocalciuric Hypercalcemia

Related Question

Question 37

The most common form of familial hypercalcemia is familial hypocalciuric hypercalcemia (FHH). It is a rare autosomal dominant condition with a high penetrance that often occurs in childhood. These patients are frequently asymptomatic, but in rare cases the calcium–sensing receptor (*CASR*) gene mutation can increase the risk of pancreatitis. Elevated serum calcium levels are caused by a mutation in the G-coupled protein *CASR* gene. These receptors are in the parathyroid glands and the kidneys. The sensor mutation results in a shift upward in the “normal” range of calcium that the receptor recognizes, resulting in a mildly elevated serum calcium level (usually less than 11.0 mg/dL [2.8 mmol/L]) and high normal or mildly elevated PTH level. An elevated PTH level is more commonly seen in patients with concomitant vitamin D deficiency. The diagnosis is made by measuring 24-hour urine calcium excretion levels. Typically, patients with FHH will have a 24-hour urine calcium level less than 200 mg/24 h (5.0 mmol/24 h). The preferred standard is the calcium-creatinine clearance ratio, using the following formula: Ca/Cr clearance ratio = [24-hour

urine Ca × serum Cr] ÷ [serum Ca × 24-hour urine Cr]. A ratio less than 0.01 confirms the diagnosis if all other causes of hypocalciuria (thiazides, lithium, vitamin D deficiency) have been excluded. FHH is usually a benign condition that requires no intervention but should be recognized to prevent unnecessary parathyroidectomy.

Other Familial Hypercalcemias

Familial hyperparathyroidism is another rare cause of hypercalcemia. The disease presentation is almost identical to sporadic primary hyperparathyroidism, and a careful family history will suggest the diagnosis. Once a diagnosis of primary hyperparathyroidism is made, screening for familial causes should be done if the patient (1) is younger than 30 years of age at the time of diagnosis, (2) has a family history of hypercalcemia, or (3) has a medical history of other endocrinopathies. These patients should be tested for multiple endocrine neoplasia syndrome types 1 and 2 (MEN1 and MEN2).

MEN1 is characterized by functional pituitary adenoma, functional pancreatic tumors, and primary hyperparathyroidism. MEN2A is characterized by medullary thyroid cancer, pheochromocytoma, and parathyroid gland hyperplasia with the associated *RET* oncogene mutation. Patients with MEN would follow similar guidelines for surgical removal of parathyroid glands.

Medications Causing Hypercalcemia

Thiazide diuretics decrease the excretion of calcium by the kidney and may result in increased serum calcium levels. Primary hyperparathyroidism, however, should also be considered if the patient remains hypercalcemic despite the discontinuation of the thiazide diuretic. In these patients, the thiazide may have been masking the PTH-mediated hypercalcemia.

Lithium decreases the parathyroid glands' sensitivity to calcium and may also reduce urine calcium excretion.

Non–Parathyroid Hormone–Mediated Hypercalcemia Related Question

Question 22

In contrast to PTH-mediated hypercalcemia, non–PTH-mediated hypercalcemia is associated with very low PTH levels, typically less than 10 to 15 pg/dL (10-15 ng/L).

Malignancy-Associated Hypercalcemia

There are two mechanisms of hypercalcemia of malignancy: local osteolytic and humoral. When lytic bone metastases are present, hypercalcemia is the result of increased mobilization of calcium from the bone. Humoral hypercalcemia is less common and occurs when the tumor itself produces parathyroid-related protein (PTHrP) that binds to and activates the parathyroid receptor, raising serum calcium levels. Squamous cell carcinomas, breast cancers, and renal cell carcinomas are the tumors most commonly associated with hypercalcemia of malignancy. In multiple myeloma, the hypercalcemia is caused by the release of factors that stimulate osteoclast activity.

Other Causes

Non–PTH-mediated hypercalcemia can be caused by several other mechanisms. Thyrotoxicosis can lead to mild hypercalcemia through increased bone resorption. Resolution of the thyrotoxicosis should lead to normalization of calcium levels. Prolonged immobilization and increased vitamin A levels can lead to increased bone resorption. Increased levels of calcium absorption from the gut can be from markedly high vitamin D levels or increased intake of calcium carbonate products (milk-alkali syndrome). Granulomatous diseases, such as sarcoidosis and Wegener granulomatosis, and malignant lymphomas cause hypercalcemia through increased 1-α-hydroxylation activity that increases 1,25-dihydroxyvitamin D levels and calcium reabsorption in the gastrointestinal tract.

Treatment of Hypercalcemia

Related Question

Question 75

The treatment of hypercalcemia should focus on decreasing the serum calcium level by increasing calcium excretion and decreasing bone resorption or intestinal calcium absorption, as well as volume repletion. Polyuria, due to the decreased concentration ability of the distal tubule, is the main cause of dehydration in these patients. Although many

patients do not require hospitalization, those with marked mental status changes, acute kidney injury, or calcium levels greater than 12 mg/dL (3 mmol/L) should be hospitalized for treatment. First-line therapy is aggressive intravenous fluid resuscitation. Once the patient is volume replete, an intravenous loop diuretic should be added if the calcium level has not normalized. Intravenous bisphosphonate therapy is usually given for longer-term control of hypercalcemia. Caution should be exercised with these agents in the setting of kidney dysfunction. Zoledronic acid, while more expensive, is a more effective therapy for patients with malignancy-related hypercalcemia. In patients resistant to or intolerant of bisphosphonate therapy, off-label use of denosumab, which also reduces osteoclast-mediated bone resorption can be used. Attention should be turned as quickly as possible to treatment of the underlying cause of the patient's hypercalcemia to ensure long-term maintenance of normocalcemia. If the underlying cause is increased 1,25-dihydroxyvitamin D hydroxylation, glucocorticoids can be effective therapy but may need to be dosed on a regular basis. For patients who present with serum calcium levels greater than 18 mg/dL (4.5 mmol/L) with neurologic symptoms or compromised kidney function, hemodialysis is an appropriate choice to quickly reduce calcium levels.

Key Points

- Primary hyperparathyroidism is the most common cause of parathyroid hormone-mediated hypercalcemia and is diagnosed with simultaneously elevated serum calcium levels, with an inappropriately normal or elevated intact parathyroid hormone level.
- Parathyroidectomy is curative in approximately 90% of patients with primary hyperparathyroidism, but should be performed by an experienced surgeon using minimally invasive techniques.
- In contrast to parathyroid hormone-mediated hypercalcemia, nonparathyroid hormone-mediated hypercalcemia is associated with very low parathyroid hormone levels, typically less than 10 to 15 pg/dL (10-15 ng/L).
- The acute treatment of hypercalcemia focuses on decreasing the serum calcium level by increasing calcium excretion with vigorous volume replacement, decreasing bone resorption with bisphosphonates.

Hypocalcemia

Clinical Features of Hypocalcemia

Hypocalcemia, defined by serum calcium levels below the normal range, may be asymptomatic if mild. As calcium levels decrease, particularly below 8.0 mg/dL (2.0 mmol/L), symptoms may develop, including paresthesias (numbness/tingling around the mouth, tingling in fingers and toes), muscle cramping (Trousseau and Chvostek signs), decreased muscle strength, electrocardiogram changes (prolonged Q/T interval), tetany, and seizures.

Diagnosis and Causes of Hypocalcemia

Asymptomatic hypocalcemia may be noted incidentally on routine laboratory tests. When this occurs, the calcium level should be repeated in conjunction with a serum albumin level. If hypocalcemia is confirmed, simultaneous intact PTH and serum calcium must be measured to confirm if PTH is responding appropriately. The appropriate physiologic response to lower calcium levels is an elevation in PTH levels.

Hypoparathyroidism

Hypoparathyroidism, commonly due to trauma during neck surgery (thyroidectomy or parathyroidectomy), is the most common cause of hypocalcemia. During head and neck surgeries, the parathyroid glands can be inadvertently removed or parathyroid hormone production can be transiently decreased due to disruption of blood supply. Only serial measurements of calcium levels will determine whether the damage is transient. Hypoparathyroidism can also be caused by damage from radiation exposure, parathyroid gland infarction, infiltrative diseases (hemochromatosis, Wilson disease, granulomas), or autoimmune hypoparathyroidism.

Other Causes of Hypocalcemia
Related Question

Question 28

Other, less common causes of hypocalcemia include poor calcium intake, activating mutations in the *CASR* gene, PTH resistance, increased phosphate binding in vascular space

(rhabdomyolysis or tumor lysis syndrome), increased citrate chelation with large volume blood transfusions, sepsis, vitamin D deficiency, and hypomagnesemia. Low levels of magnesium (due to alcohol abuse or malnutrition) activate G-proteins that stimulate calcium-sensing receptors and decrease PTH secretion.

Key Point

- The most common cause of hypocalcemia is hypoparathyroidism, which is most often due to trauma during surgery to the neck.

Treatment of Hypocalcemia

Related Question

Question 34

Mild, asymptomatic hypocalcemia (serum calcium 8.0-8.5 mg/dL [2.0-2.1 mmol/L]), is a common finding and does not require treatment.

Calcium carbonate and calcium citrate are the most common oral calcium formulations. Calcium carbonate requires an acidic environment to be absorbed; therefore, all patients who are on proton pump inhibitors should be prescribed calcium citrate. Adequate levels of both 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D are also essential. In the acute phase of repletion, 1,25-dihydroxyvitamin D is more effective than 25-hydroxyvitamin D. If the patient is symptomatic or if the hypocalcemia is acute, calcium gluconate and calcium citrate are both available in intravenous form. Goal calcium is 7.0 to 7.5 mg/dL (1.8-1.9 mmol/L) with intravenous repletion, and oral forms can be used once that goal is achieved. The overall goal of repletion is the low to low-normal range (serum calcium 8.0-8.5 mg/dL [2.0-2.1 mmol/L]).

If a patient requires chronic replacement, usually due to hypoparathyroidism, care must be taken to avoid hypercalciuria as calcium nephrolithiasis and decreased glomerular filtration rate can occur. Chronic replacement typically includes calcitriol, calcium, and occasionally magnesium. Calcitriol is the vitamin D source of choice because PTH is needed for optimal conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D. Serum calcium, magnesium,

creatinine, and urine calcium levels should be measured at each follow-up visit. The goal calcium levels should be low-normal without hypercalciuria. The magnesium level should ideally be greater than 2 mg/dL (0.83 mmol/L) and creatinine levels should remain in the normal range. If the urine calcium level is greater than 300 mg/24 h (hypercalciuria), calcium and/or vitamin D replacement needs to be decreased. Calcium is usually decreased first if the vitamin D levels are within the normal sufficiency range.

Key Point

- If hypoparathyroidism is the cause of hypocalcemia, correction of any coexisting hypomagnesemia to serum magnesium 2 mg/dL (0.8 mmol/L) or higher is necessary.

Metabolic Bone Disease

Related Question

Question 12

Osteopenia and Osteoporosis

Physiology

Bone mineral density begins to increase with puberty, and peak bone mass is achieved in early adulthood. Sex hormones, estrogen and testosterone, are crucial to increasing bone mineral density in women and men, respectively. Specifically, estrogen has impact on osteoclast and osteoblast activity in both men and women. Towards the end of puberty, estrogen halts bone resorption and signals the closure of epiphyseal plates. Bone mass begins to decline in women after menopause, with decreased estrogen levels, and in men over age 50 years. In men, the loss of testosterone typically accelerates bone loss after 70 years of age. Early cessation of sex hormone production in either sex, for any reason, may accelerate the loss of bone mineral density. Bone loss occurs when the removal of old bone (osteoclastic activity) exceeds the replacement with new bone (osteoblastic activity). Accelerated bone loss can often be attributed to hypogonadism or medications that promote bone loss.

Risk Assessment and Screening Guidelines

Declining bone mineral density is associated with future fracture risk and therefore is an important component of fracture risk assessment. Individual peak bone mass is determined by genetic factors, nutrition, changes in hormone (estrogen, testosterone, thyroxine) levels, concomitant health conditions, and physical activity level.

The National Osteoporosis Foundation recommends that all postmenopausal women and men older than 50 years of age be evaluated for osteoporosis. This evaluation includes a thorough history for potential risk factors and physical examination. This preliminary screening will determine if bone mineral density (BMD) or vertebral imaging is necessary. **Table 33** lists several common risk factors for osteoporosis. If a patient is deemed high risk, a study of BMD with DEXA may help further assess fracture risk. The DEXA is designed to measure BMD and establish risk of fracture in postmenopausal women. In young men and premenopausal women, assessment of BMD for fracture risk is not advised or validated. **Table 34** lists the U.S. Preventive Services Task Force recommendations for BMD testing.

Table 33. OPEN IN NEW WINDOW Low Bone Mineral Density Associations

Lifestyle	Comorbid Illness	Hormonal States	Medications	Nonmodifiable Risk Factors
Alcohol use	Vitamin D insufficiency	Premature menopause	Anticonvulsants	Race
BMI <17	Hypercalciuria	Premature ovarian insufficiency	Glucocorticoids (≥5 mg/d of prednisone or equivalent for ≥3 months)	Age
Low calcium intake	Osteogenesis imperfect	Panhypopituitarism		Gender
Smoking	Homocystinuria	Hyperprolactinemia	GnRH antagonists and agonists	First-degree relative with low bone mineral density
Immobilization	Hemochromatosis	Androgen insufficiency		
Weight loss				

Table 33. OPEN IN NEW WINDOW Low Bone Mineral Density Associations

Lifestyle	Comorbid Illness	Hormonal States	Medications	Nonmodifiable Risk Factors
Malabsorptive bariatric surgery Gastric bypass surgery Recurrent falls	Glycogen storage disease Cystic fibrosis Celiac disease Cushing syndrome Inflammatory bowel disease Diabetes mellitus (types 1 and 2)	Thyrotoxicosis	SSRIs Thiazolidinediones Aromatase inibitors Anticoagulants Lithium	

- GnRH = gonadotropin-releasing hormone; SSRI = selective serotonin reuptake inhibitor.

Table 34. OPEN IN NEW WINDOW U.S. Preventive Services Task Force Recommendations for Measurement of Bone Mineral Density and Vertebral Imaging

Bone Mineral Density Testing[a]
Women age 65 and older and men age 70 and older
Postmenopausal women and men age 50 to 69, based on risk factor profile
Those who have had a fracture, to determine degree of disease severity

Table 34. OPEN IN NEW WINDOW U.S. Preventive Services Task Force Recommendations for Measurement of Bone Mineral Density and Vertebral Imaging

Bone Mineral Density Testing[a]
Radiographic findings suggestive of osteoporosis or vertebral deformity
Glucocorticoid therapy for more than 3 months
Primary hyperparathyroidism
Treatment for osteoporosis (to monitor therapeutic response)
Vertebral Imaging[b]
Women ≥70 and men ≥80 if T-score at the spine, total hip, or femoral neck is ≤ −1.0
Women aged 65-69 and men aged 75-79 if T-score at the spine, total hip, or femoral neck is ≤1.5
In postmenopausal women age 50-64 and men aged 50-69 with the following risk factors:
Low-trauma fractures
Historic height loss of 1.5 in or more (4 cm)

Table 34. OPEN IN NEW WINDOW U.S. Preventive Services Task Force Recommendations f
Measurement of Bone Mineral Density and Vertebral Imaging

Bone Mineral Density Testing[a]
Height loss of 0.8 inches or more (2 cm)
Recent or ongoing long-term glucocorticoid treatment

- [a]BMD testing should be performed at DEXA facilities using accepted quality assurance measures.
- [b]Vertebral imaging should be repeated when a new loss of height is noted or new back pain is reported.

Diagnosis

The diagnosis of osteopenia is based on BMD testing. Osteoporosis, however, can be diagnosed by BMD testing or clinically in the patient with history of fragility fracture, hip fracture, or vertebral compression fracture.

DEXA assesses the density of the vertebral and hip bones compared with healthy young-adult sex-matched reference values. The distal one-third of the radius can be used in patients when the hip or vertebral BMD cannot be measured. The score is based on the number of standard deviations above or below the mean reference value and is known as the T-score. Those patients with T-scores at −1.0 and above have normal bone density. A T-score between −1.0 and −2.5 is defined as low bone mass (osteopenia). Osteoporosis is defined as a T-score below −2.5. Severe osteoporosis is defined as a T-score of −2.5 or below with one or more fractures. In women and men younger than 50 years, the International Society for Clinical Densitometry recommends that ethnic- or race-adjusted Z-scores be used. The Z-score compares a patient's BMD with others of their same age and ethnicity, and osteoporosis/osteopenia cannot be diagnosed in these patients. A Z-score of −2.0 or lower should be described as “low bone mineral density for chronologic age” or “below the expected range for age.” Patients with Z-scores above -2.0 are “within the expected range for age.”

In 2008, the World Health Organization (WHO) created the Fracture Risk Assessment Tool (FRAX) calculator that further defines the 10-year fracture risk for patients with osteopenia, defined as a T-score between −1.0 to −2.5 on DEXA. The FRAX score notes the probability of major osteoporotic fracture and hip fracture in the next 10 years. If the risk of major osteoporotic fracture is greater than or equal to 20% or the risk of hip fracture is greater than or equal to 3%, the patient's benefit from therapy exceeds the risk, and treatment should be offered.

The FRAX was validated for use in persons 40 to 90 years of age who are not currently or previously treated with pharmacotherapy for osteoporosis. The WHO has a web site that offers an online FRAX calculator at www.shef.ac.uk/FRAX.

In additional to BMD testing, vertebral imaging using radiographs is recommended in high-risk groups since many vertebral fractures are asymptomatic. The presence of a vertebral compression fracture establishes the clinical diagnosis of osteoporosis, regardless of T-score on DEXA, and treatment is recommended. Once a vertebral image is obtained, it only needs to be repeated if there is noted height loss or new back pain.

Evaluation of Secondary Causes of Bone Mineral Density Loss Related Question

Question 25

Most cases of osteoporosis are due to declining levels of sex hormones which are non-modifiable, such as age, sex, menopause, height, and build. Some patients, however, have osteoporosis caused by secondary causes. Measurement of complete blood count (for malignancy), complete metabolic panel (for calcium levels and kidney function), thyroid-stimulating hormone, 25-hydroxyvitamin D, and urine calcium (screening for hypercalciuria) is an appropriate set of laboratory tests to screen for secondary causes of BMD loss. These are modifiable conditions that, if corrected, will result in increased BMD. These patients are typically young with either markedly low BMD for age or a new fracture or patients of any age with multiple fractures.

With all secondary causes of decreased BMD, reversal of the cause should be the first line of therapy and subsequent DEXA should be performed. If the BMD has not improved or the FRAX score suggests increased risk of fracture, treatment should be started. In the event of a fracture, the underlying cause should still be addressed in addition to initiating pharmacologic therapy for osteoporosis.

Pharmacologic Treatment Options Related Question

Question 78

Currently there are six categories of pharmacologic agents that are FDA approved for the treatment of postmenopausal osteoporosis. These medications are bisphosphonates, calcitonin, estrogens, estrogen agonists, parathyroid hormone, and the receptor activator of nuclear factor κB (RANK) ligand inhibitor family. Bisphosphonates are usually first-line therapy unless there is a compelling reason why another therapy should be used. The other modalities are typically used after a bisphosphonate failure or inability to use the medication. Most of these medications can also be used for prevention of osteoporosis. Prevention therapy may be used in patients with osteopenia who do not meet FRAX standards for therapy but have multiple risk factors such as high-risk medications (glucocorticoids or antiestrogen, antiandrogen, or antiseizure medications) in combination with a strong family history of osteoporosis.

Bisphosphonates

Bisphosphonate medications work by inhibiting osteoclastic activity. Before starting any bisphosphonate therapy, vitamin D status and calcium levels should be evaluated, as bisphosphonates can lead to hypocalcemia. For oral bisphosphonates, integrity of the esophageal lining and ability to swallow pills are important. Kidney function should be assessed as bisphosphonates are contraindicated in patients with an estimated glomerular filtration rate less than 35 mL/min/1.73 m^2. Although rare, osteonecrosis of the jaw has been reported with bisphosphonate usage, particularly with high-dose intravenous administration and increased duration of the bisphosphonate. Additionally, atypical femur fractures have been reported with long-term usage. Regular questioning about pain in the thigh or groin

area is recommended for patients on bisphosphonates. If patients report discomfort, a radiograph should be obtained. To reduce the risk of these side effects, a drug holiday has been suggested in patients with low-risk osteoporosis (T-score greater than −2.5 or single fractures) who have been on therapy for 3 to 5 years with stable BMD. During bisphosphonate therapy for prevention or treatment, men 50 to 70 years of age should consume 1000 mg/d of calcium and women aged 51 years and older and men aged 71 years and older consume 1200 mg/d of calcium.

Alendronate has been approved by the FDA for prevention and treatment of osteoporosis. The prevention dose is a 5-mg tablet daily or a 35-mg tablet weekly. The treatment dose is a 10-mg tablet daily or a 70-mg tablet weekly. Alendronate is also approved for treatment of men with osteoporosis as well as treatment of both women and men with glucocorticoid-induced osteoporosis. Alendronate has been shown to reduce the incidence of spine and hip fractures by approximately 50% over 3 years in patients with previous fractures.

Ibandronate is FDA approved for the treatment and prevention of postmenopausal osteoporosis. The dosage is a 150-mg tablet monthly or 3 mg every 3 months by intravenous injection. There is FDA approval for the oral formulation for osteoporosis prevention only. Ibandronate primarily reduces risk of vertebral fractures by 50% in 3 years.

Risedronate is FDA approved for the prevention and treatment of osteoporosis. The treatment dose is a 5-mg tablet daily, a 35-mg tablet weekly, a 75-mg tablet on two consecutive days every month, or a 150-mg tablet monthly. Risedronate is also approved for treatment of osteoporosis in men and women with glucocorticoid-induced osteoporosis. Risedronate reduces the incidence of vertebral fracture by approximately 45% and nonvertebral fractures by one-third over 3 years.

Zoledronic acid has been FDA approved for the prevention and treatment of postmenopausal osteoporosis in women, for improvement of bone mass in men with osteoporosis, and for the prevention and treatment of glucocorticoid-induced osteoporosis in men and women. Recently zoledronic acid has been approved for secondary prevention of

fractures in patients who have had recent low-trauma hip fracture. The treatment dose of zoledronic acid is 5 mg intravenously annually or once every 2 years for prevention.

Calcitonin

Calcitonin is FDA approved for the treatment of osteoporosis in women who are 5 or more years postmenopausal. Calcitonin (200 U) is delivered in a single daily intranasal spray. Subcutaneous administration is also available but is used less frequently. Calcitonin should be used with caution with patients who have an allergy to salmon, allergic rhinitis, or epistaxis. Very rarely, patients can also have an anaphylactic response that requires emergency attention and discontinuation of the medication.

Estrogen Agonists and Antagonists

The use of estrogen to maintain bone health in postmenopausal women has fallen out of favor because of data indicating that estrogen increases the risk of cardiovascular disease and breast cancer. Therefore, estrogen use for osteoporosis prevention should be limited to younger women with premature ovarian failure and postmenopausal women who also require its beneficial effects for hot flushes or vaginal dryness.

Raloxifine has been approved for the treatment of postmenopausal osteoporosis. The treatment dose is a 60-mg tablet to be taken with or without food.

Parathyroid Hormone

Teriparatide (recombinant human PTH [1-34]) has been FDA approved for the treatment of osteoporosis in postmenopausal women and men who are at high risk for fracture. “High risk” is defined as patients with a T-score of -3.0 or less or patients who have either had a fracture or decreased BMD while on bisphosphonate therapy. It is also approved for men and women at high risk of fracture due to long-time glucocorticoid use. Teriparatide has bone-building properties in addition to the antiresorptive properties of the other agents. It is the only bone-building treatment option for osteoporosis.

Teriparatide is an anabolic steroid that is administered by a 20-µg daily subcutaneous injection; it is approved for up to 24 months over a patient's lifetime. After the 24-month

duration, an antiresorptive agent (such as bisphosphonates or denosumab) can be administered to maintain BMD gains achieved with teriparatide.

Receptor Activator of Nuclear Factor κB (RANK) Ligand Inhibitors

Denosumab is a receptor activator of nuclear factor κB (RANK) ligand inhibitors that is FDA approved for the treatment of osteoporosis in postmenopausal women who are at high risk of fracture. It is an antiresorptive agent, like the bisphosphonates with much the same effect and outcomes. It is also approved for treatment of osteoporosis in men and those undergoing treatment of certain cancers, such as prostate cancer, who are at high risk for fractures. Denosumab is given by subcutaneous injection (60 mg every 6 months).

Annual Reassessment of Patients with Low Bone Mass

Once an initial DEXA scan has been obtained, every effort should be made to have subsequent scans done on the same machine. Once a repeat scan has been done, change in BMD, not T-score, from year to year is the appropriate way to interpret whether there has been a significant change in BMD. Most reports will not show a statistically significant change in the BMD from the previous test. If not noted on the report, a calculated change of about 4% likely represents a statistically significant change. Annually, a complete clinical evaluation of the patient, determination of risk factors for bone loss, and evaluation for development of secondary causes of bone loss should be performed, starting with a history and physical examination.

Vitamin D Deficiency

Related Question

Question 15

In promoting absorption from the gut, vitamin D enables proper bone mineralization by maintenance of calcium and phosphorus levels. Vitamin D also modulates the actions of osteoblasts and osteoclasts to ensure proper bone growth and remodeling. Chronically low levels of vitamin D can lead to rickets in children and osteomalacia in adults (see MKSAP 17 Nephrology).

In addition to bone health, vitamin D plays a role in inflammation reduction, growth regulation of various cell types, immune function, and neuromuscular signaling.

In assessing serum levels of vitamin D, concentrations of 25-hydroxyvitamin D are the best indicator of vitamin D status. It reflects vitamin D produced cutaneously and that obtained from food and supplements and has a circulating half-life of 15 days.

There are three levels of vitamin D status: sufficient (25-hydroxyvitamin D ≥30 ng/mL [75 nmol/L]), insufficient (25-hydroxyvitamin D 21-29 ng/mL [52.4-72.4 nmol/L]), and deficient (25-hydroxyvitamin D ≤20 ng/mL [50 nmol/L]). Because vitamin D levels can be affected by sun exposure, fall through winter months are ideal times to measure vitamin D levels. It is best to measure vitamin D levels at the same time each year unless treatment is being followed. In general, the optimal levels of vitamin D are those that prevent PTH levels from increasing to above normal levels. Increased PTH levels will lead to increased calcium withdrawal from the bones. In an attempt to find the optimal vitamin D level, several studies have looked at vitamin D levels related to cancer incidence, muscle stability and falls, immune status, and mood, in addition to bone health. Among most experts, a level between 30 and 40 ng/mL (75-100 nmol/L) is deemed sufficient for preventive health. Based on these levels, about 30% to 60% of Americans have low vitamin D levels, therefore most expert groups recommend screening all patients at least once. Those with darker skin, decreased sun exposure, or increased demands (pregnancy) often have low levels.

Special populations will have lower levels of vitamin D owing to medical conditions or medication side effects. In addition, obesity has been correlated with lower vitamin D levels possibly related to fat sequestration. Certain antiseizure medications (phenobarbital and phenytoin) may increase the metabolism of vitamin D to inactive forms. Glucocorticoids can decrease vitamin D metabolism. Agents that decrease absorption such as orlistat and cholesterol lowering agents can decrease vitamin D absorption. Similarly, patients with malabsorption disorders, including those with celiac disease and those who had bariatric surgery, can have decreased levels of vitamin D. In these special patient populations, not only does screening for deficiency need to be more frequent, but repletion may be more

challenging. It is recommended that these populations be given at least two to three times more vitamin D to maintain adequate levels.

Recommendations

The current National Osteoporosis Foundation and Endocrine Society recommendation for adults 19 to 70 years of age is at least 600 U/d of vitamin D to maximize bone health; however, to raise blood levels consistently above 30 ng/dL (75 nmol/L) may require 1500 to 2000 U/d. In adults older than 70 years of age, 800 U of supplemental vitamin D per day is recommended to maximize bone health; however, 1500 to 2000 U/d may be required to keep levels consistently above 30 ng/dL (75 nmol/L). In treating the deficient patient, 50,000 U of either ergocalciferol or cholecalciferol is recommended, once weekly for 8 weeks. Once sufficiency is attained, maintenance therapy of 1500 to 2000 U/d is recommended.

Vitamin D toxicity is a very rare entity but one to be aware of. The effects of vitamin D levels greater than 90 ng/mL (225 nmol/L) include hypercalcemia. As a fat-soluble vitamin, decreasing vitamin D levels that are once elevated can be a slow process requiring continued monitoring.

Key Points

- The U.S. Preventive Services Task Force recommends screening for osteoporosis in women aged 65 years and older and in younger women whose fracture risk is equal to or greater than that of a 65-year old white women who has no additional risk factors.
- The presence of a vertebral compression fracture makes the clinical diagnosis of osteoporosis, regardless of T-score on dual-energy x-ray absorptiometry (DEXA) scan, and treatment is recommended.
- Fracture Risk Assessment Tool (FRAX) score can help identify which patients are most likely to benefit from osteoporosis treatment; bisphosphonate therapy is first-line therapy for postmenopausal osteoporosis treatment and prevention.
- A 25-hydroxyvitamin D level between 30 and 40 ng/mL (75-100 nmol/L) is deemed sufficient for bone health; most expert groups recommend screening all groups at least once for evidence of deficiency since U.S. incidence is 30% to 60% of the population, however, it should not be a serial, recurring screening test.

Paget Disease of Bone

Related Question

Question 40

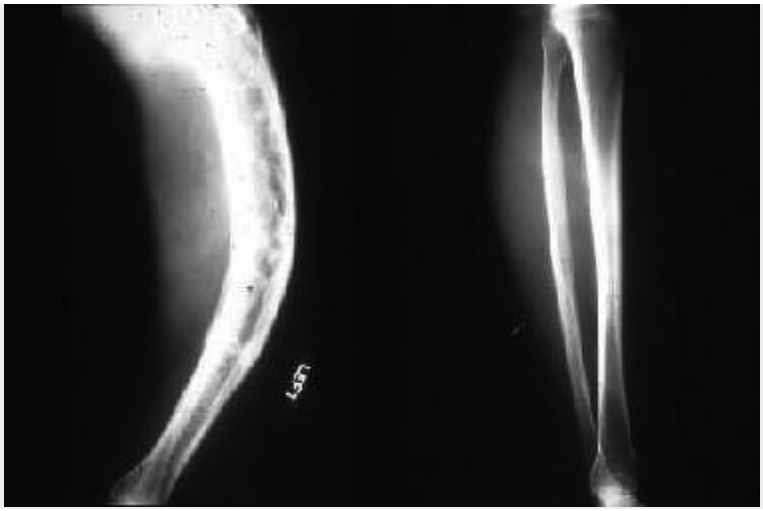
Paget disease of bone is characterized by rapid and chaotic bone remodeling leading to disorganized bone microarchitecture. This disease more commonly affects persons of European descent during the sixth decade, with a prevalence of 3% to 10% in the elderly. Paramyxovirus infection of osteoclastic precursors is thought to be one possible cause, although about 15% of people with Paget disease have a family member with the disease. Paget disease appears to be inherited in an autosomal dominant manner with incomplete penetrance.

Clinical Presentation

The most common clinical manifestation is asymptomatic elevated serum alkaline phosphatase levels; only 30% of patients have symptoms at diagnosis. In some patients, the dysfunctional bone structure creates expansion in the bone leading to pain, swelling, and warmth. Bones of the axial skeleton are most frequently affected, namely the pelvis (70%), femur (55%), lumbar spine (53%), skull (42%), and tibia (30%). As a result, patients tend to have headache, sensorineural hearing loss, and bowing of the long bones (**Figure 16**). The abnormal bone growth may also lead to nerve impingement causing pain or neurologic deficits. Rarely, patients can develop increased vascular shunting to bones with resultant right-sided heart failure, cellular transformation to osteosarcoma, and hypercalcemia of immobilization.

Figure 16. OPEN IN NEW WINDOW

Radiograph showing Paget disease of bone in the left lateral tibia of a 71-year-old woman. Note the anterior bone, cortical thickening, and bone enlargement as compared with the normal radiograph on the right. The long-standing Paget disease resulted in a left leg that was 2.5 cm (1 in) shorter than the right.



Diagnosis

The diagnosis of Paget disease should be suspected in asymptomatic patients with an isolated elevation of alkaline phosphatase without evidence of liver disease. In these patients the most sensitive test is a nuclear bone scan which will detect areas of increased metabolic activity. Plain films of these areas should be obtained to identify pathognomonic pagetic lesions such as focal osteolysis with coarsening of the trabecular pattern and cortical thickening. In symptomatic patients with bone pain, plain films of painful areas may be the initial imaging test, although many experts recommend a baseline bone scan once the diagnosis is confirmed prior to initiating treatment.

Treatment

The main therapies for Paget disease of bone are the nitrogen-containing bisphosphonate medications (alendronate, pamidronate, risedronate, and zoledronic acid). The main indications for antiresorptive therapy are (1) pain caused by the increased metabolic activity; (2) planned surgery at site of pagetic bone disease, and (3) hypercalcemia due to multiple affected sites. There is no evidence that antiresorptive therapy is beneficial in asymptomatic patients. These medications are ideal because they suppress the rapid bone turnover that is characteristic of Paget disease. Decreases in alkaline phosphatase can be noted within 10 to 14 days after the initiation of therapy with a nadir reached in 3 to 6 months. NSAIDs and antineuropathic medications can also be used for pain control in these patients. For patients with pseudofractures, orthopedic stabilization may be required.

Key Points

- The most common clinical manifestation of Paget disease of bone is asymptomatic elevated alkaline phosphate levels.
- The main therapy for Paget disease of bone is the nitrogen-containing bisphosphonate medications (alendronate, pamidronate, risedronate, and zoledronic acid).