in the clinic

Hypothyroidism

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CME Objective: To provide information on the screening, diagnosis, and treatment of hypothyroidism.

The information contained herein should never be used as a substitute for clinical judgment.

Annals of Internal Medicine

Hypothyroidism is a condition in which the thyroid gland cannot make enough thyroid hormone to meet the requirements of peripheral tissues. It is the most common functional disorder of the thyroid gland. Primary hypothyroidism occurs when thyroid failure results from disease of the thyroid gland itself and it accounts for more than 99% of all cases of hypothyroidism (Figure 1). The most common causes of primary hypothyroidism in adults are chronic lymphocytic thyroiditis (Hashimoto disease); radioiodine thyroid ablation; thyroidectomy; high-dose head and neck radiation therapy; and medications, such as lithium, α-interferon, and amiodarone. Central hypothyroidism occurs when thyroid failure results from pituitary or hypothalamic disorders that cause insufficient production of thyroid-stimulating hormone (TSH) by the pituitary gland (Figure 2). The most common causes of central hypothyroidism in adults are tumors, inflammatory conditions, infiltrative diseases, infections, pituitary surgery, pituitary radiation therapy, and head trauma.

Primary hypothyroidism is overt when the serum TSH level is high and the serum total thyroxine (T_4) or free T_4 level is less than the population reference range. Subclinical hypothyroidism is a milder degree of thyroid failure characterized by mildly to moderately increased levels of serum TSH but with total T_4 and free T_4 values still within the population range. The prevalence of overt hypothyroidism is approximately 1% to 2% in women and 0.1% in men (1, 2), whereas subclinical hypothyroidism has been identified in 4% to 10% of different population groups (1, 2) and in up to 18% of elderly persons (1–3). Progression from subclinical to overt hypothyroidism occurs in 5% to 18% of persons with subclinical hypothyroidism per year.

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Screening

Which patients are at elevated risk for hypothyroidism?

Patients at increased risk for hypothyroidism are those who have 1 or more symptoms of thyroid hormone deficiency; a goiter; history of thyroid disease or treatment for a thyroid condition; personal history of other autoimmune diseases, particularly type 1 diabetes mellitus, adrenal insufficiency, or vitiligo; family history of thyroid disease; high-dose head and neck radiation therapy; use of medications, such as lithium, α-interferon, and amiodarone; pituitary surgery; pituitary radiation therapy; or advanced age.

Should clinicians screen nonpregnant patients for hypothyroidism?

Aggressive case finding is recommended for all patients who are at increased risk for hypothyroidism. Screening the rest of the population is controversial, with different organizations making different recommendations (4–9). The U.S. Preventive Services Task Force (6, 7) and a separate multidisciplinary expert panel (8) concluded that evidence is insufficient to recommend for or against population screening. Screening for hypothyroidism has been more strongly advocated by other groups (9).

A computer model–based cost–utility analysis estimated that screening for hypothyroidism is as cost-effective as mammography and other generally recommended screening procedures (4).

Should clinicians screen pregnant women for hypothyroidism?

Screening as part of a prepregnancy or early pregnancy evaluation remains controversial. An expert panel concluded that evidence is insufficient to recommend for or against routine TSH testing but did recommend TSH testing in women with symptoms of thyroid dysfunction, personal or family history of thyroid disease, an abnormal thyroid gland on palpation, or type 1 diabetes mellitus or other

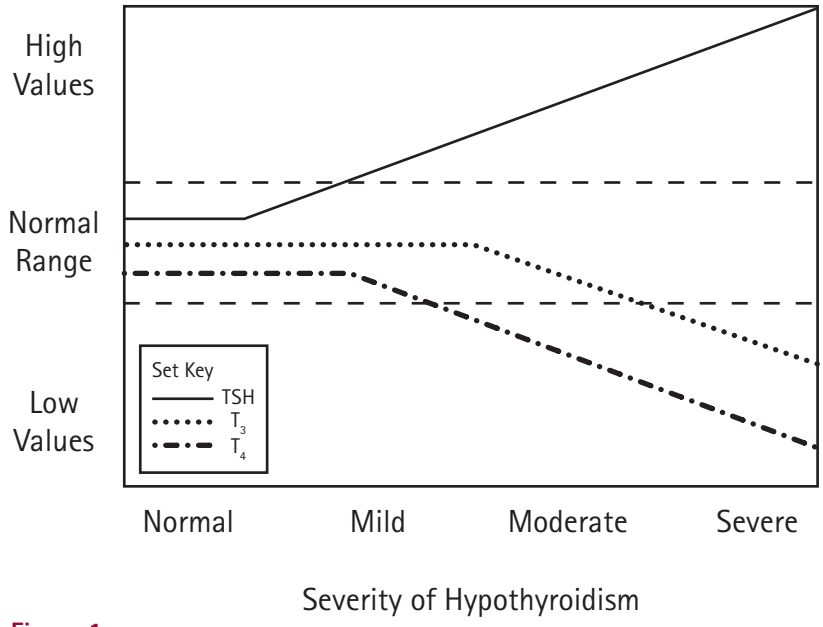

Figure 1
Hormone changes occurring during the development of primary hypothyroidism.

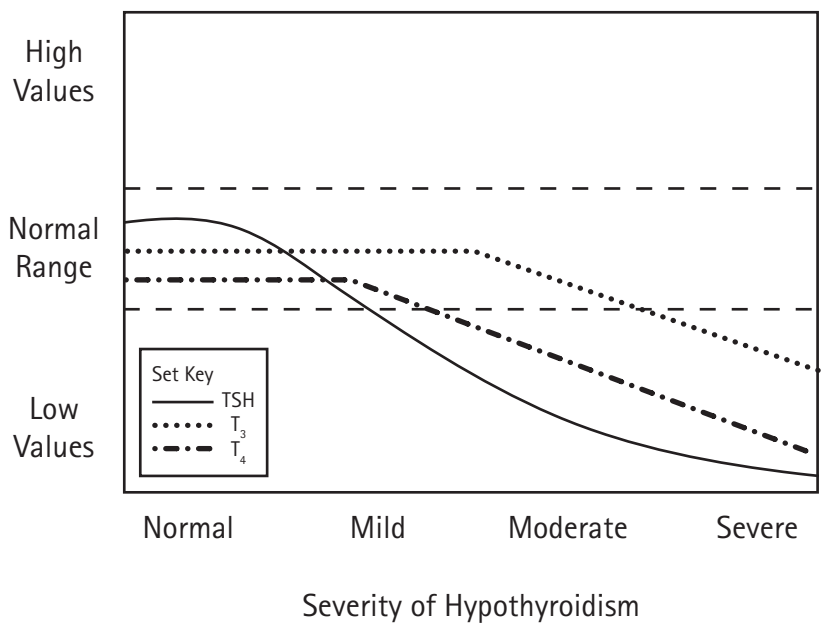

Figure 2
Hormone changes occurring during the development of central hypothyroidism.

autoimmune disorders (8). A separate panel of thyroid experts disagreed with this position and unequivocally recommended routine TSH testing during prepregnancy or early pregnancy examinations in all women (9).

Prospective screening and outcome studies have reported that pregnant women with subclinical hypothyroidism are 3 times more likely to have placental abruption and 2 times more likely to have a preterm delivery (10), that perinatal

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intraventricular hemorrhage and respiratory distress syndrome occur more often in infants of women with subclinical hypothyroidism (10), and that children born to mothers who had untreated or inadequately treated hypothyroidism during pregnancy have lower IQ scores than do children whose mothers were euthyroid during pregnancy (11). A prospective cohort study determined that screening only high-risk patients would miss 30% of pregnant women with hypothyroidism (12).

If clinicians screen for hypothyroidism, which test should they use?

The serum TSH level is the screening test of choice for hypothyroidism because more than 99% of hypothyroidism cases are primary hypothyroidism and an elevated serum TSH level is the first laboratory abnormality to occur in this condition (5, 6).

CLINICAL BOTTOM LINE

Screening... Population screening for thyroid dysfunction is controversial, but aggressive case-finding is appropriate in patients at increased risk for hypothyroidism, such as those who have symptoms of thyroid hormone deficiency; a goiter; history of previous thyroid disease or treatment for a thyroid condition; personal history of other autoimmune diseases, particularly type 1 diabetes mellitus, adrenal insufficiency, or vitiligo; or family history of thyroid disease. Screening should also be considered for all women who are planning a pregnancy or who are pregnant. Serum TSH level is the best screening test for primary hypothyroidism.

Diagnosis

What symptoms should prompt clinicians to consider hypothyroidism as a possible diagnosis?

The most common symptoms of hypothyroidism are fatigue, weakness, lethargy, weight gain, impaired memory, impaired learning, cold intolerance, dry skin, constipation, paresthesias, hoarseness, sleepiness, hair loss, sexual dysfunction, menstrual irregularity, and depression (13, 14).

What physical examination and laboratory findings indicate possible hypothyroidism?

Physical findings most commonly seen in hypothyroidism include hypertension, bradycardia, goiter, periorbital puffiness, dry skin, coarse skin, cold skin, thinning of the lateral eyebrows, and delayed relaxation phase of the deep tendon reflexes (13, 14). Routine laboratory abnormalities that may suggest hypothyroidism include macrocytic anemia, hyponatremia, hypercholesterolemia, and elevated level of serum creatine kinase.

What laboratory tests should clinicians use to diagnose hypothyroidism?

Measurement of the serum TSH level is the best test to diagnose primary hypothyroidism (Table 1) (5). If the TSH level is high, further measurement of the serum free T_4 should be done. A low serum free T_4 in conjunction with an elevated serum TSH level establishes a diagnosis of overt hypothyroidism. If a patient is suspected of having central hypothyroidism, measurement of free T_4 is the test of choice, because TSH level cannot be accurately interpreted in this situation. When central hypothyroidism is identified, magnetic resonance imaging or computed tomography of the pituitary gland and hypothalamus should be ordered.

What other conditions should clinicians consider in patients who present with possible hypothyroidism?

In addition to the causes of hypothyroidism (Table 2), the serum TSH level may be mildly elevated during

Table 1. Laboratory and Other Studies for Hypothyroidism*

Test	*Sensitivity, %*	*Specificity, %*	*Likelihood Positive*	*Likelihood Negative*	*Notes*
TSH	>99	>99	>99	<0.01	
FT_4	90	90	9	0.11	
Total T_4	90	80	4.5	0.12	
Anti-TPO antibodies					Found in >90% of patients with Hashimoto disease
ESR					Elevated in >90% of patients with subacute thyroiditis

ESR = erythrocyte sedimentation rate; FT_4 = free T_4; T_4 = thyroxine; TPO = thyroid peroxidase; TSH = thyroid-stimulating hormone.

** Adapted from Dolan JG, Wittlin SD. Hyperthyroidism and hypothyroidism. In: Black ER, Bordley DR, Tape TG, Panzer RJ, eds. Diagnostic Strategies for Common Medical Problems. 2nd ed. Philadelphia: American Coll of Physicians; 1999:473-83.*

Table 2. Differential Diagnosis of Hypothyroidism

Disease	*Characteristics*	*Notes*
Hashimoto disease	TSH high; TPO antibodies	Slowly progressive
Thyroidectomy	TSH high; history of surgery	Surgical scar
Radioiodine therapy	TSH high; history of 131-I treatment	History of thyrotoxicosis
External radiation therapy	TSH high; history of radiation therapy	History of cancer
Iodine deficiency	TSH high; urine iodine low	Iodine deficient area
Postpartum thyroiditis	TSH high; TPO antibodies	Recent pregnancy
Silent thyroiditis	TSH high; TPO antibodies	Recent thyrotoxicosis
Subacute thyroiditis	TSH high; painful; ESR elevated	Recent thyrotoxicosis
Drug induced	TSH high; use of amiodarone, lithium, interferon, iodine, or thionamides	Medication history
Pituitary/hypothalamic mass	TSH low or normal; FT_4 low; abnormal MRI/CT scan	Headaches, visual field cuts, ophthalmoplegia
Pituitary/hypothalamic surgery	TSH low or normal; FT_4 low	History of surgery
Pituitary/hypothalamic radiation therapy	TSH low or normal; FT_4 low	History of radiation therapy
Pituitary/hypothalamic infiltration/infection	TSH low or normal; FT_4 low; abnormal MRI/CT scan	Headaches, visual field cuts, ophthalmoplegia

CT = computed tomography; ESR = erythrocyte sedimentation rate; FT_4 = free thyroxine; MRI = magnetic resonance imaging; TPO = thyroid peroxidase.

the recovery phase of a variety of nonthyroidal illnesses (15). If a patient with a mildly elevated serum TSH level has recently had such an illness, the TSH level should be rechecked in 6 to 8 weeks. Also, TSH levels may be elevated in the recovery phase of DeQuervain or silent thyroiditis. TSH levels are otherwise elevated only in very rare conditions, such as TSH-secreting pituitary tumors and the syndrome of Generalized Resistance to Thyroid Hormone. Medications, such as glucocorticoids, dopamine, and octreotide, may be associated with transient decreases in TSH level (16).

What is subclinical hypothyroidism, and is it associated with adverse health outcomes?

Subclinical hypothyroidism, or mild thyroid failure, is an elevated serum TSH level with serum free T_4 or total T_4 levels still within the population reference range (17, 18). High TSH level indicates a serum T_4 value that is within the reference range but is lower than normal for that person. The increase in serum TSH stimulates the thyroid gland to compensate, at least temporarily, and produce nearly adequate amounts of thyroid hormone.

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Subclinical hypothyroidism may be associated with various nonspecific symptoms and signs that are similar to but generally milder than those of overt hypothyroidism (2, 17–26). Similarly, subclinical hypothyroidism can result in elevated serum total cholesterol and low-density lipoprotein cholesterol levels (2, 26–28) and abnormal lipoprotein remnant metabolism (29). Mildly impaired thyroid function is also associated with features of the metabolic syndrome, including hypertension, increased waist circumference, elevated serum triglyceride level, low serum high-density lipoprotein cholesterol level, and insulin resistance (30). Subclinical hypothyroidism has been associated with subtle abnormalities of cardiac function (31–35), impaired blood pressure regulation (36), impaired endothelial function (37, 38), increased levels of C-reactive protein (39), increased carotid artery intima-media thickness (40), increased arterial stiffness (41), and increased arterial pulse wave velocity (36). In addition, subclinical hypothyroidism has been associated with abnormal cerebral nerve conduction latency (42) and alterations of cerebral blood flow (43). Although gross neuropsychological function does not seem to be affected (44), working memory has been shown to be impaired (25).

Subclinical hypothyroidism progresses to overt hypothyroidism at a rate of 5% to 18% per year (45). Progression is more likely in patients who have circulating antithyroid antibodies but is most reliably predicted by the magnitude of the TSH elevation (46, 47).

Large cross-sectional and longitudinal observation studies have reported that mild thyroid failure is a significant risk factor for the development of atherosclerosis (31, 48–52) and congestive heart failure (53), although 1 study did not find an increased risk for cardiovascular disorders or mortality (54).

When should clinicians consult with an endocrinologist for patients with possible hypothyroidism?

Consultation with an endocrinologist is recommended when a patient with hypothyroidism has DeQuervain or silent thyroiditis or known or probable coronary artery disease, has cardiac rhythm disturbances, has central hypothyroidism, or is suspected of having myxedema coma. Consultation may also be helpful if the clinician is uncertain about whether an abnormal thyroid hormone profile is the result of hypothyroidism or of a nonthyroidal illness (the euthyroid sick syndrome).

Diagnosis... Patients with hypothyroidism often have a spectrum of clinical features that can be identified by a complete history and physical examination and routine laboratory testing. An elevated serum TSH level is the most reliable laboratory test for the diagnosis of primary hypothyroidism. Measurement of the serum free T_4 level should be done in all patients who have elevated serum TSH levels to determine the severity of the hypothyroidism. When central hypothyroidism is suspected, radiographic imaging of the pituitary and hypothalamus is indicated.

CLINICAL BOTTOM LINE

Treatment

How should clinicians choose drug therapy and dose for hypothyroidism?

Levothyroxine (LT_4) is the treatment of choice because it safely, effectively, and reliably relieves symptoms and normalizes laboratory test results in most patients with hypothyroidism (5, 55, 56). LT_4 is converted to liothyronine

(LT_3) by peripheral tissues at a rate that is appropriate for overall metabolic needs (57). Bedtime LT_4 dosing may normalize serum TSH levels more effectively than morning dosing (58). Residual symptoms may persist in some patients with treated hypothyroidism (59, 60), suggesting that undertreatment may be relatively common. LT_4 is available in several doses, allowing precise titration until the TSH level is within the optimal range. The relatively slow intestinal absorption and long serum half-life of LT_4 produce stable serum TSH, T_4, and T_3 levels with minimal diurnal variation (55, 56).

Prospective intervention studies have determined that the average LT_4 replacement dose in adults with overt hypothyroidism is 1.6 μg/kg per day (61, 62) and that lean body mass is a better predictor of thyroid hormone requirements than total body weight (63).

Young, otherwise healthy patients tolerate initial full doses well and usually obtain rapid relief of symptoms that are due to thyroid hormone deficiency. In obese patients, the initial dose should be calculated by using ideal body weight with subsequent titration of the LT_4 dose every 6 to 8 weeks until the serum TSH level is in the optimal range. Patients with known heart disease and elderly patients, who sometimes have undiagnosed heart disease, may develop dysrhythmias, angina pectoris, or myocardial infarctions when started on full replacement doses or when their dose is increased too rapidly (64). Overt hypothyroidism in a patient older than 60 years should be treated with an initial LT_4 dose of 25 to 50 μg/d and dose increases in 12.5- to 25-μg increments every 6 to 8 weeks until the desired dose is reached.

Does evidence show differences in effectiveness and safety of various thyroid hormone preparations?

No high-quality randomized, controlled trials compare the safety and efficacy of name-brand LT_4 with generic LT_4 products (Table 3). The U.S. Food and Drug Administration (FDA) currently requires all LT_4 preparations to contain between 95% and 105% of the stated amount of LT_4. Some generic LT_4 manufacturers also have shown that, by FDA standards, their products provide blood levels equivalent to the name-brand products, which means that pharmacists can sometimes switch from 1 generic formulation to another without notifying the prescriber. Because of the narrow therapeutic index of LT_4, even small differences in bioavailability between formulations may cause clinical hypo- or hyperthyroidism. Therefore, many experts recommend using LT_4 from a single manufacturer, which is easier to do with name-brand than generic products, especially because the differences in cost are small.

One RCT reported that co-administration of LT_4 and LT_3 (Cytomel) preparations improved some symptoms more than LT_4 alone (65); however, multiple subsequent RCTs using LT_4 and LT_3 in various ratios have not confirmed a beneficial effect of combined LT_4–LT_3 therapy (66, 67).

Combined LT_4–LT_3 products, such as Liotrix and desiccated thyroid, contain a higher fixed ratio of T_4 to T_3 than that of normal thyroid secretions (68, 69). T_3 in these preparations is rapidly absorbed into the circulation and may result in supraphysiologic serum T_3 levels for several hours after administration. This may be particularly hazardous to patients with underlying coronary artery disease or dysrhythmias.

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Table 3. Drug Treatment for Hypothyroidism

Agent	*Mechanism of Action*	*Dosage*	*Benefits*	*Side Effects*	*Notes*
Synthroid (LT_4)	Hormone replacement	1.6 μg/kg per d	Effective, reliable, inexpensive	Thyrotoxicosis if dose is excessive	Consistent potency, first-line agent
Levoxyl (LT_4)	Hormone replacement	1.6 μg/kg per d	Effective, reliable, inexpensive	Thyrotoxicosis if dose is excessive	Consistent potency, first-line agent
Unithroid (LT_4)	Hormone replacement	1.6 μg/kg per d	Effective, reliable, inexpensive	Thyrotoxicosis if dose is excessive	Consistent potency, first-line agent
Generic (LT_4)	Hormone replacement	1.6 μg/kg per d	Effective, inexpensive	Thyrotoxicosis if dose is excessive	Inconsistent potency, not recommended at present
Thyrolar (liotrix)	Hormone replacement	50 μg/12.5 μg or 100 μg/25 μg	T_4/T_3 combination	Thyrotoxicosis if dose is excessive	T_3/T_4 ratio too high, not recommended at present
Desiccated thyroid	Hormone replacement	1–2 grains/d	T_4/T_3 combination	Thyrotoxicosis if dose is excessive	T_3/T_4 ratio too high, not recommended at present
Cytomel (LT_3)	Hormone replacement	5–12.5 μg/d	Pure T_3; short acting	Thyrotoxicosis if dose is excessive	Thyrotoxic T_3 level 2–6 h after dose taken, not recommended at present for most patients
Synthroid (parenteral LT_4)	Hormone replacement	500 μg, then 50–100 μg/d for myxedema coma. 80% of usual oral dose for NPO patients.	Rapid T_4 repletion in myxedema coma. Ensures LT_4 delivery for NPO patients.	Thyrotoxicosis if dose is excessive	Careful monitoring required. Treatment of myxedema coma. Treatment of hypothyroid patients unable to take oral medications
Triostat (parenteral LT_3)	Hormone replacement	50–100 μg, then 10–20 μg q 8–12 h	Rapid T_3 repletion	Thyrotoxicosis if dose is excessive	Careful monitoring required. Treatment of myxedema coma
Hydrocortisone	Adrenal hormone replacement	100 mg IV q 8 h for 2 d	To cover possible decreased adrenal reserve in myxedema	None for short-term use	Treatment of myxedena should be accompanied by administration of intravenous glucocorticoids, support of vital functions, and treatment of any known precipitating events

IV = intravenous; LT_3 = liothyronine; LT_4 = levothyroxine; NPO = nil per os; T_3 = thyronine; T_4 = thyroxine.

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50. Imaizumi M, Akahoshi M, Ichimaru S, et al. Risk for ischemic heart disease and all-cause mortality in subclinical hypothyroidism. J Clin Endocrinol Metab. 2004;89:3365-70. [PMID: 15240616]
51. Walsh JP, Bremner AP, Bulsara MK, et al. Subclinical thyroid dysfunction as a risk factor for cardiovascular disease. Arch Intern Med. 2005;165:2467-72. [PMID: 16314542]

What are the indications for treating subclinical hypothyroidism?

Patients who have serum TSH levels higher than 10 mU/L should be strongly considered for LT_4 treatment (8, 9). Patients with serum TSH levels of 5 to 10 mU/L should also be considered for LT_4 treatment if they have symptoms suggestive of thyroid hormone deficiency, elevated serum low-density lipoprotein (LDL) cholesterol levels, goiters, or positive antithyroid antibodies (10, 11). Patients with subclinical hypothyroidism can be effectively treated with initial LT_4 doses of 25 to 50 μg/d and subsequent daily dose increments of 25 μg until the desired TSH goal is reached.

Patients with subclinical hypothyroidism may experience significant improvement in their various nonspecific symptoms with LT_4 replacement therapy (17–19, 20, 21, 24, 70). Psychological well-being correlates with serum free T_4 levels in patients treated with LT_4 (71). Furthermore, LT_4 treatment improves elevated serum LDL cholesterol concentrations (19, 27, 28, 70), abnormal lipoprotein remnant metabolism (29), elevated levels of C-reactive protein (39), impaired blood pressure regulation, subtle abnormalities of cardiac function (31, 32, 34, 35, 72), increased carotid artery intimamedia thickness (40), increased arterial stiffness (41), impaired endothelial function (37,

38, 70), and abnormal cerebral nerve conduction latency (42). RCTs to determine whether treatment of subclinical hypothyroidism reduces the rate of adverse cardiovascular events or mortality are needed (8, 26).

Most of the evidence showing beneficial effects of LT_4 treatment on symptoms, lipid and lipoprotein profiles and tests of vascular and neurological function in subclinical hypothyroidism comes from RCTs involving patients with TSH levels of 10 mU/L or greater (8, 26). RCT evidence that patients with serum TSH levels of 5 to 10 mU/L show similar improvement in symptoms and lipid profiles with LT_4 treatment is inconclusive (8, 26) but suggestive (70). One observational study reported an unexpected increase in cardiovascular morbidity in patients treated for hypothyroidism (73); however, the authors conceded that this was probably related to atherosclerosis from the preexisting hypothyroidism, inappropriate thyroid hormone dosing, or both (73).

What are the adverse effects of thyroid replacement therapy?

Side effects of proper thyroid hormone replacement, except in rare patients, occur only when the medication is given in excessive doses. Excessive LT_4 doses may result in symptoms of thyrotoxicosis. In elderly patients, LT_4 excess may also cause bone loss and atrial fibrillation.

How should clinicians monitor patients with hypothyroidism?

Clinicians should assess symptoms and signs of hypothyroidism at each follow-up visit for patients on thyroid hormone therapy (Table 4). LT_4 effectively relieves the manifestations of thyroid hormone deficiency in most patients with overt (55, 56) and subclinical (18–21) hypothyroidism. Serum LDL and non–high-density lipoprotein cholesterol levels also decrease with treatment (19, 27, 28, 70, 74). Also, clinicians should evaluate compliance with LT_4 dosing instructions and the use of other medications at each follow-up visit.

Requirements for thyroid hormone replacement may change over time in response to changes in health status and the use of certain medications. Situations in which LT_4 dose requirements increase include pregnancy (75–77); the use of estrogens (78); noncompliance (79); weight gain; malabsorption;

Table 4. Elements of Follow-up for Hypothyroidism

Category	*Issue*	*How?*	*How often?*	*Note*
History	Weakness	Question	Every visit	Improvement expected
History	Lethargy	Question	Every visit	Improvement expected
History	Fatigue	Question	Every visit	Improvement expected
History	Cold intolerance	Question	Every visit	Improvement expected
History	Impaired memory	Question	Every visit	Improvement expected
History	Adherence	Question	Every visit	Adherence essential
History	Other drugs	Question	Every visit	May interfere with LT_4
Physical examination	Dry skin	Palpation	Every visit	Improvement expected
Physical examination	Coarse skin	Palpation	Every visit	Improvement expected
Physical examination	Periorbital puffiness	Inspection	Every visit	Improvement expected
Laboratory	TSH	Measure by second-generation TSH assay	q6–8 wk until normal, 3–6 mo later, then annually	Normal: 0.5–5.0 mU/L; Optimal: 0.5–2.0 mU/L

LT_4 = levothyroxine; TSH = thyroid-stimulating hormone.

52. Rodondi N, Aujesky D, Vittinghoff E, et al. Subclinical hypothyroidism and the risk of coronary heart disease: a meta-analysis. Am J Med. 2006;119:541-51. [PMID: 16828622]
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59. Samuels MH, Schuff KG, Carlson NE, et al. Health status, psychological symptoms, mood, and cognition in L-thyroxine-treated hypothyroid subjects. Thyroid. 2007;17:249-58. [PMID: 17381359]
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64. Becker C. Hypothyroidism and atherosclerotic heart disease: pathogenesis, medical management, and the role of coronary artery bypass surgery. Endocr Rev. 1985;6:432-40. [PMID: 3896769]
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Table 5. Drugs That May Alter Thyroid Hormone Requirements

Drugs that decrease thyroid-hormone absorption
Iron supplements
Calcium supplements
Fiber supplements
Soy supplements
Antacids
Bile acid resins
Raloxifene
Drugs that increase serum T_4–binding proteins
Estrogens
Drugs that enhance T_4 metabolism
Anticonvulsants
Rifampin
Drugs that inhibit T_4 to T_3 conversion
Propranolol
Glucocorticoids
Amiodarone
Lithium
Mechanism unknown
Sertraline
Drugs that may cause thyroiditis
Amiodarone
Interferon
Tyrosine kinase inhibitors (sunitinib)
Drugs that suppress TSH secretion
Bexarotene
Metformin
Octreotide
Dopamine
Glucocorticoids

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

Helicobacter pylori–related gastritis and atrophic gastritis (80); progression of underlying thyroid disease; and the use of medications that decrease LT_4 absorption, increase serum LT_4 binding proteins, enhance LT_4 metabolism, or inhibit T_4 to T_3 conversion (Table 5). LT_4 dose requirements may be decreased by aging (81), self-administration of excess LT_4, androgen use (82), reactivation of Graves disease, or the development of autonomous thyroid nodules.

Prospective observation and intervention trials demonstrated that LT_4 dose requirements increase by nearly 50% during the first trimester of pregnancy (75, 76) and that the increased requirement is greater in patients with previous thyroidectomies than in those with Hashimoto thyroiditis (76, 77).

TSH levels should be used as the guide to thyroid hormone dosage requirements because the serum TSH level is the most accurate indicator of thyroid hormone status (83). Once treatment is started, serum TSH levels should be checked every 6 to 8 weeks and the LT_4 dose adjusted until the TSH value is in the optimal

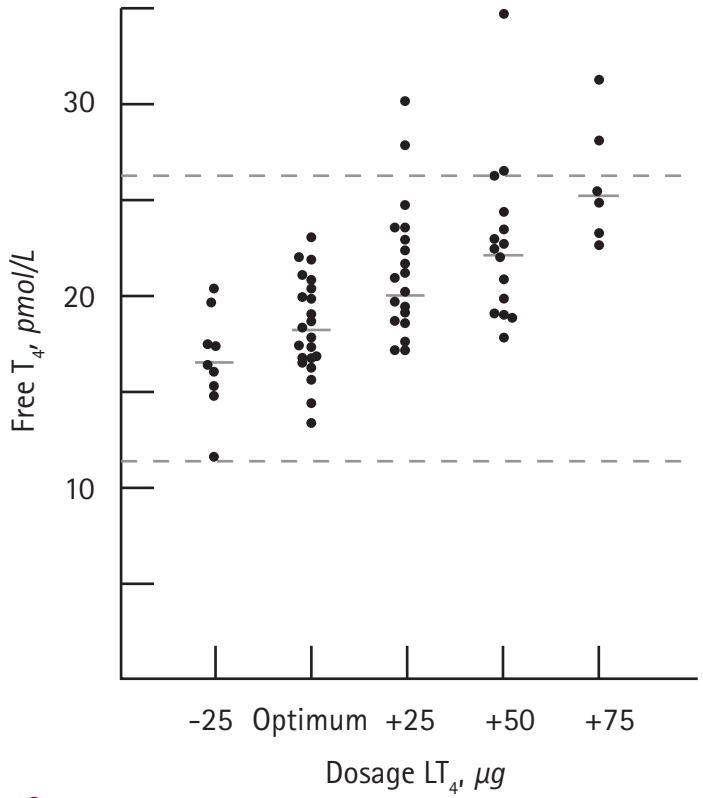

Figure 3

The effect on free T_4 of fine adjustment of LT_4 doses in patients with primary hypothyroidism. Reprinted with permission from Carr D, McLeod DT, Parry G, Thornes HM. Fine adjustment of thyroxine replacement dosage: comparison of the thyrotrophin releasing hormone test using a sensitive thyrotrophin assay with measurement of free thyroid hormones and clinical assessment. Clin Endocrinol (Oxf). 1988;28:325-33.

range; the TSH level should then be rechecked 3 to 6 months later, and annually thereafter. When follow-up serum TSH levels drift outside the normal range, adjusting the daily LT_4 dose by 12.5- to 25-μg will usually return the serum TSH level to normal (84) (Figure 3). The optimal TSH level is 0.5 to 2.0 mU/L, because most persons have TSH levels in this lower end of the population normal range (3).

When should patients with hypothyroidism be hospitalized?

Myxedema coma is a life-threatening condition that is the most severe expression of hypothyroidism (Table 6) (85, 86). It most often occurs in elderly patients who have untreated or inadequately treated hypothyroidism and who then develop a precipitating event, such as use of a drug that suppresses the central nervous system, myocardial infarction, stroke, pulmonary embolus, sepsis, or prolonged exposure to cold temperatures. Without appropriate treatment, the mortality rate of this condition approaches 100%. Patients should be hospitalized in an intensive care unit for intensive monitoring and treatment when they are suspected of having myxedema coma because prompt

68. Rees-Jones RW, Rolla AR, Larsen PR. Hormonal content of thyroid replacement preparations. JAMA. 1980;243:549-50. [PMID: 7351788]
69. Pilo A, Iervasi G, Vitek F, et al. Thyroidal and peripheral production of 3,5,3'-triiodothyronine in humans by multicompartmental analysis. Am J Physiol. 1990;258:E715-26. [PMID: 2333963]
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72. Turhan S, Tulunay C, Ozduman Cin M, et al. Effects of thyroxine therapy on right ventricular systolic and diastolic function in patients with subclinical hypothyroidism: a study by pulsed wave tissue Doppler imaging. J Clin Endocrinol Metab. 2006;91:3490-3. [PMID: 16822817]
73. Flynn RW, Macdonald TM, Jung RT, et al. Mortality and vascular outcomes in patients treated for thyroid dysfunction. J Clin Endocrinol Metab. 2006;91:2159-64. [PMID: 16537678]
74. Ito M, Arishima T, Kudo T, et al. Effect of levo-thyroxine replacement on non-high-density lipoprotein cholesterol in hypothyroid patients. J Clin Endocrinol Metab. 2007;92:608-11. [PMID: 17148561]

Table 6. Key Clinical Features of Myxedema Coma

Element, by Category	*Notes*
History	
Hypothyroidism; undiagnosed, untreated or inadequately treated	The underlying hypothyroidism does not have to be severe
Precipitating factor	
Prolonged cold exposure	Particularly in elderly persons
Sedative use	Particularly in elderly persons
Infection	Particularly in elderly persons
Pulmonary embolus	Particularly in elderly persons
Respiratory failure	Particularly in elderly persons
Myocardial infarction	Particularly in elderly persons
Congestive heart failure	Particularly in elderly persons
Stroke	Particularly in elderly persons
Gastrointestinal bleeding	Particularly in elderly persons
Trauma	Particularly in elderly persons
Surgery	Particularly in elderly persons
Physical	
Hypothermia	
Bradycardia	
Hypotension	
Hypoventilation	
Seizures	
Stupor	
Coma	
Myxedematous skin changes	
Periorbital edema	
Delayed relaxation of reflexes	
Distended abdomen	Ileus
Distended bladder	Urinary retention
Radiology	
Pleural effusions	
Pericardial effusions	
Electrocardiogram	
Low voltage, bradycardia	
Laboratory	
Macrocytic anemia	
Hyponatremia	
Elevated creatine kinase	
Hypercarbia (CO_2 retention)	
Elevated serum thyroid-stimulating hormone	Need not be significantly elevated
Low serum free thyroxine	Need not be significantly depressed

75. Mandel SJ, Larsen PR, Seely EW, et al. Increased need for thyroxine during pregnancy in women with primary hypothyroidism. N Engl J Med. 1990;323:91-6. [PMID: 2359428]
76. Alexander EK, Marqusee E, Lawrence J, et al. Timing and magnitude of increases in levothyroxine requirements during pregnancy in women with hypothyroidism. N Engl J Med. 2004;351:241-9. [PMID: 15254282]
77. Rotondi M, Mazziotti G, Sorvillo F, et al. Effects of increased thyroxine dosage pre-conception on thyroid function during early pregnancy. Eur J Endocrinol. 2004;151:695-700. [PMID: 15588235]
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82. Arafah BM. Decreased levothyroxine requirement in women with hypothyroidism during androgen therapy for breast cancer. Ann Intern Med. 1994;121:247-51. [PMID: 7518657]
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recognition and proper management significantly improve the prognosis. Nonetheless, the mortality rate of myxedema coma remains nearly 50% because of comorbid precipitating conditions.

The cornerstone of treatment of myxedema coma is rapid replacement of the thyroid hormone deficit with intravenous LT_4, LT_3, or a combination of the 2 (85). Aggressive thyroid hormone replacement should be accompanied by administration of stress doses of intravenous glucocorticoids, support of vital functions, and treatment of any known precipitating events (85).

Treatment... Levothyroxine replacement is the cornerstone of therapy for hypothyroidism. Young and otherwise healthy patients can be started on a full replacement dose of 1.6 μg/kg per day based on ideal body weight. Elderly patients and those with known or suspected cardiac disease should be started on lower doses, such as 25 to 50 μg/d with gradual titration upward. Serum TSH levels should be checked at 6- to 12-week intervals to guide dosage titrations until the serum TSH level is within the population reference range or, optimally, within 0.5 to 2.0 mU/L. The clinical manifestations of hypothyroidism resolve in the majority of patients treated with adequate LT_4 doses. Myxedema coma, the most severe form of hypothyroidism, is a life-threatening emergency that should be treated in an intensive care unit with rapid intravenous repletion of the large thyroid hormone deficit, in conjunction with stress glucocorticoid therapy, maintenance of vital functions and treatment of any identified precipitating causes.

CLINICAL BOTTOM LINE

Practice Improvement

What measures do stakeholders use to evaluate the quality of care for patients with hypothyroidism?

Federal legislation passed in 2006 required the Centers for Medicare & Medicaid Services (CMS) to create a physician quality reporting system that included an incentive payment for eligible professionals who satisfactorily report data on quality measures for covered services furnished to Medicare beneficiaries. CMS named this program the Physician Quality Reporting Initiative (PQRI). Eligible professionals who meet the criteria for satisfactory submission of data for services provided from 1 January, 2009 to 31 December, 2009 will earn an incentive payment of 2.0% of their total allowed charges. The 2009 PQRI consists of 153 quality measures and 7 measures groups. None of these measures applies specifically to persons with hypothyroidism.

What do professional organizations recommend regarding the care of patients with hypothyroidism?

The American Thyroid Association published its most recent treatment guidelines for patients with hypothyroidism in 1995 (5) and guidelines for the detection of thyroid dysfunction in 2000 (87).

The American Association of Clinical Endocrinologists published clinical practice guidelines for managing people with hypothyroidism and suspected hypothyroidism in 2002 that were amended in 2006 (www.aace.com/pub/pdf/guidelines/hypo_hyper.pdf). These guidelines emphasize the use of a sensitive TSH or thyrotropin assay as the best screening test for hypothyroidism, and in most outpatient clinical situations, the use of serum TSH level as the most sensitive test for detecting mild thyroid hormone excess or deficiency. In clinical hypothyroidism, the guidelines recommend LT_4 as standard treatment, which must be tailored to the individual patient. These guidelines emphasize awareness of subclinical thyroid disease, which often remains undiagnosed, and a system of care that incorporates regular follow-up surveillance by 1 physician as well as education and involvement of the patient.

In 2007, the Endocrine Society published guidelines for the management of thyroid dysfunction during pregnancy (88). These guidelines emphasize that management of thyroid diseases during pregnancy requires special considerations because pregnancy induces major changes in thyroid function, and maternal thyroid disease can have adverse effects on the

84. Carr D, McLeod DT, Parry G, et al. Fine adjustment of thyroxine replacement dosage: comparison of the thyrotrophin releasing hormone test using a sensitive thyrotrophin assay with measurement of free thyroid hormones and clinical assessment. Clin Endocrinol (Oxf). 1988;28:325-33. [PMID: 3139338]
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86. Yamamoto T, Fukuyama J, Fujiyoshi A. Factors associated with mortality of myxedema coma: report of eight cases and literature survey. Thyroid. 1999;9:1167-74. [PMID: 10646654]
87. Ladenson PW, Singer PA, Ain KB, et al. American Thyroid Association guidelines for detection of thyroid dysfunction. Arch Intern Med. 2000;160:1573-5. [PMID: 10847249]

pregnancy and the fetus. Care requires coordination among several health care professionals. Avoiding maternal (and fetal) hypothyroidism is of major importance because of potential damage to fetal neural development, an increased incidence of miscarriage, and preterm delivery. Autoimmune thyroid disease is associated with both increased rates of miscarriage, for which the appropriate medical response is uncertain, and postpartum thyroiditis. Radioactive isotopes must be avoided during pregnancy and lactation. Universal screening of pregnant women for thyroid disease is not supported by adequate studies, but case finding targeted to specific groups of patients who are at increased risk is strongly supported.

In 2005, the American Association of Clinical Endocrinologists, the American Thyroid Association, and the Endocrine Society published a consensus statement about the management of subclinical thyroid dysfunction (11). Although the statement found that the correct approach to subclinical thyroid dysfunction remained unsettled, it recommended routine screening for thyroid disease in the general population, especially in pregnant women. It also recommended that most patients with subclinical hypothyroidism should be treated and cautioned that best clinical practice should combine clinical judgment and patients' preferences.

In 2008, several British organizations, including the Royal College of Physicians, the Society for Endocrinology, and the British Thyroid Association, published a statement about the diagnosis and management of primary hypothyroidism that expressed concern about the possibility that some people were being diagnosed and managed inappropriately (www.rcplondon.ac.uk/specialties/Endocrinology-Diabetes/Documents/Hypothyroidism.pdf). The statement concluded that patients with suspected primary hypothyroidism should be diagnosed only with blood tests, not tests of other bodily fluids, such as urine; that patients with primary hypothyroidism should be treated only with LT_4 tablets, not thyroid extracts or combinations of LT_4 with LT_3; and that patients with all thyroid blood tests in the reference ranges should not be treated for hypothyroidism, even if they have some symptoms compatible with hypothyroidism.

88. Abalovich M, Amino N, Barbour LA, et al. Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2007;92:S1-47. [PMID: 17948378]

in the clinic

Tool Kit

Hypothyroidism

PIER Modules

pier.acponline.org

Access the PIER module on hypothyroidism. PIER modules provide evidence-based, updated information on current diagnosis and treatment in an electronic format designed for rapid access at the point of care.

Patient Education Resources

www.annals.org/intheclinic/toolkit-thyroid.html

Access the patient information located on the following page to download and distribute to your patients.

www.acponline.org/patients_families/diseases_conditions/hypothyroidism/

Access information for patients with hypothyroidism prepared by the American College of Physicians.

www.nlm.nih.gov/medlineplus/ency/article/000353.htm

Access information for patients with hypothyroidism prepared by the National Library of Medicine of the National Institutes of Health.

www.thyroid.org/patients/patient_brochures/hypothyroidism.html

Access information for patients with hypothyroidism prepared by the American Thyroid Association.

in the clinic

THINGS YOU SHOULD KNOW ABOUT HYPOTHYROIDISM

What is the thyroid gland?

The thyroid gland is a hormone-secreting gland located in the neck, just below the Adam's apple.

What do thyroid hormones do?

Thyroid hormones regulate the body's use of energy.

What is hypothyroidism?

Hypothyroidism is a condition in which the thyroid gland secretes too little thyroid hormone into the circulation.

What are the symptoms of hypothyroidism?

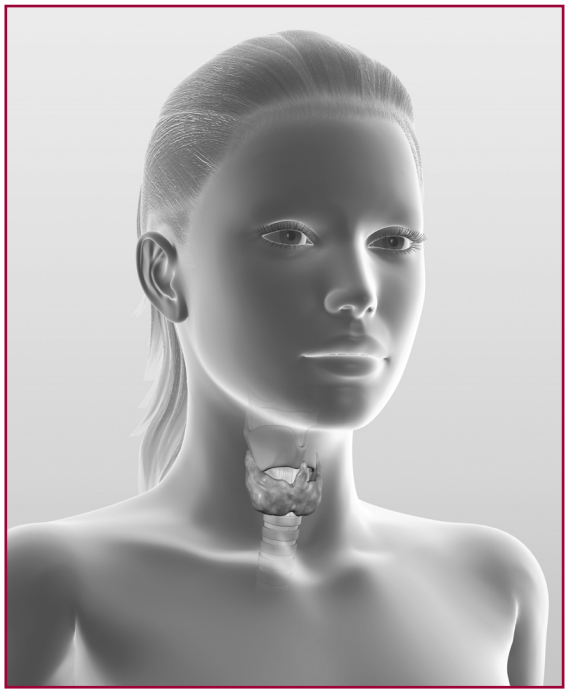
Symptoms include fatigue, depression, increased need for sleep, dry skin, cold intolerance, hoarseness, weight gain, menstrual irregularity, and constipation.

How is the diagnosis of hypothyroidism made?

Blood tests can detect low levels of thyroid hormones.

How is hypothyroidism treated?

Hypothyroidism is treated with oral thyroid hormone replacement.



How long do I have to take thyroid hormone replacement?

Once a person has developed hypothyroidism, the condition is usually permanent. Thyroid hormone replacement is a lifelong requirement.

For More Information

Web Sites With Good Information About Hypothyroidism

www.acponline.org/patients_families/diseases_conditions/hypothyroidism/
Access information for patients with hypothyroidism prepared by the American College of Physicians.

www.nlm.nih.gov/medlineplus/ency/article/000353.htm
Access information for patients with hypothyroidism prepared by the National Library of Medicine of the National Institutes of Health.

www.thyroid.org/patients/patient_brochures/hypothyroidism.html
Access information for patients with hypothyroidism prepared by the American Thyroid Association.

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Patient Information

CME Questions

MKSAP
MEDICAL KNOWLEDGE Self-Assessment Program

1. A 28-year-old woman is evaluated for fatigue, weight gain, and occasional constipation. The patient has history of craniopharyngioma, which was resected; she was subsequently given radiation therapy. She has hypopituitarism and diabetes insipidus after tumor resection and radiation. Her medications include hydrocortisone, levothyroxine, oral contraceptives, and desmopressin. She does not have dizziness, nausea, vomiting, polyuria, or polydipsia. She has regular menstrual cycles. The physical examination is unremarkable. Her complete blood count and electrolyte panel are normal. Her TSH level is 0.1 mU/mL and her free T_4 level is 6.4 pmol/L (0.5 ng/dL).

   Which of the following changes should be made to the patient's therapy?

   A. Hydrocortisone dose should be lowered
   B. Oral contraceptives should be discontinued
   C. Desmopressin should be discontinued
   D. Thyroid hormone dose should be increased

2. A 45-year-old obese woman undergoes evaluation after learning her nonfasting serum total cholesterol level, which was measured at a health screening fair 1 month ago, was 6.72 mmol/L (260 mg/dL). The review of systems indicates increasingly heavy menstruation and constipation. Her family history is negative for coronary artery disease. The patient is otherwise healthy and does not smoke.

   On physical examination, blood pressure is 120/80 mm Hg. The remainder of the examination is normal. Her serum total cholesterol level is 6.62 mmol/L (256 mg/dL). Her serum triglyceride level is 2.31 mmol/L (205 mg/dL). Her serum high-density lipoprotein cholesterol level is 1.03 mmol/L (40 mg/dL). And her serum low-density lipoprotein cholesterol level is 4.53 mmol/L (175 mg/dL).

   Which of the following is the most appropriate next step in the management of this patient?

   A. Fibric acid derivative
   B. Statin
   C. Fish oil supplement
   D. Serum thyroid-stimulating hormone measurement

3. A 45-year-old man presents with fatigue, constipation, and a 2-kg (5-lb) weight gain. The patient has Hashimoto thyroiditis and is adherent with his levothyroxine regimen, 0.25 mg/d. Six months ago, the serum thyroid-stimulating hormone (TSH) level was 1.9 mU/mL and the serum free T_4 level was 16.5 pmol/L (1.3 ng/dL). The serum TSH is now 12.0 mU/mL, and the serum free T_4 level is 10.2 pmol/L (0.8 ng/dL).

   What is the most likely explanation for the change in thyroid hormone levels?

   A. He has been taking sertraline for depression starting 3 months ago.
   B. He has begun taking an over-the-counter vitamin B complex supplement and high-dose vitamin C tablets.
   C. The pharmacy inadvertently dispensed 0.025-mg tablets to him 3 months earlier.
   D. His weight gain has led to a decreased volume of distribution.
   E. He has developed adrenal insufficiency.

4. A 23-year-old woman is evaluated in the emergency department for nausea, anorexia, dizziness, and diffuse moderate abdominal discomfort. Three weeks ago, she had been evaluated for fatigue and cold intolerance and was noted to have a firm goiter, with the thyroid estimated to be twice the size expected in a woman of her build. Thyroid peroxidase antibodies were positive, and her serum thyroid-stimulating hormone (TSH) level was 20 mU/mL. Hashimoto thyroiditis was diagnosed, and therapy with levothyroxine, 100 µg/d, is begun. In addition to her symptoms, she has had a 2-kg (4.5-lb) weight loss. In the emergency department, the blood pressure is 90/60 mm Hg; the pulse rate is 100/min, and she seems darkly pigmented. Laboratory results include serum sodium, 132 mmol/L, potassium, 5.0 mmol/L, TSH level, 6.0 mU/mL, and normal thyroxine (T4).

   Which of the following would be the most appropriate next test in the evaluation of this patient?

   A. Triiodothyronine (T_3)
   B. Adrenocorticotropic hormone, cortisol followed by cosyntropin stimulation
   C. Thyroid-stimulating immunoglobulins
   D. 24-hour urine collection for free cortisol

Questions are largely from the ACP's Medical Knowledge Self-Assessment Program (MKSAP). Go to www.annals.org/intheclinic/ to obtain up to 1.5 CME credits, to view explanations for correct answers, or to purchase the complete MKSAP program.