Endocrine Disorders and the Heart

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Key Points

- Increased mortality from cardiovascular disease among adults with hypopituitarism is perhaps related to growth hormone deficiency.
- Major cardiovascular manifestations of acromegaly include cardiomegaly, cardiac hypertrophy, hypertension, congestive heart failure, coronary artery disease, and arrhythmias.
- The excess mortality of acromegaly is abolished by successful treatment of acromegaly.
- The major cardiovascular manifestation of adrenal insufficiency is arterial hypotension.
- Major cardiovascular manifestations of Cushing’s syndrome include hypertension, myocardial hypertrophy, and a prothrombotic state.
- The major cardiovascular manifestation of mineralocorticoid excess is hypertension, more common than previously thought.
- Hypokalemia is important in mineralocorticoid disorders, but most patients are normokalemic.
- Treatment with mineralocorticoid antagonist is beneficial following myocardial infarction and in congestive heart failure.
- In pheochromocytoma, prompt treatment is important.
- Metabolic syndrome is important as a risk factor for the development of atherosclerotic disease and type 2 diabetes mellitus.
- The increased cardiovascular mortality in diabetes mellitus is reduced by aggressive treatment of multiple risk factors.
- Intensive treatment of hyperglycemia reduces mortality in critical illness.
- There is excess cardiovascular mortality in primary hyperparathyroidism.
- The “euthyroid sick syndrome” results from non-thyroidal illness.
- Major cardiovascular manifestations of hyperthyroidism include bradycardia, cardiac enlargement, hypertension, low voltage on the ECG, and sometimes pericardial effusion.
- “Subclinical hyperthyroidism” is associated with increased lipids, but not yet conclusively linked to excess cardiovascular events.
- Overt and “subclinical” hyperthyroidism are linked to atrial fibrillation.
- Major cardiovascular manifestations of carcinoid syndrome include tricuspid regurgitation and pulmonic valve damage related to right-sided endocardial plaques.
- In carcinoid syndrome, there is increased morbidity and mortality in patients with carcinoid heart disease.

Hypothalamic-Pituitary Axis

This chapter reviews selected endocrine disorders and their influences on the cardiovascular system. The classic hormones of the anterior pituitary gland can be divided into three classes of related polypeptides: growth hormone [GH] and prolactin, adrenocorticotropin [ACTH] and other peptides derived from the pro-opiomelanocortin precursor, and...
the glycoprotein hormones thyrotropin [thyroid-stimulating hormone, TSH], luteinizing hormone [LH], and follicle-stimulating hormone [FSH]. Synthesis and secretion of pituitary hormones are regulated in part by hypothalamic neuropeptides. These neurohormones are transported from the hypothalamus via the pituitary portal circulation, thereby escaping dilution in the systemic circulation. They include growth hormone–releasing hormone (GHRH), somatostatin, thyrotropin-releasing hormone (TRH), dopamine, corticotropin-releasing hormone (CRH), and gonadotropin-releasing hormone (GnRH). Adrenocorticotropic and the glycoproteins have no major cardiovascular effects except those mediated by their respective target organs: the adrenal cortex, the thyroid, and the gonads.

**Somatostatin**

The term somatostatin encompasses a family of homologous peptides with multiple endocrine and paracrine actions. The major sources of somatostatins are the brain, the D cells of the pancreatic islets, and the gastrointestinal mucosa. Somatostatin from brain acts via the pituitary portal system to inhibit secretion of thyrotropin and growth hormone.

In the endocrine pancreas, somatostatin inhibits secretion of insulin, glucagon, and somatostatin itself. Somatostatin also has diverse inhibitory effects on gastric and pancreatic exocrine secretion and on gastrointestinal activity. Somatostatin receptors, of which there are five subtypes, are widely distributed throughout the body. The various actions of somatostatin appear to be mediated by G, proteins.

Somatostatin may have a function in cardiac physiology, as it has been reported that cardiac nerves contain somatostatin. However, to date there has been no description of cardiac symptomatology in states of somatostatin excess. No clinical syndrome of somatostatin deficiency has yet been recognized.

Uncontrolled studies have shown purported beneficial effects of treatment with octreotide, an analogue of somatostatin, in small numbers of patients with dilated or hypertrophic cardiomyopathy. These results await confirmation in larger, randomized studies.

**Prolactin**

There is no established cardiovascular syndrome associated with excessive or deficient prolactin. One group of investigators has reported an association between hyperprolactinemia and venous thromboembolism, and has provided evidence that prolactin promotes adenosine diphosphate (ADP)-induced platelet activation. These results await confirmation.

**Adult Growth Hormone Deficiency**

Several studies have shown increased mortality from cardiovascular disease among adults with hypopituitarism. Some of this excess mortality may be related to deficiency of growth hormone. There is growing recognition of a syndrome of growth hormone deficiency in adults, the clinical features of which include loss of lean body mass, increased adiposity, muscular weakness, various psychological abnormalities, dyslipidemia, insulin resistance, abnormal endothelial function, osteopenia, bradycardia and impaired left ventricular systolic function. These features include several recognized cardiovascular risk factors. This problem should be suspected in individuals with known hypothalamic-pituitary disease of any etiology. For adults, the standard test for diagnosis of growth hormone deficiency has been the peak response of serum growth hormone to induced hypoglycemia. A synthetic analogue of hypothalamic growth hormone releasing hormone has become available and shows promise as a diagnostic agent that can avoid the risks of hypoglycemia.

A deficiency of growth hormone can be treated with injections of recombinant human growth hormone. Treatment of adult GH deficiency increases left ventricular mass and indices of cardiac performance and exercise tolerance, and improves the lipid profile by increasing high-density lipoprotein (HDL) cholesterol and reducing low-density lipoprotein (LDL) cholesterol. However, to date there are no data regarding the effect of treatment on cardiovascular mortality.

**Acromegaly**

**Pathophysiology**

Acromegaly is the clinical syndrome of excessive circulating GH with onset in adult life. It is nearly always caused by inappropriately high levels of GH secreted by a pituitary adenoma. Very rarely, it may be caused by secretion of GHRH by an extrapituitary tumor. Normally, secretion of GH from the anterior pituitary is regulated by the hypothalamic peptides, GHRH and somatostatin. There are several molecular variants of circulating GH, of which the relative physiologic significance remains to be elucidated. GH stimulates the production in various tissues of insulin-like growth factor-I (IGF-I, also known as somatomedin C) and, to a lesser extent, IGF-II. These two peptides are structurally homologous to proinsulin. Many of the effects of growth hormone are mediated by the IGFs, especially by IGF-I. Growth hormone, acting directly or via IGFs, has a number of important metabolic effects. Broadly speaking, it promotes net protein anabolism while stimulating lipolysis and ketogenesis. As a result, lipid-derived fuels (i.e., nonesterified fatty acids and ketone bodies) are used for energy by various tissues, including myocardium. Amino acids are spared for protein synthesis. When GH is administered chronically, uptake and catabolism of glucose by muscle and adipose tissue are diminished, leading to insulin resistance and a tendency toward hyperglycemia. Echocardiographic studies indicate that administration of GH to humans increases heart rate and myocardial contractility.

**Clinical Manifestations**

The principal manifestations of acromegaly can be classified according to the organ systems affected. Growth of
bone in adults, in whom the epiphyses are closed, leads to broadening of the hands and feet, with increases in shoe, glove, and ring size. There is also enlargement of the mandible, with prognathism and dental malocclusion. Hypertrophic bone growth leads to osteoarthritis and nerve entrapment syndromes, which may be major causes of morbidity. Manifestations of soft tissue growth include thickened, greasy skin, enlargement of abdominal viscera, macroGLOSSIA, and goiter. Skin tags are common. An increased incidence of colonic polyps and colon cancer has been reported in patients with acromegaly. Metabolic manifestations include hypercalcemia and hyperphosphatemia. Hyperinsulinemia, indicative of insulin resistance, is found in most patients. However, clinical evidence of diabetes mellitus occurs in only approximately 10% of these individuals. The principal cardiovascular manifestations of acromegaly are cardiac hypertrophy, hypertension, premature coronary artery disease (CAD), congestive heart failure (CHF), and arrhythmias.11,32–37

Acromegaly is a serious disease. The major causes of death and disability are cardiovascular and respiratory disease, neoplasms, and degenerative joint disease. Age-specific mortality, principally from cardiovascular and respiratory complications, is increased from 1.5 to 3-fold.41

Arterial hypertension occurs in approximately 30% of people with acromegaly, especially those with longer duration of disease. The hypertension usually responds to medical treatment. In patients with acromegaly, there appears to be reduced activity of the renin-angiotensin-aldosterone axis, confirmed by pressor responses to angiotensin II antagonists, enhanced pressor responsiveness to angiotensin II, and increases in total exchangeable sodium. In addition, intravascular volume expansion occurs in many patients. Each of these alterations may contribute to the development of systemic arterial hypertension. Successful treatment of acromegaly reduces arterial pressure in many hypertensive acromegalic patients.

Premature atherosclerosis occurs in some patients with acromegaly, but its prevalence is not clear. Virtually all patients with acromegaly have cardiomegaly, especially older individuals. The increase in cardiac mass, including asymmetric septal hypertrophy, is not directly related to hypertension. Some patients have left ventricular (LV) dilatation and reduction of ejection fraction. Clinical evidence of cardiomyopathy includes cardiomegaly, CHF, and occasional arrhythmias. Approximately 10% to 20% of patients with acromegaly have CHF, and in perhaps 20% of these there is no obvious predisposing cause. Diastolic dysfunction is found in some patients with acromegaly in the absence of hypertension or atherosclerosis. The CHF may be relatively resistant to conventional medical therapy. At autopsy, lymphocytic infiltration and small vessel disease of the myocardium have been found in some patients. Some histologic observations have demonstrated cellular hypertrophy, patchy fibrosis, and myofibrillar degeneration [Fig. 108.1]. Autopsy studies of some patients after sudden death have demonstrated degenerative or inflammatory changes in the sinoatrial (SA) nerve plexus and the atroventricular (AV) node.

Diagnosis

Because GH levels are highly variable, it is important to obtain them under standardized conditions. The most useful diagnostic test involves the oral administration of 75 to 100 g of glucose. In normal individuals, GH levels are less than 2 ng/mL, 90 to 120 minutes after administration of the test dose. Serum IGF-I levels, which correlate well with integrated measurements of GH, are also very helpful in diagnosis. In considering the possible diagnosis of acromegaly, it is also important to determine whether there are other alterations in pituitary or hypothalamic function.

Treatment

Recent surveys of large numbers of patients have shown that those with very low posttreatment GH levels exhibit no increase of mortality compared to the age-adjusted general population, highlighting the importance of reduction of excessive secretion of growth hormone. Criteria for successful treatment include normalization of both growth hormone and IGF-I levels. The recommended initial treatment in most cases is surgery, usually by the transsphenoidal approach. Reported surgical success rates depend on the size of the adenoma and on the stringency of the definition of cure [reviewed elsewhere]. Probably at least 40% of patients require some mode of adjunctive therapy, either drugs or irradiation. An effective treatment modality is administration of octreotide, an analogue of somatostatin. Octreotide decreases left ventricular mass in acromegalic patients with cardiac hypertrophy. Octreotide must be injected several times daily, but longer-acting analogues are available. Pegvisomant is a compound now available for clinical use that acts as an antagonist at the GH receptor. It has been shown to be effective in reducing IGF-I levels and ameliorating the clinical manifestations of acromegaly. Dopaminergic agonists, such as bromocriptine often provide subjective relief of symptoms, but do not significantly reduce GH levels in the majority of patients.
Primary adrenal insufficiency (Addison’s disease) can occur at any age and affects both sexes equally. Its major manifestations are weakness, increased skin or mucosal pigmentation, weight loss, anorexia, nausea, vomiting, and hypotension, often with postural hypotension. Hyponatremia is caused by loss of sodium into the urine as the result of aldosterone deficiency, coupled with inability to excrete free water. Hyperkalemia occurs as a result of mineralocorticoid deficiency and reduction in the glomerular filtration rate. Hypercalcemia, probably related to volume contraction, may also be present.

In patients with impaired secretion of ACTH, there is usually adequate secretion of mineralocorticoids by the adrenal zona glomerulosa, which continues to enjoy trophic stimulation by circulating angiotensins. Consequently, hyperkalemia is not usually a problem. However, because impaired excretion of free water is a consequence of glucocorticoid deficiency, hyponatremia may occur.

Arterial hypotension is the most common cardiovascular finding in patients with adrenal insufficiency. Syncope occurs in many of these individuals. Heart size is normal or small, pulse volume is reduced, and orthostatic hypotension may be present. Echocardiographic studies of limited numbers of patients with Addison's disease have shown reduced LV dimensions and mitral valve prolapse, which disappeared with appropriate steroid replacement. Rarely, cardiomyopathy and heart failure have been reported as presenting manifestations of adrenal insufficiency.

Diagnosis

The most convenient screening test for adrenocortical insufficiency is measurement of plasma cortisol following intravenous injection of cosyntropin, a synthetic preparation of the 1 to 24 sequence of ACTH. For determination of the cause of adrenocortical insufficiency, there are several useful tests, including measurements of plasma ACTH levels and of plasma cortisol after prolonged infusion of cosyntropin.

Treatment

Treatment of adrenal insufficiency entails replacement of glucocorticoids as well as mineralocorticoids, if necessary. In previously untreated patients who manifest signs of volume depletion, the vascular compartment should be repleted with intravenous saline. Prompt administration of saline solution is especially important in Addisonian crisis, characterized by hypotension and cardiovascular collapse. In acute adrenal insufficiency or in patients experiencing physiologic stress, the dosage of glucocorticoid should be several times the usual daily maintenance dose. For treatment of acute adrenal crisis, the recommended dose of hydrocortisone is 100mg IV q6h. Given in “stress” doses, hydrocortisone, the major natural glucocorticoid, exhibits substantial mineralocorticoid effects. As soon as the patient’s condition stabilizes, the dose of hydrocortisone should be reduced quickly to a maintenance dose.

For maintenance therapy, either hydrocortisone or a less costly short-acting synthetic glucocorticoid, such as prednisone, should be given orally in physiologic replacement dosage (e.g., prednisone 5–7.5mg daily, or hydrocortisone 15–20mg in the morning and 5–10mg in the afternoon). The usual injectable mineralocorticoid is desoxycorticosterone (DOC), and the oral preparation is fludrocortisone. The replacement dosage for mineralocorticoids should be determined on an individual basis. The usual replacement dosage of fludrocortisone is 0.05 to 0.2mg daily, together with a liberal intake of dietary sodium. Hyperkalemia or elevation of plasma renin activity suggests the need for a higher dose of mineralocorticoid.

Cushing’s Syndrome

Pathophysiology

Cushing’s syndrome results from the actions of excessive circulating glucocorticoids. Its most frequent cause is treatment with pharmacologic doses of antiinflammatory glucocorticoids for nonendocrine conditions. Most patients with endogenous Cushing’s syndrome have bilateral adrenal hyperplasia with resultant excess production of glucocorticoids.
coids, mineralocorticoids, and androgens. These patients usually have ACTH-producing tumors of the pituitary (Cushing’s disease) or ectopic ACTH production (e.g., from a lung cancer). Approximately 20% of cases of endogenous Cushing’s syndrome are ACTH-independent and are due to primary adrenal adenoma, carcinoma, or nodular dysplasia. Three times as many women as men have endogenous Cushing’s syndrome. Onset usually occurs in the third or fourth decade of life.

Clinical Manifestations
Depending on the cause of Cushing’s syndrome, the clinical picture may include the effects of increased androgens or mineralocorticoids in addition to those of glucocorticoids. Major manifestations are truncal obesity, plethora, systolic hypertension, proximal muscle weakness, thinning and fragility of the skin with ecchymoses and purple abdominal striae, hyperglycemia, osteoporosis, psychiatric disturbances, and fatigue. Many patients experience wide swings in mood, ranging from severe depression to frank psychosis or confusion. Overt diabetes mellitus is present in approximately 20% of patients. Hyperpigmentation, although uncommon, is a clue to hypersecretion of ACTH from the pituitary. In women with endogenous Cushing’s syndrome, hirsutism, a male escutcheon, amenorrhea, and deepening of the voice are due to androgen excess. The major signs of excessive mineralocorticoids are hypertension and hypokalemia (see below).

Clinical Cardiovascular Manifestations
Mortality is significantly increased in Cushing’s syndrome, related largely to cardiovascular problems. Even people with “subclinical” Cushing’s syndrome, characterized by autonomous cortisol secretion without absolute elevation of circulating cortisol levels, exhibit unfavorable cardiovascular risk profiles. The major cardiovascular abnormality is arterial hypertension, occurring in 80% of patients. Possible causes of the hypertension include volume expansion caused by mineralocorticoids and high levels of cortisol, increased production of angiotensin II, and vascular hyperreactivity. Unlike patients with essential hypertension, hypertensive patients with Cushing’s syndrome of any cause lack the normal nocturnal decline of blood pressure. As the normal diurnal rhythm of pituitary-adrenal secretion is disrupted in Cushing’s syndrome, blood pressure may normally be modulated by physiologic fluctuations of circulating adrenal steroids.

Hemodynamic, electrocardiographic [ECG], and echocardiographic manifestations are usually associated with systemic arterial hypertension. There may be ECG or echocardiographic evidence of LV hypertrophy, left atrial (LA) enlargement, and, on occasion, evidence of diastolic dysfunction. Recent echocardiographic investigations suggest that increased LV wall thickness and asymmetric septal hypertrophy, with normal LV systolic function and diastolic dysfunction, are common findings in patients with endogenous Cushing’s syndrome of any cause. Chronic excess production of cortisol may also lead to hyperlipidemia, which can promote the development of atherosclerosis. Additionally, Cushing’s syndrome is a prothrombotic state, owing to increased circulating clotting factors and decreased fibrinolysis.

Atrial myxomas and ACTH-independent Cushing’s syndrome may coexist in the Carney complex, a rare familial syndrome that comprises multiple small pigmented adrenal nodules; spotty cutaneous pigmentation including lentigines and blue nevi; subcutaneous, mammary, or cardiac myxomas; and other endocrine disorders such as acromegaly, thyroid adenomas, and testicular tumors.

Diagnosis
Dexamethasone, 1 mg given orally late in the evening, with measurement of plasma cortisol between 7 a.m. and 9 a.m. the next morning, serves as a sensitive screening test for endogenous Cushing’s syndrome. In normal individuals, serum cortisol levels will be less than 1.8 μg/dL with this test. Measurement of 24-hour urinary free cortisol serves as an important confirmatory test. False-positive responses may occur with obesity, major depression, treatment with estrogen, or alcoholism, among other conditions. Discrimination of these conditions from true Cushing’s syndrome may be aided by measurement of plasma cortisol after suppression of ACTH secretion by dexamethasone, followed by stimulation with ovine CRH. For discrimination among the several causes of endogenous Cushing’s syndrome, various tests are available, including computed tomographic (CT) and magnetic resonance imaging (MRI) of the adrenal glands and pituitary, and measurement of cortisol levels after administration of ovine CRH, metyrapone, or graded doses of dexamethasone. In patients with ACTH-dependent endogenous Cushing’s syndrome, the aforementioned techniques may not distinguish unequivocally between pituitary and ectopic sources of ACTH. In this circumstance, determination of ACTH levels in the inferior petrosal sinuses may be required. Efforts should be made to replenish potassium, and if a hypokalemia is present, should be given anticoagulant prophylaxis for surgery and procedures. Hypertension associated with Cushing’s disease is usually treated with agents that block the effects of angiotensin II, often angiotensin-converting enzyme (ACE) inhibitors. Because hypokalemia is present in some patients with Cushing’s syndrome, diuretics must be prescribed with great care. Efforts should be made to replenish potassium, and if a diuretic is used, potassium-sparing diuretics or potassium supplementation in excess of what might be ordinarily required should be considered. In patients with hypokalemia, cardiac glycosides should be used with caution.
Disorders of Mineralocorticoids

Pathophysiology

Hyperaldosteronism was once thought to be rare. However, recent epidemiologic data suggest that autonomous secretion of aldosterone with suppression of the renin-angiotensin system is present in up to 30% of individuals with hypertension. Hyperaldosteronism may arise from an adrenal adenoma or from bilateral adrenal hyperplasia. A similar syndrome caused by an excess of 11-desoxycorticosterone or other mineralocorticoids can develop in patients with functioning adrenal tumors, Cushing's disease, ectopic ACTH syndrome, and the 11β-hydroxylase or 17α-hydroxylase varieties of congenital adrenal hyperplasia. Other conditions that produce a similar clinical picture include [1] glucocorticoid-remediable hypertension, caused by inappropriate production of mineralocorticoids by the adrenal zona fasciculata; [2] the syndrome of apparent mineralocorticoid excess, caused by action of cortisol on renal mineralocorticoid receptors owing to impaired renal inactivation of cortisol; and [3] Liddle's syndrome, owing to excessive renal reabsorption of sodium and excretion of potassium, caused by mutations in the epithelial sodium channel.

In addition to the relationship of aldosterone secretion to hypertension, physiologic levels of mineralocorticoids may play an important role in heart disease. The high affinity [type 1] mineralocorticoid receptor, which has been identified in the heart, binds cortisol and mineralocorticoids with equal affinity. Hormonal specificity is provided by local type II 11β-hydroxysteroid dehydrogenase (11β-HSD), an enzyme that inactivates cortisol by converting it to cortisone. As cardiac activity of 11β-HSD is low, both cortisol and aldosterone can bind to these receptors. In sodium-loaded rats, mineralocorticoids produce myocardial hypertrophy and fibrosis. Both experimental and clinical evidence suggest that aldosterone has roles in the pathophysiology of hypertension, inflammation, and endothelial dysfunction [reviewed elsewhere].

Clinical Manifestations

The major clinical consequences of hyperaldosteronism are systemic arterial hypertension, hypokalemia, and metabolic alkalosis. Although not essential for the diagnosis of hyperaldosteronism, hypokalemia is important because it can predispose to development of frequent and complex ventricular arrhythmias. Polyuria and muscular weakness are other significant consequences of hypokalemia. Primary hyperaldosteronism may lead to LV hypertrophy and diastolic dysfunction, but malignant arterial hypertension is unusual.

Diagnosis

The most useful screening procedure for primary hyperaldosteronism is measurement of plasma renin and aldosterone in a patient with systemic arterial hypertension. An elevated ratio of aldosterone to renin (the exact number depends on the assay for renin) suggests the diagnosis, which can be confirmed by lack of suppression of serum or urinary aldosterone during volume expansion or salt loading. Elevation of both renin activity and circulating aldosterone suggests secondary hyperaldosteronism associated with renal vascular disease, or with renal or cardiac failure. For the patient with primary hyperaldosteronism, it is important to discriminate adrenal adenoma from bilateral hyperplasia. Several tests have been developed for this purpose, including [1] CT of the adrenal glands; [2] measurement of the precursor steroid, 18–hydroxycorticosterone, which is usually markedly elevated in patients with adenoma; [3] response of plasma aldosterone to standing in the morning, with the level declining in patients with adenoma and rising in patients with hyperplasia; and [4] bilateral adrenal vein catheterization, with determination of ratios of aldosterone to cortisol.

Treatment

Surgical removal leads to cure of hypertension only in about 30% to 60% of patients with aldosterone-producing adrenal adenomas. Clinical attributes associated with successful surgery include age under 45 years, less than 5 years' duration of hypertension, absence of a family history of hypertension, preoperative treatment with two or fewer anti-hypertensive drugs, and preoperative response to spironolactone. Medical therapy provides adequate control of hypokalemia and hypertension for patients with bilateral adrenal hyperplasia, and for many individuals with adrenal adenomas. Hyperaldosteronism can be treated with a competitive inhibitor of mineralocorticoid action, either spironolactone or eplerenone. Spironolactone has antiandrogenic activities that may produce gynecomastia and impotence, especially when doses greater than 200 mg/day are required. Eplerenone, which lacks these side effects, has recently been approved for clinical use [reviewed elsewhere]. In patients whose primary hyperaldosteronism is caused by bilateral hyperplasia, surgery is not usually effective. Therefore, treatment with spironolactone and other appropriate antihypertensive agents is preferred. Every effort should be made to replete serum potassium.

Antagonism of mineralocorticoid action appears to have benefits in situations other than primary aldosteronism. In randomized clinical trials, treatment with mineralocorticoid receptor antagonists has reduced mortality in patients with severe CHF treated optimally with diuretics and ACE inhibitors, and among individuals with left ventricular dysfunction following myocardial infarction. The results of these clinical trials suggest that cardiac mineralocorticoid receptors are physiologically significant in humans. The role of mineralocorticoid receptor antagonism in treatment of heart disease has recently been reviewed. Hyperkalemia is a major side effect of treatment with mineralocorticoid antagonists, particularly when they are used in combination with ACE inhibitors or angiotensin receptor blockers, and in patients with diabetes and impaired renal function. When treating heart disease with mineralocorticoid antagonists, the clinician must remain alert to the risk of potentially dangerous hyperkalemia.
Diseases of the Adrenal Medulla: Pheochromocytoma

Pathophysiology

Pheochromocytomas are tumors derived from chromaffin cells of the sympathetic nervous system, usually in the adrenal medulla (90% in adults and 70% in children). Their most important secretory products are the catecholamines norepinephrine and epinephrine. Biochemically and physiologically, the adrenal medulla is an integral part of the sympathetic nervous system. The location of adrenal medullary cells is associated with their ability to form epinephrine, as glucocorticoids secreted from the cortex pass in high concentration directly to the medulla, inducing the synthesis of phenylethanolamine-N-methyltransferase, the enzyme that converts norepinephrine into epinephrine. Catecholamines stimulate glycogenolysis, gluconeogenesis, and lipolysis, inhibit secretion of insulin, increase systemic vascular resistance, and exert positive inotropic and chronotropic actions on the myocardium.

The prevalence of pheochromocytoma was less than 0.05% in an autopsy series from Sydney, close to 0.5% in patients tested for hypertension, 1.9% in patients screened biochemically for suspicion of pheochromocytoma, and 4.2% among those with incidentally discovered adrenal nodules. In at least 10% of patients, the tumor is discovered incidentally during CT or MRI of the abdomen.

The prevalence of malignancy in sporadic adrenal pheochromocytoma is 9%, however, up to 36% of pheochromocytomas can be malignant depending on the genetic background and location of the tumor. Ten percent of patients have metastatic disease at the time of initial diagnosis. Ten percent of pheochromocytomas in adults and 35% in children are bilateral. Pheochromocytomas occur as part of a hereditary syndrome in up to 25% of patients. Approximately 5% of pheochromocytomas are inherited as part of one of the multiple endocrine neoplasia type II (MEN-II) syndromes, in which bilateral pheochromocytomas and medullary carcinoma of the thyroid coexist. The MEN-IIa syndrome may include hyperparathyroidism, and the MEN-IIb syndrome includes marfanoid habitus and multiple mucosal neuromas of the tongue, lips, gastrointestinal tract, or conjunctivae, usually without parathyroid disease.

In the MEN-II syndromes, bilateral adrenal pheochromocytomas are the rule and mutations in the ret proto-oncogene on chromosome 10 can usually be identified. Pheochromocytomas may also coexist with the phakomatoses, including neurofibromatosis and von Hippel-Lindau disease, which includes, in addition, cerebellar or retinal hemangioblastomas, and renal and pancreatic tumors.

Extraadrenal pheochromocytomas arising from the sympathetic ganglia are also called paragangliomas. About 85% of them are intraabdominal. Cardiac paragangliomas are extremely rare with about 50 cases reported in the literature. They have a characteristic appearance on transesophageal echocardiography.

Clinical Manifestations

Pheochromocytoma is a rare cause of systemic arterial hypertension in humans, but the morbidity and mortality associated with these tumors is significant. These tumors produce paradoxical or sustained hypertension, often with postural hypotension, tachycardia inappropriate to the level of blood pressure, headaches, palpitations, chest pain, arrhythmias, profound sweating, signs of hypermetabolism, glucose intolerance, or hypertension after abdominal trauma or surgery. In a patient with hypertension, the coexistence of headache, sweating, and palpitations is highly suggestive of pheochromocytoma. In patients with pheochromocytoma, systemic arterial hypertension is typically paroxysmal but may be fixed. Postural hypotension is common, caused by reduction of plasma volume or impairment of sympathetic reflexes.

Electrocardiographic and echocardiographic manifestations in patients with pheochromocytoma are usually the result of systemic arterial hypertension. Electrocardiographic signs include evidence of LV hypertrophy, LA enlargement, left axis deviation, nonspecific ST-T wave changes, and ventricular and atrial arrhythmias. Occasionally, the ECG suggests the presence of myocardial ischemia during attacks of hypertension. The echocardiogram often demonstrates LV hypertrophy with relatively normal LV function. During a hypertensive crisis, the echocardiogram may demonstrate systolic anterior motion of the anterior leaflet of the mitral valve ("SAM pattern") and paradoxical septal motion. The most common cardiovascular causes of death are arrhythmias and the consequences of systemic arterial hypertension, including strokes.

Hypertrophic cardiomyopathy or a clinical picture indistinguishable from idiopathic dilated cardiomyopathy have been described. The chronic cardiomyopathy seems to depend on persistently high circulating levels of catecholamines because surgical removal of the tumor leads to significant improvement of cardiac function. Autopsy studies have demonstrated the presence of myocarditis in about half of patients who die from pheochromocytoma. Histologic findings include focal necrosis with infiltration of inflammatory cells, perivascular inflammation, and contraction band necrosis. Scattered areas of fibrosis are also found.

Diagnosis

Hypertensive patients with any of the clinical problems noted above should be evaluated for pheochromocytoma, as detection may be lifesaving. Tests commonly employed for diagnosis include measurement of urinary catecholamines, vanillylmandelic acid (VMA), fractionated and total metanephrines, and measurement of serum catecholamines and plasma free metanephrines (metanephrine and normetanephrine). Vanillylmandelic acid and metanephrines are metabolites of catecholamines. Plasma-free metanephrines have sensitivity of 97% and 99% and specificity of 96% and 82% in detecting hereditary and sporadic disease, respectively. Urinary total metanephrines offer slightly higher specificity but are less sensitive, while fractionated urine metanephrines have sensitivity similar to the plasma-free
metanephrines but lower specificity, especially for the detection of sporadic disease.\textsuperscript{152} In patients with paroxysmal hypertension, it is helpful to collect the urine and blood samples when blood pressure is elevated. In patients with equivocal results, clonidine suppression testing might be of further help.\textsuperscript{148}

Imaging techniques for localization of pheochromocytoma include CT, MRI, nuclear scanning with \textsuperscript{123}I or \textsuperscript{131}I-metaiodobenzylguanidine (MIBG), somatostatin receptor imaging (SRI), and positron emission tomography (PET). Computed tomography has a sensitivity of 93\% to 100\% for detecting adrenal pheochromocytomas \textsuperscript{149} and about 90\% for extraadrenal disease.\textsuperscript{150} Magnetic resonance imaging is superior for the detection of extraadrenal, juxtacardiac, and juxtavascular tumors.\textsuperscript{131,151} Both imaging methods have poor specificity, as low as 50\%.\textsuperscript{152} Therefore, it is critically important to establish the diagnosis with biochemical tests, before proceeding to imaging studies. MIBG scanning is especially helpful for patients who have already had surgery and those who have malignant pheochromocytoma or tumors at unusual locations. Although not sensitive enough to exclude pheochromocytoma (77\%–90\%), MIBG is highly specific (95\%–100\%).\textsuperscript{149,153–156} SRI has poor sensitivity (25\% for adrenal pheochromocytoma) but may be particularly helpful for metastatic disease,\textsuperscript{154} paragangliomas, and MIBG scanning-negative disease.\textsuperscript{153,156} PET using \textsuperscript{6-}[\textsuperscript{18}F]fluorodopamine is a recently introduced method that offers excellent visualization of primary and metastatic pheochromocytoma.\textsuperscript{157,158}

**Treatment**

Pharmacologic therapy should be initiated as soon as the diagnosis of pheochromocytoma is made, to minimize the risk of life-threatening hypertensive crisis or arrhythmia. Adequate control of arterial blood pressure is mandatory before initiation of any diagnostic or therapeutic procedures, especially surgery to remove the pheochromocytoma. Traditionally, phenoxybenzamine hydrochloride has been used at an initial dose of 10 mg every 12 hours, which is gradually increased every 2 to 3 days until arterial blood pressure is normalized. Selective \(\alpha\)-receptor antagonists are acceptable alternatives, because they do not produce reflex tachycardia and have shorter duration of action and reduced duration of postoperative hypotension.\textsuperscript{130,159} During treatment with \(\alpha\)-adrenergic antagonists, sodium intake should be liberalized, as untreated patients are chronically volume depleted. One must be careful to detect postural hypotension associated with hypovolemia.\textsuperscript{136,160}

\(\beta\)-receptor blocking agents may help in patients who have significant tachycardia, palpitations, and catecholamine-induced arrhythmias. However, it is important to establish \(\alpha\)-adrenergic blockade before commencement of \(\beta\)-receptor blockade. If \(\beta\)-receptor blockade is begun before establishment of adequate \(\alpha\)-receptor blockade, severe hypertension may occur as a result of unopposed \(\alpha\)-adrenergic stimulation associated with the increase in circulating catecholamines.

Calcium channel antagonists have been shown to control blood pressure and symptoms of pheochromocytoma. They can be used as alternatives to \(\alpha\)-receptor antagonists or can be combined with selective \(\alpha\)-receptor antagonists. They reduce catecholamine production\textsuperscript{161} and inhibit norepinephrine mediated action on vascular smooth muscle.\textsuperscript{162} They may prevent catecholamine-induced coronary vasospasm and myocarditis, so they can be especially useful in managing patients with cardiovascular complications. They can be used safely in normotensive patients with episodes of paroxysmal hypertension.\textsuperscript{130}

Surgical removal of the tumor can be accomplished after adequate blood pressure control is obtained. The anesthesiologist should be experienced in the management of these patients, with special regard to treatment of intraoperative tachyarrhythmias. Hypotension after tumor excision should be treated with aggressive volume repletion.

**Diabetes Mellitus**

**Pathophysiology**

Diabetes mellitus is not a single disease but rather is a constellation of metabolic and pathologic abnormalities, with a variety of causes. Type 1 diabetes is caused by immunologically mediated destruction of the \(\beta\) cells of the pancreatic islets of Langerhans.\textsuperscript{163–165} Susceptibility to type 1 diabetes is determined by human leukocyte antigen (HLA) genotype,\textsuperscript{166} with the destructive process being triggered by some envi-
environmental event, perhaps viral infection. Patients with type 1 diabetes mellitus may develop other endocrine manifestations of organ-specific autoimmunity, including chronic lymphocytic thyroiditis, Graves’ disease, and idiopathic adrenal insufficiency. Type 1 diabetes exhibits a predilection for Caucasians, and extreme geographic variability of prevalence. Since the peak incidence is during adolescence, type 1 diabetes has been called juvenile diabetes, although new cases occur throughout life, even into old age. Patients with type 1 diabetes usually eventually develop absolute deficiency of insulin, so they are prone to develop ketoacidosis unless treated regularly with exogenous insulin.

In the United States, over 90% of patients with diabetes are characterized by strong hereditary predisposition unrelated to HLA type, and association with aging and obesity. This presentation of diabetes has been termed “type 2” but may be etiologically heterogeneous. Type 2 diabetes is the most common form of diabetes throughout the world. In the United States, it is the most prevalent form of diabetes among white people of European descent. Its prevalence is greater still among Native Americans, African Americans, and Mexican Americans. This form of diabetes is not accompanied by any detectable immunologic attack on the pancreas. Because the hyperglycemia is stable and does not lead to metabolic decompensation, type 2 diabetes may be present for a long time prior to diagnosis. Studies of the prevalence of retinopathy suggest that the mean duration of type 2 diabetes prior to diagnosis is at least 4 to 7 years.

The pathophysiology of type 2 diabetes includes both insulin resistance, that is, impairment of the action of insulin, and abnormal secretion of insulin, especially in response to hyperglycemia. However, these patients usually have detectable and often substantial circulating insulin levels, especially early in the course of the disease. Although insulin secretory capability tends to decline over many years, most patients do not require exogenous insulin to prevent metabolic decompensation. Ketoacidosis ordinarily occurs only in the context of a stressful event, such as severe infection or infarction of an organ. The metabolic features of diabetes, which vary in severity from individual to individual, are those that are characteristic of inadequacy of insulin action. These abnormalities include (1) inadequately restrained catabolism of stored glycogen, triglycerides, and protein; (2) inappropriately increased gluconeogenesis; (3) decreased fractional utilization of circulating glucose by skeletal muscle and adipose tissue; and (4) accelerated ketogenesis in patients with absolute deficiency of insulin. These changes result in hyperglycemia, hyperlipidemia, and, in severe cases, net catabolism of protein.

People with diabetes are especially prone to develop atherosclerotic disease, particularly coronary heart disease. The risk factors for initiation and progression of atherosclerosis are similar to those for development of type 2 diabetes, suggesting common pathogenetic mechanisms. The metabolic syndrome, known also as insulin resistance syndrome and syndrome X, consists of a set of physiologic attributes that share the property of being risk factors both for atherosclerotic events and for development of type 2 diabetes mellitus. These attributes tend to cluster in individuals, suggesting pathophysiologic linkage. For a given person, the risk of a cardiovascular event is related to the number of components of the metabolic syndrome exhibited by that person. The metabolic syndrome may be viewed as the set of metabolically related risk factors that predispose to atherosclerotic disease. The primary abnormality has not been identified with certainty, although visceral obesity, insulin resistance, and inflammation are strong possibilities. Population surveys have shown this cluster of abnormalities to be present in about 85% of people with type 2 diabetes mellitus over the age of 50 years in the United States. In type 2 diabetes mellitus, much of the elevated cardiovascular risk seems to be attributable to the high prevalence of the metabolic syndrome.

Obesity is a key component of the metabolic syndrome. Mounting evidence suggests that adipose tissue plays an important role in linking energy surplus and obesity to cardiovascular disease. Fat cells are not mere repositories for passive storage of excess fuel. They are metabolically highly active, and secrete a variety of mediators, known as adipokines, that influence the heart and circulation as well as insulin action. The known adipokines include tumor necrosis factor-α [TNF-α], plasminogen activator inhibitor-1 [PAI-1], interleukin-6 [IL-6], and monocytic chemotactic protein-1 [MCP-1], which may contribute to systemic prothrombosis and generation of inflammatory mediators that may promote atherosclerosis.

Table 108.1. Components of the metabolic syndrome

| Abdominal obesity |
| Dyslipidemia |
| Small, dense LDL particles |
| Low HDL-cholesterol |
| Hypertriglyceridemia |
| Hypertension |
| Insulin resistance |
| Hyperglycemia |
| Proinflammatory state |
| Prothrombotic state |

Leptin is an adipokine, circulating levels of which inversely to obesity and insulin resistance. Moreover, clinical studies have shown low circulating adiponectin to be correlated with atherosclerotic events, suggesting that adiponectin protects against cardiovascular risk. Another recently described secretory product of fat cells is visfatin, which interacts with insulin receptors and mimics some of the actions of insulin; its physiologic role has not been elucidated.

Premenopausal women with hyperandrogenism tend to be insulin resistant and to exhibit increased numbers of
cardiovascular risk factors, including elevated LDL cholesterol, hypertriglyceridemia, hypertension, increased waist circumference, and reduced adiponectin levels. Some studies have found increased arterial calcification and plaque in such individuals. Accordingly, hyperandrogenism seems to be linked to the metabolic syndrome. The relationship between excessive androgens and insulin resistance is complex. On the one hand, hyperandrogenism is part of the phenotype of impaired insulin receptor function, probably mediated by elevated circulating insulin, and treatments that improve insulin sensitivity tend to reduce androgen levels [reviewed elsewhere]. On the other hand, treatments that lower circulating androgens tend to improve insulin sensitivity to some extent.

Clinical Manifestations

The prevalence of diabetes mellitus is high, and rising. It is estimated that the lifetime risk of developing diabetes mellitus for an individual born in the United States in 2000 is on the order of 35% to 40%, and higher among women than men. The risk is especially high among Hispanic individuals, 45% and 52% for men and women, respectively. Moreover, diabetes mellitus is an important cause of death. Current United States mortality data suggest that the diagnosis of diabetes implies a 30% to 50% reduction of an individual's remaining life expectancy. The major causes of death and disability in patients with diabetes include [1] atherosclerosis, manifested by occlusive coronary, cerebral, and peripheral vascular disease; [2] glomerulosclerosis leading to chronic renal failure; [3] arterial hypertension, which exacerbates cerebral vascular disease, renal insufficiency, and heart failure; [4] congestive heart failure, related to hypertension and ischemic heart disease; [5] peripheral and autonomic neuropathies; [6] proliferative retinopathy, the most common cause of blindness among working-age adults in the United States; and [7] metabolic decompensation, including ketoacidosis and nonketotic hyperosmolar hyperglycemia. Microvascular disease produces widening of basement membranes of capillaries in the retina, conjunctiva, glomerulus, brain, pancreas, and myocardium. The clinical significance of these capillary lesions has not yet been fully elucidated. There is considerable evidence that control of hyperglycemia, hypertension, and dyslipidemia can help prevent the ocular, renal, neurologic, and vascular lesions that account for most of the death and disability in patients with both type 1 and type 2 diabetes.

Type 2 diabetes tends to occur in individuals who are already burdened with various cardiovascular risk factors, including central adiposity; dyslipidemia consisting of elevated triglycerides, low HDL cholesterol, and small, dense LDL-cholesterol particles; hypertension, systemic inflammation, and a thrombotic tendency as indicated by elevated levels of circulating PAI-1. In animal models, experimentally induced diabetes results in ventricular dysfunction that may be at least partially corrected by the administration of insulin. Diabetic rats or rabbits develop a cardiomyopathy manifested functionally by decreased contractility, with slowing of both contraction and relaxation. These changes occur within a few months of induction of diabetes, and can be reversed by treatment of the diabetic animals with insulin for 4 weeks. In other experimental models, treatment with insulin does not correct abnormalities of ventricular function. Therefore, the explanation for development of cardiomyopathy in diabetes remains unclear.

There is an increased risk for development of CHF in the diabetic patient, as established in the Framingham Study. This increased risk is present even when patients with prior coronary or rheumatic heart disease are excluded and the influences of age, blood pressure, weight, and cholesterol are taken into consideration. This argues for the existence of a diabetic cardiomyopathy. Noninvasive studies have revealed a variety of abnormalities in diabetic patients, including...
increased fractional shortening during systole, asynchronous of early diastole, and slowed diastolic filling. These observations suggest that, at least in some individuals, there is a cardiomyopathy not based on the presence of myocardial ischemia. In patients with diabetes and cardiomyopathy, common histologic abnormalities are interstitial fibrosis [Fig. 108.3A], arteriolar hyalinization and narrowing of the lumina of intramyocardial arterioles, and with interstitial deposition of periodic acid-Schiff (PAS)-positive glycoproteins (Fig. 108.3B). Diabetic dogs and humans exhibit diastolic dysfunction associated with interstitial deposition of periodic acid-Schiff (PAS)-positive glycoproteins (Fig. 108.3C).

The combination of diabetes and hypertension seems to promote accelerated development of CAD and cardiomyopathy. Rats with experimental renovascular hypertension and diabetes develop myocardial fibrosis and hypertrophy, as well as microvascular abnormalities. These anatomic lesions are not seen in normotensive diabetic animals. Treatment with diltiazem reduces mortality in hypertensive diabetic rats, suggesting a pathogenic role for intracellular calcium. Other factors that may contribute to abnormalities in LV function in diabetics include hypertension, increases in GH that develop in patients with difficult-to-control diabetes, which may play a role in the increased collagen deposition in the LVs of some diabetics, and an alteration in calcium transport associated with increased sarcolemmal Ca-adenosine triphosphatase (ATPase) activity.

In patients with diabetes, cardiovascular disease, hypertension, and nephropathy are closely interrelated. Nephropathy evolves over decades, beginning with glomerular hyperfiltration, followed by excretion of progressively greater amounts of plasma proteins, and culminating in renal failure. Thickening of mesangial matrix is characteristic of diabetic nephropathy, particularly in the glomerular tuft, where nodular glomerulosclerosis may be found. Microalbuminuria, defined as consistent excretion of more than
Diabetes mellitus is diagnosed by measurement of circulating glucose levels. The glycemic criteria for diagnosis of diabetes have recently been revised \(^{279}\) (Table 108.2). For example, reproducible fasting plasma glucose levels of greater than 126 mg/dL (7 mM) are considered diagnostic of diabetes. However, the cutoff values should not be interpreted too strictly, as there is no absolute definition of diabetes. Serum glucose values are continuously distributed in the population. \(^{280}\) Epidemiologic studies show an increased burden of cardiovascular events including death, among people with diabetes mellitus (reviewed elsewhere \(^{275}\)) and progression of diabetic nephropathy. \(^{207},208\) Peripheral vascular disease is a significant problem for patients with diabetes mellitus \(^{276}\) and is a major factor leading to lower extremity amputation. \(^{277}\) Arteries in the legs below the knees are more likely to be involved by atherosclerosis in patients with diabetes than in those without diabetes. \(^{278}\) Noninvasive testing with ultrasound is more sensitive than medical history or physical examination for detection of peripheral arterial insufficiency. \(^{279}\) Cerebral vascular disease and infarction occur more frequently in people with diabetes. The renal vasculature may be affected by atherosclerosis in large vessels and by thickening of capillary basement membranes.

### Diagnosis

Diabetes mellitus is diagnosed by measurement of circulating glucose levels. The glycemic criteria for diagnosis of diabetes have recently been revised \(^{279}\) (Table 108.2). For example, reproducible fasting plasma glucose levels of greater than 126 mg/dL (7 mM) are considered diagnostic of diabetes. However, the cutoff values should not be interpreted too strictly, as there is no absolute definition of diabetes. Serum glucose values are continuously distributed in the population. \(^{280}\) Epidemiologic studies show an increased burden of cardiovascular events including death, among people with diabetes mellitus (reviewed elsewhere \(^{275}\)) and progression of diabetic nephropathy. \(^{207},208\) Peripheral vascular disease is a significant problem for patients with diabetes mellitus \(^{276}\) and is a major factor leading to lower extremity amputation. \(^{277}\) Arteries in the legs below the knees are more likely to be involved by atherosclerosis in patients with diabetes than in those without diabetes. \(^{278}\) Noninvasive testing with ultrasound is more sensitive than medical history or physical examination for detection of peripheral arterial insufficiency. \(^{279}\) Cerebral vascular disease and infarction occur more frequently in people with diabetes. The renal vasculature may be affected by atherosclerosis in large vessels and by thickening of capillary basement membranes.

<table>
<thead>
<tr>
<th>TABLE 108.2. Criteria for the diagnosis of diabetes mellitus</th>
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<tbody>
<tr>
<td>Symptoms of diabetes and a casual plasma glucose &gt;200 mg/dL.</td>
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<tr>
<td>The classic symptoms of diabetes include polyuria, polydipsia,</td>
</tr>
<tr>
<td>and unexplained weight loss.</td>
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<tr>
<td>Casual is defined as any time of day without regard to time</td>
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<tr>
<td>since last meal.</td>
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<tr>
<td>OR</td>
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<tr>
<td>Fasting plasma glucose ≥126 mg/dL.</td>
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<tr>
<td>Fasting is defined as no caloric intake for at least 8 hours.</td>
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<tr>
<td>OR</td>
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<tr>
<td>Two-hour plasma glucose ≥200 mg/dL during an oral glucose</td>
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<tr>
<td>tolerance test.</td>
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<tr>
<td>The glucose tolerance test should be performed as described by</td>
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<tr>
<td>the World Health Organization, using a glucose load</td>
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<tr>
<td>containing the equivalent of 75 g anhydrous glucose dissolved</td>
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<tr>
<td>in water. The patient should consume a high-carbohydrate</td>
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<tr>
<td>diet for 3 days prior to performance of the test.</td>
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<tr>
<td>In the absence of unequivocal hyperglycemia, these criteria</td>
</tr>
<tr>
<td>should be confirmed by repeat testing on a different day.</td>
</tr>
</tbody>
</table>

20 µg of albumin per minute or more than 30 µg of albumin per milligram of creatinine in a random urine specimen, \(^{263}\) is an index of diabetic nephropathy that precedes declining excretory function. The presence of microalbuminuria predicts cardiovascular mortality \(^{264},265\) as well as development of renal failure. \(^{266},269\) Arterial hypertension \(^{207},208\) and dyslipidemia \(^{273},274\) are major risk factors for development and progression of diabetic nephropathy.

Peripheral vascular disease is a significant problem for patients with diabetes mellitus \(^{275}\) and is a major factor leading to lower extremity amputation. \(^{276}\) Arteries in the legs below the knees are more likely to be involved by atherosclerosis in patients with diabetes than in those without diabetes. \(^{278}\) Noninvasive testing with ultrasound is more sensitive than medical history or physical examination for detection of peripheral arterial insufficiency. \(^{279}\) Cerebral vascular disease and infarction occur more frequently in people with diabetes. The renal vasculature may be affected by atherosclerosis in large vessels and by thickening of capillary basement membranes.

### Prevention and Treatment

The Diabetes Prevention Program showed that intensive lifestyle modification, including dietary intervention and an exercise program, delayed or prevented onset of type 2 diabetes in a diverse group of high-risk individuals with impaired glucose tolerance. \(^{286},287\) In high-risk individuals with insulin resistance, progression from normoglycemia to overt diabetes mellitus appears to be related to declining insulin secretary responsiveness. In this situation, drugs that reduce demand for insulin might potentially block the development of hyperglycemia. In the Diabetes Prevention Program, treatment with metformin was effective, but less so than the lifestyle program. One study has shown that treatment with a thiazolidinedione seemed to slow the rate of decline of pancreatic insulin secretary capability in some women with a history of gestational diabetes. \(^{289}\) If this observation is confirmed in other populations, this class of drugs may be helpful for prevention of type 2 diabetes.

Control of blood glucose levels is important for the prevention or retardation of the development of long-term morbidity and mortality in people with diabetes mellitus. \(^{211},212\) Randomized clinical trials involving patients with both type 1 and type 2 diabetes have shown convincingly that intensive management of glycemia improves outcomes with regard to onset and progression of nephropathy, retinopathy, and neuropathy. \(^{206},209\) It is less clear whether glycemia is closely related to progression of atherosclerosis. \(^{207},209\)

A randomized, prospective study of patients with type 2 diabetes has shown that intensive treatment of blood pressure reduced complications related to diabetes. \(^{290}\) A recent study has shown that intensive combined management of blood pressure, albuminuria, lipids, and glycemia reduced the risk of atherosclerotic and microvascular events by about 50%, among patients with type 2 diabetes mellitus and microalbuminuria. \(^{211}\) The relative importance of each of the individual interventions remains to be elucidated.

Observational evidence suggests that hyperglycemia contributes to mortality among hospitalized patients. \(^{292}\) One randomized study showed that vigorous treatment of capillary glucose levels greater than 110 mg/dL, irrespective of any prior diagnosis of diabetes, reduced mortality in an intensive care unit from 8% to 4.6%. \(^{293}\) A recent meta-analysis implied that treatment with insulin reduces mortality among critically ill patients. \(^{294}\) A randomized, prospective study of patients admitted to the hospital with myocardial infarction, the Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study, showed improved in-hospital and postdischarge survival when hyperglycemia was treated aggressively with insulin and the patients were sent home on insulin, compared with “usual care.” \(^{295}\)

In patients with type 1 diabetes mellitus, diet and insulin therapy are critical to management of hyperglycemia. For
patients with type 2 diabetes mellitus, diet and regular exercise can improve insulin resistance. Several oral agents, including sulfonylureas, meglitinides, metformin, glycosidase inhibitors, and thiazolidinediones, alone or in combination, may be effective in lowering glycemia. For reasons unknown, over time there is continuing decline of pancreatic secretory capability in type 2 diabetes, so treatment with insulin eventually becomes necessary for many patients. Insulin may be given alone, or combined with oral hypoglycemic agents.

Treatment with thiazolidinediones increases circulating adiponectin and reduces levels of inflammatory markers, suggesting that these drugs might inhibit progression of atherosclerosis. A recent study showed a very modest reduction of cardiovascular events, coupled with increased risk of hospitalization for heart failure, in patients treated with pioglitazone. Treatment with thiazolidinediones tends to promote fluid retention, perhaps owing to vasodilatation or increased vascular permeability. About 5% of individuals treated with thiazolidinediones and insulin develop clinically significant edema. A recent retrospective survey found that 4.5% of patients on thiazolidinediones developed heart failure, versus 2.6% of those not on thiazolidinediones, over 8.5 months’ mean observation. The treatments were not assigned randomly, so it is not possible to estimate the risk of heart failure attributable to thiazolidinediones. However, clearly thiazolidinediones should be given very cautiously to patients at risk of development of heart failure. The American College of Cardiology and American Diabetes Association have recently published joint guidelines concerning this issue.

Attempts at tight glycemic control entail a substantially increased risk of hypoglycemia, especially among individuals with type 1 diabetes, or advanced type 2 diabetes with minimal endogenous β-cell function. Patients being treated intensively with insulin may have few or no warning signs of hypoglycemia (hypoglycemic unawareness), as well as impaired spontaneous recovery from hypoglycemia (hypoglycemic unresponsiveness). This may add to the risk for hypoglycemic brain damage. Much of this problem seems to be related to impairment of the autonomic response to hypoglycemia by prior episodes of hypoglycemia. Clinical studies have shown partial restoration of hypoglycemic awareness and responsiveness by scrupulous avoidance of hypoglycemia. Hypoglycemia during sleep has been linked to fatal cardiac arrhythmia—the “dead in bed” syndrome. The mechanism of arrhythmia has been postulated to be prolongation of the Q-T interval owing to sympathetic activation. The electrophysiologic changes can be prevented by infusion of potassium or β-adrenergic blockade.

It is important to choose antihypertensive drugs carefully. Guidelines for choosing antihypertensive drugs have been published. β-adrenergic blocking agents reduced complications in patients with type 2 diabetes but may entail special risks for patients with type 1 diabetes who are attempting strict blood sugar control. In such patients these drugs, especially the nonselective β-blockers such as propranolol, may contribute to hypoglycemic unresponsiveness. In patients with preserved hypoglycemic responsiveness, β-blockers will blunt the tachycardia but not the diaphoretic response to hypoglycemia. Furthermore, nonspecific β-blockers may diminish pancreatic secretion of insulin, impair the responsiveness of tissues to insulin, elevate circulating triglycerides, and reduce plasma levels of HDL cholesterol. One must also be careful with diuretic therapy, which can cause deterioration of insulin resistance in patients with type 2 diabetes mellitus.

Patients with diabetes should be screened for microalbuminuria, defined as consistent excretion of more than 20 μg of albumin per minute or 30 μg of albumin per milligram of creatinine in a random urine specimen. Currently, many clinicians consider inhibition or blockade of the renin-angiotensin-aldosterone system to be the strategy of first choice for treatment of albuminuria and hypertension in patients with diabetes. Angiotensin-converting enzyme inhibitors reduce albuminuria, prevent or retard the progression of diabetic nephropathy, and reduce mortality. Angiotensin II receptor antagonists also reduce albuminuria effectively, and provide further reduction of albuminuria when combined with ACE inhibitors. It is not yet known whether angiotensin II receptor antagonists confer a survival benefit. Patients started on ACE inhibitors or angiotensin II receptor antagonists should be checked for development of hyperkalemia and deterioration of glomerular filtration.

Among patients with diabetes, hyperlipidemias appear to respond to the same dietary measures and drugs that are appropriate for nondiabetics. In patients with type 1 diabetes, excellent blood sugar regulation with insulin can produce normal circulating lipoprotein levels. Some recently published clinical trials confirm that reduction of LDL cholesterol levels by treatment with statins reduces the risk of cardiovascular events among people with diabetes. Based on this information, an expert panel has recommended an LDL cholesterol goal of <100 mg/dL for individuals with diabetes, with a more stringent goal of <70 mg/dL being a reasonable option for those at very high risk. It should be noted that nicotinic acid may exacerbate insulin resistance, requiring intensification of glycemic management.

Disorders of Calcium Metabolism

Pathophysiology

Maintenance of the concentration of ionized calcium in extracellular fluid (ECF) within narrow limits is essential for normal neuromuscular excitability and for preservation of skeletal mass. The major hormonal regulator of ECF calcium is parathyroid hormone (PTH), a single-chain polypeptide of 84 amino acids. Its rate of secretion is inversely proportional to the concentration of ionized calcium over the physiologic range of calcium values in ECF. The relationship between extracellular ionized calcium and secretion of parathyroid hormone is governed by a calcium-sensing receptor protein, which is expressed on the surfaces of parathyroid and renal tubular cells. The primary physiologic effect of PTH is...
to increase the concentration of ionized calcium in ECF. This is a result of augmentation of bone resorption, reduction of the fractional urinary excretion of filtered calcium, and stimulation of phosphaturia. In addition, PTH elevates serum calcium concentration by increasing the rate of conversion of 25–hydroxyvitamin D to 1,25–dihydroxyvitamin D, which enhances gastrointestinal absorption of calcium.

Parathyroid hormone has a number of actions on the cardiovascular system, some but not all of which are mediated by hypercalcemia. Given in vivo or in vitro, PTH produces an increased heart rate, positive inotropic action, and cardiac hypertrophy. These changes are believed to result from entry of calcium into cardiac cells and from increased release of endogenous myocardial norepinephrine. Calcium and PTH-mediated activation of the protein kinase C cascade produces hypertrophic and metabolic effects on the cardiomyocyte. If PTH mediates excessive entry of calcium into cardiac muscle cells, it may also cause necrosis and depressed ventricular function. In addition, PTH has a direct vasodilatory effect on vascular smooth muscle, although it has not been established whether this is a physiologically relevant action of the hormone.

The major causes of hypercalcemia include primary hyperparathyroidism, secretion of osteolytic factors (e.g., prostaglandins, cytokines, or PTH-related protein) from a variety of neoplasms, excessive formation of 1,25–dihydroxyvitamin D by the granulomas of sarcoidosis or chronic infections such as tuberculosis, and the milk-alaki syndrome caused by ingestion of calcium and absorbable alkali.

Primary hyperparathyroidism involves the excessive production of PTH. In many patients, primary hyperparathyroidism is asymptomatic and is discovered as an incidental result of routine laboratory testing. It is most often caused by a solitary parathyroid adenoma. Less frequently, there is generalized parathyroid hyperplasia or carcinoma of the parathyroid gland. The hypercalcemia associated with MEN-I and -II is usually caused by parathyroid hyperplasia. Germ line mutations that decrease the sensitivity of the calcium-sensing receptor, also cause hypercalcemia. Heterozygotes for such mutations have an alteration in the set-point for regulation of PTH secretion, known as familial hypocalciuric hypercalcemia. Secondary hyperparathyroidism, most commonly associated with renal disease, gastrointestinal malabsorption, or a disorder of vitamin D economy, arises from chronic hypercalcemic stimulation of PTH secretion, resulting in hyperplasia of the parathyroid glands.

Hypocalcemia most often arises from renal insufficiency with hyperphosphatemia, inadequate secretion of PTH (hypoparathyroidism), cellular resistance to the action of PTH [pseudohypoparathyroidism], or some disorder of vitamin D economy. The most important causes of hypoparathyroidism are surgical removal of the glands, usually as the unintended result of operations on the thyroid, and idiopathic hypoparathyroidism, often reflecting immunologically mediated destruction as part of one of the polyglandular autoimmune syndromes. Common problems with vitamin D include dietary deficiency, malabsorption, or some derangement in the multiorgan, multienzyme sequence that produces the final active metabolite, 1,25–dihydroxyvitamin D. Hypovitaminosis D is a widespread health problem, particularly in the elderly and individuals with darker skin.

### Clinical Manifestations

The typical manifestations of hypercalcemia include polyuria, nocturia, nausea, vomiting, constipation, nonspecific joint and back pain, renal stones, nephrocalcinosis, and renal failure. There is also decreased neuromuscular excitability. In patients with very long-standing or severe hyperparathyroidism, elevation of serum alkaline phosphatase, osteopenia, localized brown tumors of bone, and spontaneous fractures may occur, caused by the effects of PTH on bone. In addition, elevation of urinary cyclic adenosine monophosphate reflects a direct effect of PTH on the kidneys.

Some hypercalcemic patients develop systemic arterial hypertension. The precise mechanisms responsible for hypertension in such patients are unclear, as the levels of serum calcium are similar in those who are normotensive and those with hypertension. Increased serum calcium may render vascular smooth muscle more sensitive to agents, such as angiotensin II and norepinephrine. In patients with hypertension and hyperparathyroidism, the hypertension is not always reversible after surgical correction.

Hypercalcemia impairs urinary concentrating ability (nephrogenic diabetes insipidus), leading to volume depletion. Deposition of calcium in the renal parenchyma may further impair renal function. Chronic hypercalcemia can lead to ventricular hypertrophy even in the absence of hypertension, and to deposition of calcium in the fibrous skeleton of the heart, the valvular tissue, coronary arteries, and myocardial fibers. The probability of extracellular deposition of calcium salts in the heart, lungs, kidneys, and other organs may be estimated by the product of circulating calcium and phosphorus. When the Ca × P (each in mg/dL) product is greater than 60, there is a risk of metastatic calcification; Ca × P products over 75 indicate a severe risk. Increases in extracellular calcium lead to subsequent increases in intracellular calcium and may provoke arrhythmias, including fibrillation in isolated cardiac muscle cells. Marked hypercalcemia shortens the Q-T interval and may lead to ventricular arrhythmias and sudden death in humans.

Patients with primary hyperparathyroidism are reported to have overrepresentation of cardiovascular death in population studies. Postulated mediators of this phenomenon include hypertension, disturbances in the renin-angiotensin system, cardiac arrhythmias, structural and functional abnormalities of the vascular wall and cardiac muscle, insulin resistance, and hyperlipidemia. Whether asymptomatic primary hyperparathyroidism confers increased mortality remains to be determined.

Hypocalcemia typically produces tetany and other manifestations of neuromuscular hyperexcitability. The ECG effects of hypocalcemia include prolongation of the Q-T interval and arrhythmias, especially torsades de pointes. In addition, decreases in gastrointestinal motility are often present. Hypoparathyroidism may cause a dilated cardiomyopathy, presumably secondary to hypocalcemia. In these situations, hypomagnesemia and reduced circulating PTH may also contribute. Hypovitaminosis D causes rickets in children and osteomalacia in adults. It has also
been linked with increased risk of hypertension, congestive heart failure, multiple sclerosis, cancer, and type 1 diabetes mellitus.

Diagnosis

Evaluation of a hypercalcemic patient should begin with measurement of the ionized fraction of circulating calcium. If ionized hypercalcemia is confirmed, the next step in differential diagnosis should be determination of PTH dependence by measurement of intact PTH with a second-generation immunoradiometric assay that is highly specific for the full length 84-amino-acid peptide. The combination of hypercalcemia and unequivocally elevated PTH levels most often indicates parathyroid adenoma or hyperplasia. However, one should exclude the diagnosis of familial hypocalciuric hypercalcemia (vide supra). This autosomal dominant condition is characterized by moderate hypercalcemia with some elevation of PTH levels. Heterozygotes exhibit a benign course, usually without renal or osseous complications, and require no specific treatment. Although the parathyroid glands are usually hyperplastic, parathyroidectomy is of no benefit in familial hypocalciuric hypercalcemia. The keys to diagnosis are ascertainmet of other affected family members and measurement of urinary calcium excretion. In patients with familial hypocalciuric hypercalcemia, the ratio of calcium to creatinine clearances is less than 0.01.

In a hypocalcemic patient, hypoparathyroidism can be confirmed by demonstration of inappropriately low serum PTH concentration together with an increased serum phosphorus level. If the PTH level measured by a full-length second-generation immunoradiometric assay is not low, one should search for another cause of hypocalcemia.

In hypovitaminosis D, serum 25-hydroxyvitamin D concentration is low, but circulating 1,25-dihydroxyvitamin D may be normal. Serum calcium usually remains in the normal range due to compensatory elevation of PTH.

Treatment

Owing to the use of multichannel screening tests, hyperparathyroidism is frequently discovered in individuals who are relatively asymptomatic. Many of these asymptomatic patients pursue a relatively benign course, without development of renal insufficiency, urinary stones, or significant bone disease. At present there is no reliable criterion for prospective identification of this subset of patients. The consensus of experts is that if the patient’s operative risk is reasonable, parathyroidectomy is recommended for patients with any of the following conditions:

- Serum calcium concentration greater than 1 mg/dL above the upper limits of normal
- Twenty-four-hour urinary calcium greater than 400 mg
- Creatinine clearance reduced by more than 30% compared with age-matched subjects
- Low bone density of lumbar spine, hip, or radius
- Age younger than 50 years
- Medical surveillance is not desired or possible

Hyperparathyroid patients who do not undergo surgery should be followed closely, with periodic measurements of serum calcium and PTH, creatinine clearance, calcium excretion, and bone mineral density.

Calcimimetics are a new class of medications that interact with the calcium-sensing receptor on the parathyroid cell. They increase the sensitivity of the receptor to extracellular calcium ions and inhibit the release of parathyroid hormone. Cinacalcet, a second-generation ligand of this class, has been approved for the treatment of hypercalcemia in patients with parathyroid cancer or for dialysis patients with secondary hyperparathyroidism. A recent double-blind randomized clinical study showed that treatment with cinacalcet maintained normocalcemia over 40 weeks in a group of patients with primary hyperparathyroidism. Drugs of this type may become a useful alternative to parathyroidectomy in patients with primary hyperparathyroidism.

The first step in medical treatment of moderate or severe symptomatic hypercalcemia of any cause should be restoration of extracellular volume with isotonic fluids. After volume expansion, cautious intravenous administration of a diuretic such as furosemide will promote excretion of calcium. If these measures do not lower the serum calcium satisfactorily, several effective drugs are available. These include subcutaneous calcitonin and bisphosphonates such as intravenous pamidronate. Glucocorticoids are employed for treatment of hypercalcemia caused by excessive circulating 1,25–dihydroxyvitamin D or by some hemato logic malignancies. Hemodialysis remains an option in cases of life-threatening hypercalcemia unresponsive to initial medical management. Treatment of hypertension or edema in patients with hypercalcemia should not be commenced by thiazide diuretics, which promote renal reabsorption of calcium and thereby elevate the serum calcium concentration.

In patients with hypoparathyroidism, supplementation of calcium is provided by the administration of calcium, and vitamin D or one of its metabolites to enhance the intestinal absorption of calcium. Hypovitaminosis D can be treated with oral vitamin D (ergocalciferol), 50,000 IU weekly for 8 weeks and maintenance doses after that.

Hypothyroidism

Pathophysiology

Approximately 90% of normal thyroidal hormone secretion is in the form of thyroxine (T₄), which is thought to be a prohormone. About 99.98% of circulating T₄ is bound with high affinity but reversibly to plasma proteins, primarily thyroxine-binding globulin (TBG) and secondarily transthyretin (thyroxine-binding prealbumin). Thyroid hormone action is exerted principally by triiodothyronine (T₃), which is formed by 5′-deiodination of T₄ in the liver and other target tissues. The major actions of T₃ are believed to be mediated by interaction with specific receptors in cell nuclei. T₃ receptors, of which several variants have been described, are members of the steroid receptor superfamily. Initiation of hormonal effects involves a three-way interaction among T₃, T₃ receptors, and specific base sequences of DNA. As a consequence of this binding, alterations occur in gene
transcription and protein synthesis, leading to many of the biochemical and metabolic effects observed with administration of thyroid hormone.

The actions of thyroid hormones on the cardiovascular system have been extensively studied. Thyroid hormones increase cardiac contractility and heart rate. Increased whole-body oxygen consumption, decreased systemic vascular resistance, expansion of blood volume, and direct effects of thyroid hormone on the myocardium all may play roles in mediation of these responses. Some investigators have reported that thyroid hormone increases cardiac sensitivity to catecholamines, but this effect remains controversial. At the cellular level, thyroid hormone increases the activity of plasma membrane Na,K-ATPase, perhaps by stimulation of synthesis of enzyme subunits. This action results in augmented hydrolysis of adenosine triphosphate (ATP) at the site of the sarcolemmal sodium pump, which stimulates cellular oxygen consumption. Thyroid hormone also affects other cellular processes, including transport of glucose and calcium and synthesis of myosin. The net effect of thyroid hormone on sarcolemmal calcium transport is to enhance myocardial relaxation. In rats and rabbits, treatment with thyroid hormone increases the amount of the mobile cardiac myosin isoenzyme [V_i], whereas the slower V_v myosin isoform is reduced. This effect is less prominent in human myocardium. The augmented myosin ATPase activity of the hyperthyroid heart appears to contribute to the enhanced contractile response, since the activity of this enzyme regulates the rate of turnover of actin-myosin cross-bridge linkages in cardiac muscle. The influence of thyroid hormone on myosin isoenzymes appears to be localized primarily in the ventricles. Hypothyroidism induces the opposite effects.

Thyroid hormone also increases peak tension development while shortening the duration of contraction in ventricular muscle. These effects may be related to a more rapid intracellular calcium transient, owing to an increase in the number of slow calcium channels with accelerated reuptake of calcium by the sarcoplasmatic reticulum. Some have suggested that the effects of thyroid hormone on protein synthesis and on myosin isoenzymes in the heart are results of changes in cardiac work rather than direct hormone actions.

Hypothyroidism is caused by reduced secretion of thyroid hormones, usually as a consequence of destruction of the thyroid gland, often mediated by an autoimmune process, and sometimes following thyroidal surgery or treatment with 131I. Occasionally, hypothyroidism results from decreased secretion of TSH, owing to pituitary or hypothalamic disease. With secondary hypothyroidism, the signs and symptoms associated with deficiency of other pituitary hormones are often present. Subclinical hypothyroidism resulting from mild thyroid failure is defined as an elevated serum TSH concentration with free T4 in the reference range.

The antiarrhythmic drug amiodarone has complex effects on pituitary-thyroid physiology. Patients who receive it are subjected to an immense pharmacologic overload of iodine, which makes up 37% of the weight of the drug. Amiodarone is stored in adipose tissue, from which iodide is slowly released into the circulation by slow deiodination. Amiodarone, in common with other organic iodides, inhibits the peripheral and pituitary forms of 5′-deiodinase, the enzymes that convert T4 to T3. This releases TSH secretion from feedback inhibition by circulating T4, and slows the clearance of T4 from the circulation. The normal physiologic response to amiodarone includes elevation of circulating T4 levels, as well as increases of plasma TSH, which usually return to normal after about 3 months of treatment. Additionally, amiodarone may produce hypothyroidism or thyrotoxicosis. In countries with abundant environmental iodine, such as the United States, amiodarone-induced hypothyroidism is more common than thyrotoxicosis. Amiodarone may cause an increase in intrathyroidal Ia-positive T cells, an abnormality found in patients with spontaneous Graves’ disease. T-cell abnormalities disappear after discontinuation of amiodarone. Amiodarone may also produce a syndrome of painful inflammatory thyroiditis.

Clinical Manifestations

Hypothyroidism is twice as common among women as men. The peak of incidence is between the ages of 30 and 60 years. Characteristic symptoms include cold intolerance, dryness of the skin, weakness, impairment of memory and intellectual function, personality change, constipation, hoarseness, and menstrual abnormalities. A case-control study showed that individual symptoms such as fatigue are poor discriminators, but combinations of symptoms may identify hypothyroid individuals. Typical physical findings include cool, dry skin, slowed mentation and speech, facial puffiness, and nonpitting edema (myxedema) of the lower extremities. Myx edema reflects a generalized tendency to accumulation of mucopolysaccharide-rich interstitial fluid, which may also be manifested as puffiness of the face and eyes, ascites, pleural or joint effusions, and pericardial effusion (see later). Other classic findings include delayed relaxation of skeletal muscle, as manifested in the Achilles tendon reflex, and development of a yellowish hue to the skin, resulting from decreased conversion of carotene to vitamin A.

Classical cardiovascular physical findings include bradycardia, cardiac enlargement, distant heart sounds, weak arterial pulses, and nonpitting peripheral edema. Electrocardiographic findings include sinus bradycardia, atrioventricular and intraventricular conduction defects, and low voltage. Although hypothyroidism prolongs the cardiac action potential and QT interval, potentially predisposing to cardiac irritability, ventricular arrhythmias and in rare cases torsades de pointes arrhythmias are infrequent in hypothyroid patients.

Hemodynamically, the hypothyroid state is characterized by bradycardia, decreased myocardial contractility, and increased total peripheral resistance. Blood and plasma volumes are reduced, as are stroke volume and cardiac output. Overt hypothyroidism is associated with higher blood pressure in patients with systemic hypertension. Ten percent to 25% of hypothyroid patients have diastolic hypertension, which combined with the increase in vascular resistance increases cardiac afterload. Although cardiac enlargement is typical, overt CHF is uncommon. When it occurs, CHF is caused by dilated cardiomyopathy. Another important cause of cardiomegaly in hypothyroidism is pericardial effusion, which occurs in up to 30% of hypothyroid
patients. The effusion is one manifestation of a generalized leakage of protein-rich fluid into interstitial spaces. Cardiac tamponade is unusual but has on occasion been reported as the presenting sign of hypothyroidism. Extensive CAD may be present in hypothyroid patients. Coronary atherosclerosis occurs with twice the frequency in patients with myxedema compared with age-and sex-matched control subjects.

Subclinical hypothyroidism has been reported to be associated with LV diastolic dysfunction at rest and with exercise, impaired flow-mediated vasodilatation indicating endothelial dysfunction, and decreased heart rate variability indicating autonomic dysfunction. Enhanced risk for atherosclerosis and increased cardiovascular risk has been reported, perhaps related to atherogenic lipid abnormalities: mildly increased levels of total cholesterol, LDL cholesterol, and oxidized LDL. However, a recent systematic review did not find adequate evidence linking subclinical hypothyroidism to either cardiac dysfunction or unfavorable cardiovascular outcomes.

Diagnosis

The typical symptoms and physical examination of a patient with hypothyroidism aid in recognition of the condition. However, as is true for hyperthyroidism, in elderly patients some of the classic clinical manifestations of hypothyroidism may be subtle or nonexistent. Hyponatremia, hyperprolactinemia, hyperhomocysteinemia, hyperglycemia, hypercholesterolemia, and hypertriglyceridemia may be caused by hypothyroidism. Hyperthyroid patients may also have elevated skeletal muscle enzymes, including creatine kinase (CK-MM band), lactic dehydrogenase (LDH), and serum glutamic-oxaloacetic transaminase (SGOT, aspartate aminotransferase [AST]). The mechanism by which these skeletal muscle enzymes are increased chronically in patients with hypothyroidism is unclear. Measurements of TSH and of serum free T4 index are the most helpful clinically, with hypothyroidism being diagnostic of primary hypothyroidism. The combination of low serum free T4 index and increased TSH concentration provides the most useful marker of the adequacy of replacement therapy.

Whether persons with subclinical hypothyroidism and serum TSH less than 10 mIU/L should be treated remains controversial. No blinded randomized controlled study has assessed the impact of thyroxine treatment on important clinical end points. Treating heart failure in the patient with myxedema is somewhat more complicated than in euthyroid individuals, because people with myxedema are often unusually sensitive to the effects of cardiac glycosides. Patients with unstable or limiting angina and untreated myxedema pose a particularly difficult clinical problem because angina may be exacerbated or an MI may be caused by too vigorous thyroid hormone replacement. One should replace thyroid hormone very carefully in such individuals, administering small doses as indicated above and initially attempting to make the patient comfortable rather than euthyroid. In the patient with extensive CAD and unstable angina, surgical revascularization can be accomplished in association with low-dose thyroid hormone replacement, followed later by full thyroid replacement during the postoperative period. Perioperative morbidity is only slightly increased for patients with mild to moderate hypothyroidism. Therefore, necessary cardiovascular surgery need not be postponed until the euthyroid state is restored. In the patient with CHF and myxedema without CAD, administration of thyroid hormone carefully and in increasing amounts, in association with the use of a diuretic, salt restriction, and digoxin in appropriately small doses, usually leads to the control of CHF in time.

Acutely or chronically ill patients often have low serum T3 and T4 values without elevation of circulating TSH, a situation known as the “euthyroid sick” syndrome. The thyroid hormone levels are inversely correlated with survival. The low T3 values are secondary to decreased extra-adrenal thyroidal 5′-deiodinase activity, with reduced conversion of T3 to T4. The reduced T4 levels are often related to alterations in protein binding of circulating T4, causing a decrease in total T4 but only minimal changes in the level of physiologically active free hormone. There may also be suppression of TSH release, owing to severe medical illness or drugs such as dopamine. In the euthyroid sick syndrome, the serum TSH is not elevated, but may increase in the recovery period. In difficult cases, further diagnostic discrimination may be obtained by measurement of serum 3,3′,5′-triiodothyronine [reverse T3], the concentration of which typically rises in the euthyroid sick syndrome but declines in hypothyroidism. There is controversy regarding whether individuals with the euthyroid sick syndrome are physiologically hypothyroid, but administration of T4 or T3 does not improve prognosis.

Many patients with acute or chronic cardiac disease exhibit the euthyroid sick syndrome. Within 4 hours after acute MI, T4 and T3 levels are reduced by about 20% and 40%, respectively. In patients with chronic heart failure, circulating thyroid hormone concentration decreases and reverse T3 increases parallel to the degree of functional impairment. Circulating T3 levels fall significantly in the postoperative period of patients undergoing cardiopulmonary surgery or coronary artery bypass. This alteration in thyroid status might modify cardiac gene expression and

Treatment

Patients with hypothyroidism should be treated with T4. Precipitation or worsening of myocardial ischemia during treatment of hypothyroidism is a clinically important problem. Accordingly, most authors recommend a low starting dose of T4 on the order of 0.025 or even 0.012 mg daily, in elderly patients and those predisposed to ischemic heart disease. With such patients, it may be prudent to titrate the dose to less than full replacement levels. For patients at less risk for myocardial ischemia, the starting dose of T4 may be 0.05 mg/day. The dose may be increased every 4 to 6 weeks until the TSH level is normalized. The usual maintenance dose for adults is about 0.1 to 0.125 mg/day. During this treatment, the patient’s cardiovascular condition should be monitored carefully. If there is worsening of angina or a marked increase in heart rate or blood pressure, the dose should be reduced to eliminate these effects. In patients with intact pituitary glands, measure-
contribute to impaired cardiac function. Although some data imply that the administration of T3 may benefit some patients with cardiovascular disease, beneficial effects on major clinical outcome variables have not been conclusively demonstrated.

Hyperthyroidism

Pathophysiology

Thyrotoxicosis, which is defined as the state of excessive circulating thyroid hormone, can have a variety of causes. The most frequent are [1] production of circulating autoantibodies that activate TSH receptors, producing diffuse toxic goiter (Graves’ disease); [2] toxic multinodular goiter or hyperfunctioning solitary thyroid adenoma; [3] subacute thyroiditis; and [4] postpartum and “silent” thyroiditis, probably of autoimmune cause. Less common causes include TSH-secretion of the pituitary, massive overproduction of chorionic gonadotropin or another low-potency thyroid stimulator in patients with hyperemesis gravidarum or trophoblastic neoplasm, and accidental or purposeful ingestion of thyroid hormone (thyrotoxicosis factitia).

Subclinical hyperthyroidism is characterized by subnormal or suppressed serum TSH concentration with circulating thyroid hormones in the reference range. It may be due to dysfunction of the thyroid gland (endogenous subclinical hyperthyroidism) but more often is the consequence of treatment with L-thyroxine (exogenous subclinical hyperthyroidism).

Clinical Manifestations

Patients with thyrotoxicosis typically have heat intolerance, warm, moist skin, brittle nails and hair, tremulousness; irritability and emotional lability; increased appetite; weight loss; resting heart rates greater than 90 beats/min; palpitations; muscle weakness; and menstrual abnormalities. On physical examination, a thyrotoxic patient typically has a very active precordium with a right ventricular [RV] lift, a palpable pulmonary artery, an enlarged heart, and a systolic ejection murmur. The patient may also have brisk reflexes, a prominent stare, lid lag, a wide pulse pressure, and bounding peripheral pulses. Proptosis and paralyses of extraocular muscles, when they occur, point to Graves’ disease as the cause of thyrotoxicosis.

In the young individual, thyrotoxicosis is usually relatively easy to identify, but in elderly patients the typical clinical features may be lacking or far more subtle. Palpable thyroid enlargement or a nodule is present in most patients, but these signs may be absent. Therefore, the diagnosis of thyrotoxicosis may be delayed or overlooked for long periods of time.

Excessive thyroid hormone causes increases in heart rate, cardiac contractility, and pulse pressure. Left ventricular ejection fraction and cardiac output are increased at rest but do not appropriately adapt to exercise due to ineffective and impaired chronotropic, contractile, and vasodilatory cardiovascular reserves. This effect, reversible with restoration of the euthyroid state, can explain the reduced exercise tolerance of hyperthyroid patients. Prolonged exposure to even slightly increased amounts of thyroid hormone can lead to cardiac hypertrophy. High-output heart failure coexists with thyrotoxicosis in some patients. Cardiac dilatation and hypertrophy, markedly increased cardiac output, and ultimately heart failure may develop. The tachycardia of hyperthyroidism appears to arise from the actions of thyroid hormones on several different ion channels in the cells of the SA node. Heart rate variability is attenuated, suggesting impaired autonomic regulation.

Although many of the cardiovascular manifestations of hyperthyroidism resemble a heightened β-adrenergic state, careful physiologic studies have not shown altered sensitivity of the cardiovascular system to adrenergic stimulation.

Atrial fibrillation with rapid ventricular rate is a particular problem. It occurs in 5% to 15% of patients with hyperthyroidism and may be the initial reason for medical evaluation. Although hyperthyroidism is more common in women, atrial fibrillation is more common among men with thyrotoxicosis, and increases in both sexes with advancing age. Atrial fibrillation was reported to occur in more than 25% of thyrotoxic individuals older than 60 years. The prevalence might be falling because hyperthyroidism is diagnosed now at an earlier stage in its natural history. In general, atrial fibrillation is a major risk factor for thromboembolism, especially stroke. About 6% of individuals with thyrotoxicosis and atrial fibrillation have been reported to suffer stroke or transient cerebral ischemia before the thyrotoxicosis is controlled; this is about the same as the risk of cerebral embolism in patients with other causes of atrial fibrillation. It is difficult to estimate the true risk of thromboembolism in thyrotoxic atrial fibrillation, because the arrhythmia is more prevalent in older persons, and age is itself strongly linked to the risk of stroke. The incidence of thromboembolism is highest among patients over 60 years of age and in those with preexisting rheumatic or hypertensive heart disease.

Thyrotoxicosis may provoke or aggravate angina pectoris owing to increased heart rate, or augmented myocardial contractility with attendant increased myocardial oxygen demand. Most patients with angina and thyrotoxicosis have coronary atherosclerosis, but occasionally the coronary arteries are normal on angiography.

In subclinical hyperthyroidism subtle hyperthyroid symptoms might be present. There is growing evidence that subclinical hyperthyroidism has important effects on the heart. A major concern is the increased risk of development of atrial fibrillation, especially in patients with TSH less than 0.1 mIU/L. A recent meta-analysis has shown that subclinical hyperthyroidism is associated with increased heart rate, atrial arrhythmias, increased LV mass with marginal concentric remodeling, impaired ventricular relaxation, reduced exercise performance, and increased risk for cardiovascular death.

Diagnosis

A measurement of serum TSH below the limits of detection by a reliable laboratory using “ultrasensitive” immunoradiometric methodology provides good evidence of thyrotoxicosis. The diagnosis can be confirmed by measurement of...
Circulating thyroid hormones. The serum T4 level is probably a more reliable index of thyrotoxicosis than is the T3 level. Owing to the frequency with which disease or drugs alter binding of T4 and T3 to plasma proteins, one should always obtain an estimate of unbound hormone, such as the free T4 index, free T3 index, or T3 by equilibrium dialysis. If the TSH concentration is low, a high value for one of these indices will confirm the diagnosis of thyrotoxicosis. Measurements of total T4 and T3 in the serum may be misleading, since patients with heart disease or other serious illnesses may have decreased peripheral conversion of T4 to T3 and decreased plasma protein binding of both hormones. As a result, serum total T3 concentration and sometimes total T4 concentration are reduced. Indeed, a normal serum T3 concentration in a patient with severe cardiac disease suggests that thyrotoxicosis may be present.

**Treatment**

Management of thyrotoxicosis caused by Graves’ disease or toxic nodular goiter ordinarily begins with treatment with an antithyroid drug, either propylthiouracil or methimazole. These drugs deplete thyroid stores of T4 and T3 by inhibiting their synthesis. The antithyroid drug should be given for several weeks until a euthyroid state is achieved. For patients with severe cardiac manifestations, such as florid CHF, tachyarrhythmia, or unstable angina, more rapid control may be obtained by concurrent treatment with intravenous iodide, which blocks the secretion of thyroid hormones. Methimazole or propylthiouracil should be given before administration of iodide, to prevent conversion of the iodide to thyroid hormone. After a few days the iodide can be discontinued and the patient can be maintained on the antithyroid drug.

After the patient has been rendered euthyroid with antithyroid drugs, definitive therapy should be undertaken. For patients with Graves’ disease and major cardiac problems, thyroidal ablation with radioactive iodine is a preferred definitive therapy. The antithyroid drug may be resumed several days after administration of radioactive iodine for continued control of symptoms. Ordinarily, several weeks are required for a dose of radioactive iodine to exert its full therapeutic effect. In some patients with Graves’ disease, a prolonged course of antithyroid drug may induce spontaneous remission. Surgery is an acceptable alternative therapy for some patients with Graves’ disease and is often the preferred form of definitive treatment of toxic nodular goiter. After either radioactive iodine or surgery, hypothyroidism often ensues, eventually requiring treatment with T4.

Treatment of subclinical hyperthyroidism is to some degree controversial due to the lack of definitive data. There is limited evidence that treatment may facilitate spontaneous reversion or cardioversion of atrial fibrillation to sinus rhythm. In the case of exogenous subclinical hyperthyroidism, decreasing the levothyroxine dose normalizes the heart rate and results in a nonsignificant reduction of LVEF. Beta-blockers decrease atrial premature beats, LV mass index, and impaired diastolic filling.

Management of amiodarone-induced thyrotoxicosis is an especially vexing problem, for several reasons: (1) hyperthyroidism can exacerbate the patient’s underlying problem with tachyarrhythmias; (2) antithyroid drugs and iodine are frequently ineffective; (3) the operative risk of thyroidectomy is often high, owing to underlying ischemic heart disease; and (4) amiodarone is an antiarrhythmic drug of last resort, so its discontinuation may be dangerous. Amiodarone-induced thyrotoxicosis usually appears after months or years of administration of the drug. There appear to be at least two mechanisms for development of thyrotoxicosis: (1) flooding of iodide into an abnormal gland that has lost its ability to suppress thyroxine production in response to an iodide load, and (2) induction of thyroiditis in a previously normal gland. The former variety of amiodarone-induced thyrotoxicosis may be treated with potassium perchlorate together with antithyroid drugs. Patients with amiodarone-induced thyroiditis have been reported to respond to treatment with glucocorticoids.

The management of CHF with thyrotoxicosis includes reducing volume overload with a diuretic, such as IV furosemide, and providing control of the heart rate when rapid atrial fibrillation exists. Digoxin or another cardiac glycoside can be given to slow the rapid ventricular rate, but in the hyperthyroid patient larger doses than usual are often required. This relative resistance has been attributed to increased clearance of the digoxin, but it may also be due to the need to inhibit the increased number of Na-K-ATPase transport units in cardiac muscle. b-adrenergic blockers such as propranolol help to control heart rate and may be useful, especially in patients without CHF. In the patient with CHF, consideration of using a beta-blocker should be carefully reviewed, since such agents may exacerbate heart failure. The decision as to whether to use the agent in a patient with CHF should be based on the extent to which increased heart rate or high-output state is believed to be the cause of the CHF. Esmolol, a rapidly acting beta-blocker, can be given IV to allow one to determine potential beneficial or detrimental effects of beta-blocking agents in such patients. As an alternative to a beta-blocking agent, a slow calcium channel blocker, such as diltiazem or verapamil, can be used to help control heart rate, although the important negative inotropic action of verapamil must be kept in mind.

Treatment of atrial fibrillation in patients with thyrotoxicosis should be directed at controlling the ventricular rate with cardiac glycosides and often with beta-blockers or the calcium antagonists diltiazem or verapamil. Successful cardioversion with maintenance of sinus rhythm usually cannot be achieved as long as the thyrotoxicosis continues. Spontaneous reversion of the rhythm to sinus usually occurs within 6 weeks after the return of the euthyroid state, although atrial fibrillation may persist in some older patients. One should consider the use of anticoagulant therapy in a patient with hyperthyroidism and atrial fibrillation. Anticoagulant therapy with warfarin reduces the frequency of embolic events in some patients with atrial fibrillation, but it is associated with an increased risk for hemorrhage. Nevertheless, we recommend anticoagulation for patients with atrial fibrillation and thyrotoxicosis with a dilated heart or heart failure and for those whose rhythm alternates between sinus rhythm and atrial fibrillation.
Carcinoid Syndrome

Carcinoid tumors are uncommon neuroendocrine malignancies with an estimated incidence of two to three cases per 100,000 people per year.\(^{552,553}\) More often, these tumors are found incidentally at autopsy.\(^{554}\) Carcinoids arise from enterochromaffin cells, which are widely distributed throughout the body. Approximately 70% of all carcinoid tumors are located in the digestive system, most often in the terminal ileum, appendix or rectum.\(^{552,555}\) The bronchial tree is the second most frequent location.\(^{552}\) The most malignant carcinoid tumors tend to arise from the terminal ileum.

Pathophysiology

Enterochromaffin cells, together with other neuroendocrine cells in the thyroid, lung, pancreas, pituitary, and adrenal medulla, constitute the amine precursor uptake and decarboxylation (APUD) system described by Pearse.\(^{556}\) Depending on their site of origin, carcinoid tumors can have the ability to secrete vasoactive amino acids and peptides. Serotonin (5-hydroxytryptamine, 5-HT) is the most prominent secretory product. Once released, serotonin is metabolized by monoamine oxidases in the liver, lungs and brain to 5-hydroxyindoleacetic acid (5-HIAA).\(^{557}\) However, 5-hydroxytryptophan, bradykinins, histamine, substance P, ACTH, and several other peptides can also be produced by carcinoids.\(^{558,559}\)

Clinical Manifestations

Carcinoid tumors are relatively slow growing. Even with metastatic disease, patients can survive for several years. Unless the secretory products are released directly into the systemic circulation, symptoms are usually not present. The carcinoid syndrome develops in about 50% of patients, principally those with liver metastases or bronchial carcinoids, owing to bypass of first-pass hepatic inactivation of secretory products. The most common clinical elements of the carcinoid syndrome are diarrhea and cutaneous flushes.\(^{559,560}\) Wheezing occurs in a few patients, principally those with bronchial carcinoid. Other endocrine manifestations, such as the ectopic ACTH syndrome, may also be present. Pellagra with dermatitis of sun-exposed areas may also be seen, secondary to the high turnover of nicotinic acid by the tumor. It has not been possible to attribute particular symptoms to specific secretory products, with the exception of diarrhea, which appears related to serotonin.\(^{551,562}\) Rectal carcinoids do not exhibit secretory activity and do not produce the syndrome. The severity of the syndrome is generally correlated with the metastatic tumor burden.\(^{560}\)

Carcinoid crisis with severe flushes, diarrhea leading to dehydration, hypotension, and arrhythmias is a potential life threatening complication. It may be provoked by administration of anesthetics during invasive procedures.

One of the striking endocrine manifestations of the carcinoid syndrome involves the heart. It occurs in 20% to 70% of patients with metastatic carcinoid tumors.\(^{553-555}\) The typical pathologic lesions are spherical white plaques, attached to the luminal surface of the endocardium of the right-sided chambers and of the pulmonic and tricuspid valves, as well as the great veins and coronary sinuses (Fig. 108.4). These lesions contain cells embedded in a collagenous stroma, which is rich in glycosaminoglycans but devoid of elastic fibers.\(^{566,567}\) The secretory product responsible for development of these lesions may well be serotonin itself. There are correlations between the presence and severity of cardiac valvular lesions and levels of circulating serotonin\(^{565}\) as well as excretion of 5-HIAA.\(^{557,568}\) Additionally, treatment of obesity with the serotonin reuptake inhibitors fenfluramine and dexfenfluramine has been found to be associated with an increased risk of development of valvular regurgitation, especially of the aortic valve.\(^{569-571}\) Examination of the affected valves has shown lesions similar to those of the carcinoid syndrome, further strengthening the association between serotonin and valvular disease.\(^{572}\)

**FIGURE 108.4.** (A) View of opened tricuspid valve from a patient with carcinoid syndrome, showing thickening and constriction of leaflets and chordae tendineae, and thickening of the atrial endocardium. (B) View of opened pulmonic valve from the same patient, showing thickened and retracted cusps and constriction of the valvular ring.
The manifestations of carcinoid heart disease are those typical of tricuspid or pulmonic regurgitation, and pulmonic outflow obstruction. Signs and symptoms are those of RV failure secondary to severe dysfunction of tricuspid and pulmonary valves. Clinical features are often subtle early in the disease course (fatigue, exertional dyspnea) and might be attributed to the primary carcinoid disease. Carcinoid patients may also have labile blood pressure with either pronounced hypotension or hypertension, owing to the presence of vasoactive substances in the circulation. Serotonin can lead to tachycardia and hypertensive crisis refractory to conventional treatment. Left-sided carcinoid heart disease may be present in patients with extensive liver metastases, patent foramen ovale, or bronchial or ovarian carcinoids.

Cardiac metastases of carcinoid tumors are mainly intramyocardial but are extremely rare.

Diagnosis

For patients with suspected carcinoid syndrome, the diagnosis can best be confirmed by measurement of excretion of metabolites of serotonin in 24-hour urine collections. For diagnostic purposes, the most important metabolite is 5-HIAA. The specificity of this determination is almost 100% but the sensitivity is reported to be much lower—35%. Urinary 5-HIAA levels can be influenced by food (e.g., bananas, pineapple) or medications. The platelet serotonin concentration might be a more sensitive marker of serotonin excess. Serum chromogranin A, an acidic protein present in the chromaffin granules of neuroendocrine cells, can be used for the detection of functioning as well as nonfunctioning tumors. It offers higher sensitivity but the specificity is lower than urinary 5-HIAA.

Imaging techniques for localization of carcinoid tumors include 111In-pentetreotide scintigraphy and 123I-MIBG scintigraphy, each with sensitivity of 80% to 90%. Combination of these tests increases the sensitivity to 95%. 111In-pentetreotide is a labeled analogue of octreotide with affinity for somatostatin receptors located on the cell membranes of carcinoid tumors. A positive finding with this compound predicts response to octreotide therapy. 123I-MIBG is an analogue of biogenic amine precursors that is taken up by chromaffin cells and stored in the neurosecretory granules. Larger doses of this compound have been used for treatment of metastatic carcinoid tumors. Positron emission tomography with [18F]-fluorodihydroxyphenylalanine ([18F-DOPA] is a new imaging technique with promising results. Computed tomography scanning can be used for visualization of hepatic and extrahepatic abdominal metastases and mediastinal and pulmonary disease. Primary tumors in the small bowel can be demonstrated with barium follow through, although small tumors can easily be missed.

Transthoracic echocardiography remains the cornerstone of diagnosis of cardiac involvement. Right atrial and ventricular enlargement is present in up to 90% of patients with carcinoid heart disease, and ventricular septal wall motion abnormalities are seen in almost half of the cases. Ventricular septal wall motion abnormalities are often thickened and retracted, leading to moderate to severe tricuspid regurgitation. Characteristic pulmonary valve involvement includes immobility of the pulmonary valve leaflets. Pulmonary annular constriction may also occur, resulting in predominant pulmonary outflow tract obstruction. A new development is the measurement of serum natriuretic peptides for early detection of myocardial damage.

Treatment

Treatment of carcinoid tumors usually involves surgical removal of accessible tumor, with removal, chemoembolization, or radiofrequency ablation of hepatic metastases when feasible. Diarrhea can sometimes be controlled with relatively nonspecific medications such as loperamide and codeine. Supplementation of vitamins and nicotinic acid is recommended. Flushes can be reduced by avoiding stress and foods known to provoke them. An important recent advance has been the introduction of the somatostatin analogues octreotide and lanreotide, which control both diarrhea and flushing. They have also been reported to inhibit tumor growth, but reduction in tumor volume is only occasionally observed. Octreotide is administered subcutaneously two to four times daily, whereas lanreotide can be injected less frequently. Long-acting analogues of octreotide are now available. The principal side effects of somatostatin analogues include malabsorption, hypomotility of the gallbladder and formation of gallstones, and mild glucose intolerance.

Interferon-α has been reported to induce biochemical response in 40% of patients. In general, carcinoid tumors are poorly responsive to standard antineoplastic drugs.

Patients with carcinoid heart disease frequently die as a result of severe tricuspid regurgitation rather than carcinomatosis. In one series mean life expectancy was 1.6 years for patients with carcinoid heart disease and 4.6 years in those without cardiac damage. Therefore, consideration should be given to the suitability of a patient for valvular surgery even with metastatic disease. It is usually considered preferable to operate early or soon after the onset of cardiac symptoms, as delay can result in worsening of the right ventricular failure and increase the risk of surgery.

Although surgical mortality is high, there is evidence to support an increase in longevity and quality of life after successful surgery.

Summary

There is increased mortality from cardiovascular disease among adults with hypopituitarism, perhaps related to growth hormone deficiency, which has been linked to known cardiovascular risk factors. Acromegaly is associated with cardiomyopathy, cardiac hypertrophy, hypertension, congestive heart failure, coronary artery disease, and arrhythmias. Successful treatment of acromegaly abolishes the excess mortality associated with the disease.

Arterial hypotension is the most common cardiovascular finding in adrenal insufficiency. Acute adrenal crisis should be treated with “stress” doses of intravenous hydrocortisone. Chronic adrenal insufficiency may require treatment with mineralocorticoids as well as glucocorticoids.
The major cardiovascular abnormalities of Cushing's syndrome are hypertension, myocardial hypertrophy, and a prothrombotic state. Hyperaldosteronism is more commonly linked to hypertension than was previously appreciated. Hypokalemia is an important complication of hyperaldosteronism, but most patients are normokalemic.

There are mineralocorticoid receptors in the heart, and treatment with mineralocorticoid antagonists can benefit individuals following myocardial infarction as well as those with congestive heart failure.

Pheochromocytoma is an uncommon cause of hypertension, but has been found in 4% of individuals with adrenal nodules and hypertension. Once the diagnosis is made, pharmacologic therapy should be started promptly, before invasive procedures or surgery are attempted.

The “metabolic syndrome” is a constellation of metabolic and constitutional abnormalities that includes obesity, insulin resistance, dyslipidemia, hypertension, and prothrombotic and proinflammatory states. This syndrome carries a high risk for development of atherosclerotic disease and type 2 diabetes mellitus. There is increased cardiovascular mortality among individuals with diabetes mellitus. Aggressive treatment of multiple risk factors, including hyperglycemia, hypertension, and dyslipidemia, can prevent cardiovascular events. For critically ill individuals in the hospital, intensive treatment of hyperglycemia reduces mortality.

Patients with primary hyperparathyroidism have excess cardiovascular mortality.

Patients with nontropical illness have low circulating thyroid hormone levels without elevation of TSH, known as the “euthyroid sick” syndrome. Treatment of this syndrome with thyroid hormone does not improve outcomes.

The major cardiovascular findings of hypothyroidism are bradycardia, cardiac enlargement, hypertension, low voltage on the ECG, and sometimes pericardial effusion. “Subclinical hypothyroidism” is associated with increased lipids and cardiac functional abnormalities, but has not yet been conclusively linked to excess cardiovascular events.

Both overt and subclinical hyperthyroidism are linked to atrial fibrillation, especially in older individuals.

The major clinical cardiovascular manifestations of carcinoid syndrome are those of pulmonic regurgitation or stenosis, or tricuspid regurgitation, related to the presence of endocardial plaques, principally on the right side of the heart.

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