Annals of Internal Medicine®

In the Clinic®

Hypothyroidism

Screening

Diagnosis

Treatment

Practice Improvement

Hypothyroidism is a common condition in which the thyroid gland provides insufficient amounts of thyroid hormone for the needs of peripheral tissues. The most common cause in adults is chronic lymphocytic thyroiditis (Hashimoto thyroiditis), but there are many other causes. Because most of the clinical features of hypothyroidism are nonspecific, the diagnosis requires laboratory testing. Serum thyroid-stimulating hormone (TSH) measurement is the best diagnostic test; an elevated TSH level almost always signals primary hypothyroidism. Serum free thyroxine levels may be below the reference range (overt hypothyroidism) or within the reference range (subclinical hypothyroidism). All patients with overt hypothyroidism should be treated, but those with subclinical hypothyroidism do not always benefit from treatment, especially elderly patients and those with baseline TSH levels below 10 mU/L. Oral L-thyroxine is the treatment of choice because of its well-demonstrated efficacy, safety, and ease of use. Therapy goals are symptom relief and maintenance of serum TSH levels within the reference range. Myxedema coma is a life-threatening form of decompensated hypothyroidism that must be treated with aggressive L-thyroxine replacement and other supportive measures in the inpatient setting.

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Hypothyroidism is a condition in which the thyroid gland produces insufficient amounts of thyroid hormone to meet peripheral tissue requirements. *Primary hypothyroidism* refers to thyroid failure resulting from disease of the thyroid gland itself; it accounts for more than 99% of all hypothyroidism (1). Primary hypothyroidism is considered to be overt when serum thyroid-stimulating hormone (TSH) levels are elevated and thyroxine (T_4) levels (free and total T_4) are below the population reference range. Subclinical hypothyroidism is a milder form of thyroid failure characterized by mildly to moderately elevated serum TSH levels but T_4 values that are still within the reference range. The prevalence of overt hypothyroidism is 0.3%–3.7% in the United States and 0.2%–5.3% in Europe (1, 2). Hypothyroidism prevalence increases with age and is higher in women, in people with other autoimmune diseases, and in those with Down syndrome and Turner syndrome (1). Subclinical hypothyroidism has higher prevalence rates, with estimates of 3%–15% (3).

The most common causes of primary hypothyroidism among adults in the United States are chronic lymphocytic thyroiditis (Hashimoto thyroiditis), radioiodine thyroid ablation, thyroidectomy, and high-dose head and neck radiation therapy. Severe endemic iodine deficiency is the most common cause worldwide (1). Nonautoimmune infiltrative diseases (amyloidosis and hemochromatosis) are less common causes of hypothyroidism. Many medications can impair thyroid function, causing primary hypothyroidism (4) (see the Screening section). Hypothyroidism can also occur transiently (duration of about 3–6 months) during the recovery phase of the 3 main types of destructive thyroiditis: postpartum thyroiditis, silent (or painless) thyroiditis, and subacute thyroiditis. Congenital disorders, including dyshormonogenesis (deficiency of an enzyme required for thyroid hormone production) and thyroid dysgenesis/hemiagenesis, are also important causes that most often manifest during childhood (1, 5). Central hypothyroidism (secondary hypothyroidism) is caused by hypothalamic or pituitary disorders that impair thyrotropin-releasing hormone and/or TSH production (1, 6). The most common causes and underlying conditions are tumors, surgery, radiation, hemorrhage, infections, infiltrative disorders, traumatic brain injury, and use of certain medications (4, 6).

Screening

Which patients are at elevated risk for hypothyroidism?

Patients at increased risk for primary hypothyroidism are those who have symptoms of thyroid hormone deficiency; a goiter; a thyroid disease or treatment history; and other autoimmune diseases, particularly type 1 diabetes, adrenal insufficiency, celiac disease, and vitiligo. Hypothyroidism is also more common with advancing age and in people with Down syndrome, Turner syndrome, a history of head and neck radiation therapy, or a family history of thyroid or autoimmune diseases. Medications that increase risk for primary hypothyroidism include amiodarone, iodine supplements, lithium, interferon-α, immune checkpoint inhibitors (most commonly ipilimumab and nivolumab), and alemtuzumab (4). Risk for central hypothyroidism is increased in

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persons who have had pituitary surgery, radiation therapy, or traumatic brain injury and with use of certain medications, such as glucocorticoids, dopamine, octreotide, bexarotene, and mitotane (4).

Should clinicians screen nonpregnant patients for hypothyroidism?

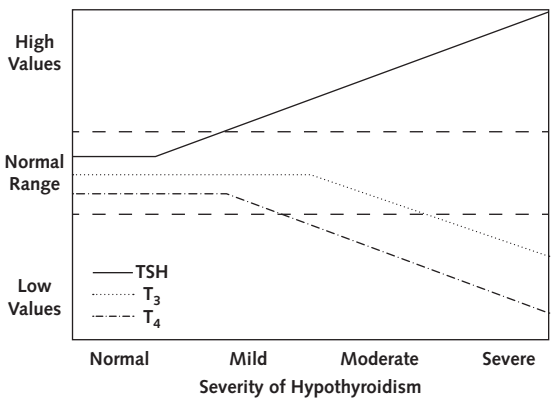
Astute case finding is always appropriate in patients who have any of the aforementioned risk factors. However, routine screening in the general population is not recommended because of insufficient evidence that diagnosing and treating asymptomatic mild hypothyroidism is beneficial. Nonetheless, specific screening recommendations for hypothyroidism vary greatly across organizations (1, 7–9).

Should clinicians screen pregnant women for hypothyroidism?

Major organizations consider current evidence to be insufficient to recommend for or against routine TSH testing during pregnancy. The American Thyroid Association (ATA) does recommend case finding (TSH testing) in women who are older than 30 years or who have a history of thyroid disease; current symptoms of thyroid dysfunction; known thyroid antibody positivity; a palpable goiter; a history of thyroid surgery or head and neck radiation therapy; type 1 diabetes or other autoimmune disorders; previous pregnancy loss, preterm delivery, or infertility; 2 or more prior pregnancies; morbid obesity (body mass index [BMI] ≥40 kg/m^2); a history of amiodarone or lithium use or recent iodinated radiocontrast administration; residence in a region of moderate to severe iodine deficiency; or a family history of thyroid disease (10, 11).

These recommendations remain controversial and could change in the future. Prospective studies have reported that children born to mothers who had untreated or inadequately treated hypothyroidism during pregnancy have lower IQs than children of euthyroid mothers (12), that placental abruption is 3 times more likely and preterm delivery is 2 times more likely in women with subclinical hypothyroidism (13), and that perinatal intraventricular hemorrhage and respiratory distress syndrome occur more often in infants of women with subclinical hypothyroidism (13). A prospective cohort study determined that screening only high-risk patients

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



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

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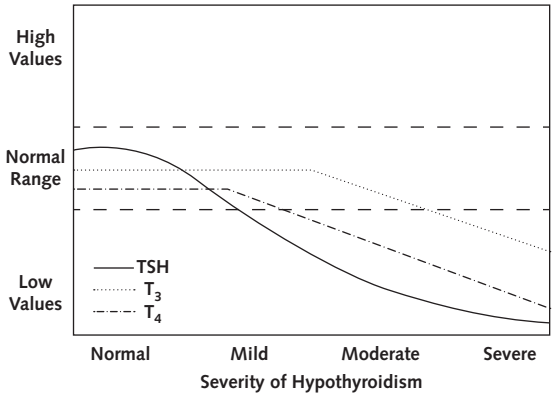
Figure 2. **Hormone changes occurring during the development of central hypothyroidism.**



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

would miss 30% of pregnant women with hypothyroidism (14).

Which test should clinicians use to screen for hypothyroidism?

Serum TSH measurement is the best test to detect hypothyroidism because more than 99% of hypothyroidism is primary hypothyroidism and serum TSH elevation is the first laboratory abnormality to occur in this condition (1) (**Figure 1**). TSH assays are standardized, accurate, and widely available. When central hypothyroidism is suspected, a serum free T_4 measurement is the appropriate test because patients with central disease cannot make TSH normally (**Figure 2**).

Screening... Serum TSH measurement is the best test to detect primary hypothyroidism. 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; previous thyroid disease or treatment; other autoimmune diseases, particularly type 1 diabetes, adrenal insufficiency, celiac disease, or vitiligo; Down syndrome; Turner syndrome; or a family history of thyroid disease. Screening may also be considered for women who are or who plan to become pregnant.

CLINICAL BOTTOM LINE

Diagnosis

What symptoms should prompt clinicians to consider a diagnosis of hypothyroidism?

Symptoms commonly experienced by hypothyroid patients are mostly nonspecific and also occur with many nonthyroidal conditions. A 1997 study reported that patients with overt hypothyroidism most often experienced dry skin (76%), cold intolerance (64%), coarse skin (60%), puffy eyelids (60%), decreased sweating (54%), weight gain (54%), paresthesias (52%), cold skin (50%), and constipation (48%) (15). A 2014 study reported fatigue (81%), dry skin

(63%), shortness of breath (51%), mood lability (46%), and constipation (39%) to be the most common. Considerable overlap with symptoms experienced by euthyroid control patients was noted in the latter study; hypothyroid patients reported a mean of 5 symptoms, euthyroid control patients reported a mean of 2 symptoms, and an equal proportion of both groups reported 3 of these symptoms (16). Symptoms tend to increase in number and severity with increasing degrees of thyroid hormone deficiency, but they may be absent or minimal in some patients with biochemically significant disease and can be numerous in those with only mild disease. Notably, hypothyroid patients are more frequently diagnosed with psychiatric disorders and treated with antidepressants, anxiolytics, and antipsychotic medications (17). Elderly hypothyroid patients generally have fewer classic symptoms; fatigue and weakness are the most prominent features in this age group (18).

Central hypothyroidism causes symptoms similar to those of primary hypothyroidism, but there may also be symptoms and signs of the hypothalamic–pituitary disorders that underlie central hypothyroidism. These may include features of mass effect, excess or deficiency of other hormones, infection, or inflammation (6).

What physical examination and laboratory findings indicate possible hypothyroidism?

Physical examination findings similarly tend to be nonspecific and subtle or even absent. The most common are coarse, dry skin; hair loss; puffy eyelids; hoarseness; and slow movements (15, 16). Delayed relaxation phase of the deep tendon reflexes is a classic physical finding, and myoedema (muscle swelling) is sometimes seen. A goiter or a thyroidectomy scar are also important signs.

General laboratory abnormalities also give suggestive but not diagnostic clues to the presence of hypothyroidism; hyponatremia, macrocytic anemia, and elevated creatine kinase levels are common findings. Hypothyroidism also causes mixed hyperlipidemia with elevation of all lipids and lipoproteins [total, low-density lipoprotein, and high-density lipoprotein cholesterol; triglycerides; and lipoprotein(a)] (19). Obstructive sleep apnea has been reported to occur in 30% of patients with overt hypothyroidism (20).

What laboratory tests should clinicians use to diagnose hypothyroidism?

Serum TSH measurement is the best test for detecting primary hypothyroidism. There is a log-linear relationship between serum TSH and free T_4 levels such that small decreases in free T_4 concentrations produce large TSH increments (**Figure 1**). High TSH levels almost always indicate primary hypothyroidism, whereas normal TSH levels strongly suggest normal thyroid function. It should be noted that serum TSH levels have a diurnal pattern, with the highest levels appearing in the late afternoon and evening (1). Furthermore, increasing age is associated with a natural increase in serum TSH levels in persons with apparently normal thyroid function (21). This has prompted a call for establishment of age-specific TSH reference ranges, although these are rarely shown on laboratory reports.

When the TSH level is elevated, measurement should be repeated, with a serum free T_4 test added to determine whether overt (low free T_4 level) or sub-

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Table 1. **Differential Diagnosis of Hypothyroidism**

Disease	*Characteristics*	*Notes*
Hashimoto disease	High TSH level; TPO antibodies	Slowly progressive
Thyroidectomy	High TSH level; history of surgery	Surgical scar
Radioiodine therapy	High TSH level; history of I-131 treatment	History of thyrotoxicosis
External radiation therapy	High TSH level; history of radiation therapy	History of cancer
Iodine deficiency	High TSH level; low urine iodine level	Iodine-deficient area
Postpartum thyroiditis	High TSH level; TPO antibodies	Recent pregnancy
Silent thyroiditis	High TSH level; TPO antibodies	Recent thyrotoxicosis
Subacute thyroiditis	High TSH level; pain; elevated ESR	Recent thyrotoxicosis
Drug-induced	High TSH level; use of amiodarone, lithium, interferon, iodine, thionamides, tyrosine kinase or multikinase inhibitors, or immune checkpoint inhibitors	Medication history
Pituitary–hypothalamic mass	Low or normal TSH level; low FT_4 level; abnormal MRI/CT scan	Headaches, visual field cuts, ophthalmoplegia
Pituitary–hypothalamic surgery	Low or normal TSH level; low FT_4 level	History of surgery
Pituitary–hypothalamic radiation therapy	Low or normal TSH level; low FT_4 level	History of radiation therapy
Pituitary–hypothalamic infiltration/infection	Low or normal TSH level; low FT_4 level; abnormal MRI/CT scan	Headaches, visual field cuts, ophthalmoplegia
Traumatic brain injury	Low or normal TSH level; low FT_4 level; normal MRI/CT scan	History of traumatic brain injury
Congenital dyshormonogenesis	High TSH level; low FT_4 level; negative TPO antibodies; elevated RAIU	Goiter; usually diagnosed in childhood
Congenital thyroid agenesis or hemiagenesis	High TSH level; low FT_4 level; negative TPO antibodies; ultrasound shows absence or partial absence of thyroid gland	Absence of goiter; usually diagnosed in childhood

CT = computed tomography; ESR = erythrocyte sedimentation rate; FT_4 = free thyroxine; I-131 = radioactive iodine; MRI = magnetic resonance imaging; RAIU = radioactive iodine uptake; TPO = thyroid peroxidase; TSH = thyroid-stimulating hormone.

clinical (free T_4 level within reference range) hypothyroidism is present. In most circumstances, there is no indication to order a serum total triiodothyronine (T_3) or free T_3 test in hypothyroid patients because circulating T_3 levels in hypothyroidism are relatively preserved through activation of tissue deiodinases; thus, they offer no additional information about the severity of hypothyroidism over that given by TSH and free T_4 values.

The presence of antithyroperoxidase (anti-TPO) antibodies and antithyroglobulin antibodies identifies chronic lymphocytic thyroiditis (Hashimoto thyroiditis) as the underlying cause of thyroid gland failure. However, thyroid antibody measurement is not recommended by the ATA and the American Association of Clinical Endocrinologists (AACE) (7) because hypothyroidism in adults, when not due to iatrogenic causes or medications, is almost always due to Hashimoto thyroiditis. Therefore, testing offers little additional information and does not usually affect treatment decisions. Nonetheless, some providers consider it important to demonstrate that a patient's hypothyroidism has an autoimmune cause; this may also facilitate a discussion about other autoimmune disorders for which increased vigilance is needed. Thyroid sonography often shows a hypoechogenic pattern in chronic lymphocytic thyroiditis (1), but thyroid imaging is not recommended in hypothyroid patients unless 1 or more nodules are identified by palpation or incidentally by other imaging studies. **Table 1** describes typical

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findings from thyroid tests and imaging studies for conditions in the differential diagnosis of hypothyroidism.

Central hypothyroidism is more challenging to diagnose. Central TSH deficiency is suggested by the presence of low free T_4 levels in association with low or low-normal TSH levels in patients who have symptoms consistent with hypothyroidism, especially with known hypothalamic–pituitary disease (1, 6). The distinction between central hypothyroidism and nonthyroidal illness syndrome can be particularly difficult; in this situation, measurement of serum total T_3 and reverse T_3 (RT_3) may be useful. TSH is often low or low normal in both conditions, but in central hypothyroidism, T_4 levels are proportionately lower than T_3 levels and RT_3 levels are low, whereas in nonthyroidal illnesses, serum T_3 levels are proportionately lower than T_4 levels and RT_3 levels tend to be elevated. If central hypothyroidism is diagnosed in someone with no history of hypothalamic–pituitary disease, dedicated hypothalamic–pituitary imaging and other pituitary hormone testing should be performed (6).

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

Serum TSH levels may be mildly elevated during the recovery phase of nonthyroidal illnesses (22). If a patient with a mildly elevated TSH level has recently been ill or hospitalized, the TSH level should be rechecked in 6–8 weeks. TSH levels are otherwise elevated mainly in rare conditions, such as TSH-secreting pituitary tumors and the resistance to thyroid hormone syndromes (1).

Assay interference can result in an erroneous diagnosis of hypothyroidism or hyperthyroidism. Biotin is a critical reagent in many hormone assays, including TSH and free T_4 assays. When patients take biotin supplements (usually for cosmetic skin, nail, and hair conditions), thyroid disorders can be erroneously diagnosed, depending on the assay technique (23). This can be avoided by asking patients to repeat thyroid testing after at least 3 days of abstinence from the biotin supplements. Heterophile antimouse antibodies occur most often in laboratory workers, farm workers, and homeless persons but can develop in anyone, and they can falsely elevate serum TSH levels. Macro-TSH, another cause of falsely elevated TSH levels, involves large molecular complexes of TSH bound to anti-TSH autoantibodies, most commonly in the context of autoimmune disease. These complexes interfere with accurate TSH measurement, resulting in anomalous TSH elevations in the presence of normal free T_4 levels (24).

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

Subclinical hypothyroidism is an elevated serum TSH level with free T_4 or total T_4 levels still within the reference range (1, 3). High TSH levels indicate that the serum T_4 concentration, although within the population reference range, is lower than normal for that person. The increased serum TSH stimulates the thyroid gland to compensate and produce nearly adequate amounts of thyroid hormone. Subclinical hypothyroidism progresses to overt hypothyroidism in approximately 2%–6% of patients per year (3). The progression rate is higher in those with positive anti-TPO antibodies (2-3 times higher) and with higher serum TSH and lower free T_4 values (3). Of note, up to

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46% of patients with elevated TSH values that are below 7 mU/L show normalization of the TSH level within 2 years if untreated (3).

Subclinical hypothyroidism can be asymptomatic or may be associated with nonspecific symptoms that are common in the general population. A study of 942 patients with TSH values of 4.1–9.9 mU/L, 70 patients with TSH levels of 10 mU/L or higher, and 8334 euthyroid control patients found that health-related quality-of-life scores did not differ in either hypothyroid group compared with the euthyroid control group (25). The cognitive effects of subclinical hypothyroidism remain unresolved because of conflicting study results (26–30) but seem to be minimal.

Subclinical hypothyroidism, even when asymptomatic, seems to increase risk for coronary artery disease (CAD), heart failure, and mortality, especially in younger patients (aged <65 years) and in those with serum TSH levels above 10 mU/L. In contrast, studies have suggested that these risks are minimal or absent in older (aged ≥65 years) populations (1, 3), especially when TSH levels are only mildly elevated (<10 mU/L). Moreover, there is evidence that mild TSH elevations may even be associated with a functional advantage in elderly persons (31).

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

Consultation with an endocrinologist is recommended when a hypothyroid patient has thyroid nodules, known or probable CAD, cardiac rhythm disturbances, central hypothyroidism, or possible myxedema coma. Consultation may also be helpful if the clinician is uncertain about whether an abnormal thyroid hormone profile is the result of hypothyroidism, a nonthyroidal illness, or assay interference.

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

CLINICAL BOTTOM LINE

Treatment

How should clinicians choose drug therapy and dose for hypothyroidism?

L-Thyroxine (LT_4) is the treatment of choice for hypothyroidism because it effectively and safely relieves symptoms and normalizes laboratory values in most patients (1, 7, 32, 33). After absorption in the duodenum, circulating LT_4 is converted to T_3 by peripheral tissue deiodinases at a rate that is regulated by the metabolic needs of each tissue (1, 34).

The average LT_4 replacement dose in otherwise healthy adults with overt hypothyroidism is 1.6 mcg/kg of body weight per day

(1, 7, 32, 33). Lean body mass (body weight that would yield a BMI of 24–25 kg/m^2 for the person's height) is a better predictor of dose requirements than total body weight (35). For example, a woman with a height of 67 inches and a weight of 190 lb (86 kg) would have a lean body weight of 153 lb (70 kg) if her BMI were 24 kg/m^2; her lean body mass dose (1.6 mcg/kg) would be 112 mcg/d, whereas the dose would be 137 mcg/d if based on her total body weight.

Younger patients without known CAD tolerate initial full doses well and usually have rapid relief of symptoms from thyroid hormone deficiency. After initiation of LT_4 therapy, serum TSH should be checked 6–8 weeks later and the dose should be titrated, usually by 12.5–25 mcg/d every 6–8 weeks, to maintain serum TSH values within the reference range. LT_4 is available in multiple doses, allowing precise dose adjustments to achieve these target TSH levels. LT_4 doses required to achieve target TSH levels tend to be higher in patients who have had a prior thyroidectomy and are proportionately higher in children (1).

Patients who are aged 60 years or older or who have known CAD should be started on lower LT_4 doses of 25–50 mcg/d, with dose titrations of 12.5–25 mcg/d every 6–8 weeks until the desired TSH level is reached. This "start low, go slow" approach is favored to prevent precipitation of dysrhythmias or ischemic events when full replacement doses are abruptly started or when doses are increased too rapidly (1, 7, 32, 33).

LT_4 should be taken with water 1 hour before or 4 hours after a meal and should be separated by at least 4 hours from iron, calcium, or soy supplements. Alternatively, it can be taken at bedtime, 2–3 hours after the last meal (1, 7, 32, 36). If a dose is missed, 2 doses can be taken together the next day and the usual daily dose can then be resumed. If 2 doses are missed, 2 doses can be taken together for 2 days and the usual daily dose can then be resumed.

Currently available thyroid hormone preparations are listed in **Table 2**. T_4 itself is not well absorbed, but synthetic LT_4, the sodium salt made by replacing a

Table 2. **Drug Treatment for Hypothyroidism**

Agent	*Mechanism of Action*	*Dose (Based on Lean Body Mass)*	*Benefits*	*Adverse Effects*	*Notes*
Synthroid (LT_4) tablets	Hormone replacement	1.6 mcg/kg per day	Effective; reliable; inexpensive	Thyrotoxicosis if dosage is excessive	Consistent potency; first-line agent
Levoxyl (LT_4) tablets	Hormone replacement	1.6 mcg/kg per day	Effective; reliable; inexpensive	Thyrotoxicosis if dosage is excessive	Consistent potency; first-line agent
Euthyrox (LT_4) tablets	Hormone replacement	1.6 mcg/kg per day	Effective; reliable; inexpensive	Thyrotoxicosis if dosage is excessive	Consistent potency; first-line agent
Unithroid (LT_4) tablets	Hormone replacement	1.6 mcg/kg per day	Effective; reliable; inexpensive	Thyrotoxicosis if dosage is excessive	Consistent potency; first-line agent
Tirosint (LT_4) gel caps	Hormone replacement	1.6 mcg/kg per day	Effective; reliable; more expensive	Thyrotoxicosis if dosage is excessive	Consistent potency; first-line agent
Tirosint-Sol (LT_4) oral liquid	Hormone replacement	1.6 mcg/kg per day	Effective; reliable; more expensive	Thyrotoxicosis if dosage is excessive	Consistent potency; first-line agent
Generic (LT_4) tablets	Hormone replacement	1.6 mcg/kg per day	Effective; reliable; least expensive	Thyrotoxicosis if dosage is excessive	Consistent potency guaranteed only if from the same manufacturer for every renewal
Desiccated thyroid tablets	Hormone replacement	1–2 grains/d (60–120 mg/d)	T_4/T_3 combination	Thyrotoxicosis if dosage is excessive	T_4-to-T_3 ratio too high; not recommended for routine use
Cytomel (LT_3) tablets	Hormone replacement	5–12.5 mcg/d	Pure T_3; short-acting	Thyrotoxicosis if dosage is excessive	Elevated T_3 level 2–6 h after dose taken; not recommended for routine use
Synthroid (intravenous LT_4)	Hormone replacement	300–500 mcg, then 50–100 mcg/d for myxedema coma 75% of usual oral dose for patients allowed nothing by mouth	Rapid T_4 repletion in myxedema coma; ensures LT_4 delivery for patients allowed nothing by mouth	Thyrotoxicosis if dosage is excessive	Careful monitoring required; treatment of myxedema coma; treatment of hypothyroid patients unable to take oral medications
Triostat (intravenous LT_3)	Hormone replacement	50–100 mcg, then 10–20 mcg every 8–12 h	Rapid T_3 repletion	Thyrotoxicosis if dosage is excessive	Careful monitoring required; treatment of myxedema coma
Hydrocortisone (Solu-Cortef)	Adrenal hormone replacement	100 mg intravenously every 8 h for 2 d	To cover possible decreased adrenal reserve in myxedema coma	None with short-term use	Treatment of myxedema coma should include administration of intravenous glucocorticoids, support of vital functions, and treatment of any known precipitating events

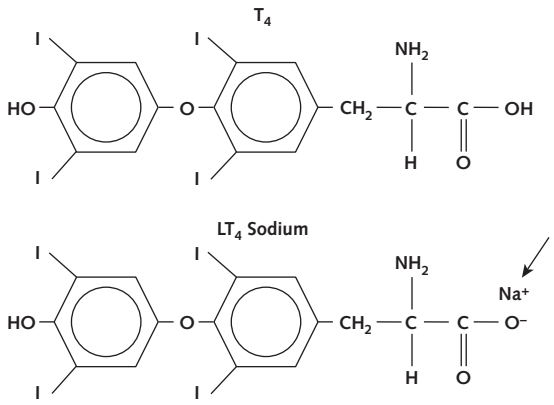
LT_3 = liothyronine; LT_4 = L-thyroxine; T_3 = triiodothyronine; T_4 = thyroxine.

hydrogen ion with sodium, is well absorbed (about 75%–80%) in the duodenum. The molecular structures of T_4 and LT_4 are shown in **Figure 3**; they are identical aside from the sodium substitution for enhanced absorption and are therefore considered bioidentical (37). The serum half-life of LT_4 is 5–7 days. Therefore, after initiation of LT_4 therapy or a change in the dose, a new steady state is reached in approximately 5–6 weeks. Liquid oral LT_4 preparations have enhanced and less variable absorption compared with LT_4 tablets in hypothyroid patients, including those with malabsorption from gastrointestinal diseases or concomitant use of proton-pump inhibitors (38, 39).

Synthetic LT_3 preparations are also available as LT_3 alone or as combination products containing both synthetic LT_4 and LT_3 (**Table 2**). Desiccated thyroid extract (DTE) preparations are made by drying and powdering porcine thyroid glands. Combined synthetic LT_4/LT_3 and DTE products consist of approximately 80% T_4 and 20% T_3 (T_4-to-T_3 ratio of 4:1, compared with 14:1 in human thyroid glands); this ratio may vary depending on the brand and manufacturing process (37, 40). 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 could be hazardous to patients with underlying CAD or dysrhythmias (7, 32, 33).

Randomized controlled trials (RCTs) evaluating long-term outcomes of treating overt hypothyroidism have not been done because nearly all affected patients are symptomatic and placebo-controlled trials are considered unethical. Residual symptoms sometimes persist in patients

Figure 3. **The molecular structures of T_4 made by the human thyroid gland and synthetic LT_4, which is most commonly used to treat hypothyroidism.**



LT_4 differs from T_4 only in replacement of a hydrogen ion with a sodium ion to enhance gastrointestinal absorption of the hormone. LT_4 = L-thyroxine; T_4 = thyroxine.

with treated hypothyroidism (41–43) despite normalization of serum TSH levels. Although the reason some patients do not have complete symptom resolution is not fully understood, a polymorphism (Thr92Ala) of deiodinase 2, the enzyme that converts T_4 to T_3 in the brain, has been identified more often in patients who have persistent symptoms while receiving LT_4 monotherapy and may predict a better response to combination LT_4/LT_3 therapy. However, identification of these patients before initiating LT_4 therapy is not currently possible, and genetic testing for the Thr92Ala D2 polymorphism is not recommended (7, 32, 44).

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

High-quality RCTs comparing the various LT_4 products have not been done. The U.S. Pharmacopeia requires that LT_4 preparations contain within 5% of their stated amount throughout their shelf life. Using brand-name LT_4 preparations or a generic preparation consistently from the same manufacturer is the best way to reduce dosage variability and variable serum thyroid hormone levels. When generic products are prescribed, dosage consistency cannot be guaranteed if the medication manufacturer changes. Therefore, when consistency is critical (pregnancy, old age, thyroid cancer), it is best to recommend brand-name products or use the same generic manufacturer for all prescription renewals. For patients who have some residual thyroid function, such as those with mild hypothyroidism, and those for whom dosage consistency is less critical, generic preparations are reasonable and less expensive.

The ATA, the AACE, and the European Thyroid Association (ETA) clinical practice guidelines, which are based on RCT evidence, literature reviews, and meta-analyses, emphasize the absence of consistent evidence for superiority of LT_4/LT_3 combination therapy over LT_4 monotherapy and recommend against routine use of combination LT_4/LT_3 therapy (7, 32, 44). They also recommend against routine use of DTE products because of potential safety concerns about the transient supraphysiologic T_3 levels that occur with DTE and the paucity of long-term safety data (7, 32). However, these organizations acknowledge

that some patients prefer treatment with combined LT_4/LT_3 or DTE and that individualized approaches are reasonable for patients who have persistent symptoms with adequate doses of LT_4, provided that these therapies are used safely, with maintenance of serum TSH levels within the reference range (7, 32, 33).

What are the indications for treating subclinical hypothyroidism?

Patients with mild subclinical hypothyroidism may not have symptomatic improvement with LT_4 treatment if they have minimal symptoms and only slight TSH elevations at baseline (1, 3). Two RCTs in elderly persons (aged >65 years [45] and >80 years [46]) reported that LT_4 treatment of mild subclinical hypothyroidism did not improve thyroid symptoms or fatigue and yielded no benefit for secondary outcome measures (blood pressure, weight, waist circumference, grip strength). However, treatment does seem to benefit patients with more prominent baseline symptoms and when serum TSH levels are above 10 mU/L (1, 3, 7, 32, 47).

Adequately powered RCTs have not yet been done to address whether LT_4 treatment of subclinical hypothyroidism reduces CAD events and mortality (1, 3). One cohort study did report a cardiovascular disease benefit in younger patients but not in elderly persons (48). Another study found that LT_4 treatment of elderly patients with subclinical hypothyroidism may even be associated with increased mortality (49).

Therefore, clinical practice guidelines recommend that providers make individualized, patient-specific decisions about treatment of subclinical hypothyroidism (7, 32, 47). LT_4 treatment should be strongly considered for patients aged 70 years or younger if the serum TSH level is 10 mU/L or greater. Treatment decisions should be individualized if the patient is older than 70 years and/or has a serum TSH level below 10 mU/L, taking into account the presence or absence of hypothyroid symptoms; presence of a goiter; the degree of TSH elevation; TPO antibody status; desire for pregnancy; and the presence of cardiovascular disease risk factors, CAD, and heart failure. If symptomatic benefit is not apparent within 3–6 months or if there are significant adverse effects, treatment should be discontinued. If a decision is made not to treat, symptoms and serum TSH levels should be monitored every 6–12 months, and treatment should be initiated if symptoms develop or worsen or the TSH level increases above 10 mU/L (1, 3, 7, 32, 47).

What are the adverse effects of thyroid replacement therapy?

Adverse effects of thyroid hormone replacement, except in rare patients, occur only when the medication is given in excessive doses. LT_4 doses that suppress serum TSH levels may cause anxiety, fatigue, excess sweating, palpitations, tremors, and insomnia. Furthermore, chronic exposure to thyroid hormone excess poses a significantly increased risk for atrial fibrillation and osteoporotic fractures in elderly and postmenopausal patients (50). The excess risk for major osteoporotic fractures is directly related to the cumulative duration of time patients spend with low serum TSH levels (51). Despite these potential risks, patients with medium- or high-risk differentiated thyroid cancer are often treated with higher LT_4 doses to suppress serum TSH levels to prevent cancer growth; the risks and benefits of suppressive LT_4 therapy in these patients therefore must be carefully balanced and periodically reevaluated. When questions arise about the possibility of adverse effects from the nonhormone ingredients and dyes in pills, LT_4 preparations that are dissolved in oil (gel caps) or that come in oral liquid forms may be considered (**Table 2**).

How should clinicians monitor patients with hypothyroidism?

Clinicians should assess symptoms and signs of thyroid hormone deficiency or excess, medication adherence, and use of concomitant medications and should monitor serum TSH levels at each follow-up visit for patients receiving thyroid hormone therapy (**Appendix Table**, available at Annals.org). Relevant symptom resolution and TSH levels should serve as the primary guides to thyroid hormone dose requirements in patients with primary hypothyroidism; serum TSH is the most accurate objective indicator of thyroid hormone status in patients with intact pituitary glands (1, 3, 7, 32). TSH should be checked every 6–8 weeks after therapy is started, and the LT_4 dose should be adjusted until TSH values are within the reference range. TSH should then be rechecked 3–6 months later and annually thereafter. When follow-up TSH levels drift outside the reference range, adjusting the daily LT_4 dose by 12.5–25 mcg every 6–8 weeks will usually return serum TSH levels to the desired range in patients who adhere to their medication regimen (1, 7, 32).

The TSH reference range in the U.S. population is about 0.45–4.5 mU/L in most laboratories. TSH levels do not follow a normal distribution in the general healthy population but instead are skewed to the left, with a population mean TSH level in

Table 3. **Drugs That May Alter Thyroid Hormone Requirements**

Drugs that decrease thyroid hormone absorption
- Iron supplements
- Calcium supplements
- Fiber supplements
- Soy supplements
- Sucralfate
- Antacids
- Bile acid resins
- Raloxifene

Drugs that increase serum T_4-binding proteins
- Estrogens

Drugs that enhance T_4 metabolism
- Antiepileptic drugs
- Antituberculosis drugs

Drugs that inhibit T_4-to-T_3 conversion
- Glucocorticoids
- Propranolol
- Amiodarone
- Lithium

Drugs with unknown mechanism
- Sertraline

Drugs that may cause thyroiditis
- Amiodarone
- Interferon-α
- Tyrosine kinase inhibitors (sunitinib)
- Immune checkpoint inhibitors (ipilimumab, nivolumab)

Drugs that suppress TSH secretion
- Bexarotene
- Octreotide
- Mitotane
- Metformin
- Dopamine
- Glucocorticoids

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

the 1.0–2.0 mU/L range. Some practitioners therefore use a target TSH level at the lower end of the reference range for patients receiving LT_4 therapy. However, the evidence for this practice has not been substantiated. Targeting the lower end compared with the middle or upper end of the TSH reference range in well-designed RCTs has not improved symptoms or cognitive function in patients receiving LT_4 therapy (29, 30). In contrast, peripheral thyroid hormone action biomarkers after thyroidectomy are reported to be closest to preoperative values only when TSH levels are maintained in the 0.03–0.3 mU/L range (52). Of note, TSH levels at the upper end or slightly above the reference range may be associated with longevity and functional mobility in elderly patients (aged >65–70 years) (1, 31). Guidelines therefore do not support targeting TSH values at the lower end of the reference range in most patients and recommend target TSH values in the 4.0–6.0 mU/L range in patients older than 70–80 years (32). During preconception planning, many experts recommend that serum TSH levels should be below 2.0 mU/L; patients should also be advised that thyroid hormone requirements increase during pregnancy and that they should notify their provider as soon as they become pregnant (10, 11).

Because patients with central hypothyroidism cannot make TSH normally, it should not be used to monitor their responses to LT_4 therapy. Instead, serum free T_4 levels should be monitored and maintained in the upper half of the reference range in these patients (1, 6).

Thyroid hormone requirements may vary over time in response to changes in health status, aging, and use of certain medications. Situations in which LT_4 dose requirements increase include pregnancy; estrogen use; nonadherence; weight gain; malabsorption, including celiac disease; *Helicobacter pylori*–related and atrophic gastritis; progression of underlying thyroid disease; and use of medications that decrease LT_4 absorption, increase serum T_4 binding proteins, enhance T_4 metabolism, or inhibit conversion of T_4 to T_3 (1, 10, 11, 32, 33) (**Table 3**). LT_4 dose requirements increase by nearly 50% during the first trimester of pregnancy (10, 11, 32, 33); the increased requirement is greater in patients with previous thyroidectomies than in those with Hashimoto thyroiditis (10, 11). LT_4 dose requirements are decreased by pregnancy completion, estrogen discontinuation, weight loss, aging, androgen use, Graves disease reactivation, or development of autonomous thyroid nodules (1, 32, 33).

When should patients with hypothyroidism be hospitalized?

Hospitalization is mandatory for management of myxedema coma and may also be considered for patients with severe hypothyroidism who are unable to take oral medication so that LT_4 can be administered by nasogastric tube or intravenously (at 75% of the oral dose). Myxedema coma, also known as decompensated hypothyroidism, is a life-threatening condition characterized by exaggerated manifestations of hypothyroidism. The condition occurs most often in elderly patients who have inadequately treated or untreated hypothyroidism and a superimposed precipitating event, such as cold exposure, infection, trauma, surgery, myocardial infarction, heart failure, pulmonary embolism, stroke, respiratory failure, gastrointestinal bleeding, and use of drugs that suppress the central nervous system (1, 53–56). The mortality rate for myxedema coma was 100% when it was originally described, but the outlook has improved

significantly for appropriately treated patients, with current mortality rates varying from 0%–45% (1, 53).

The diagnosis is based largely on clinical grounds. Common features are hypothermia, bradycardia, and hypopnea. Pericardial, pleural, and peritoneal effusions; ileus; and urine retention are often present. Central nervous system manifestations include seizures, stupor, and coma. Deep tendon reflexes are absent or have a delayed relaxation phase. Hypothyroid skin and hair changes are often apparent. A goiter or thyroidectomy scar can be helpful findings.

Anemia, hyponatremia, hypoglycemia, and elevated serum cholesterol and creatine kinase levels are common laboratory abnormalities. Arterial blood gases usually show CO_2 retention and hypoxemia. Electrocardiographic findings often include sinus bradycardia, various degrees of heart block, low voltage, and T-wave flattening. Serum TSH levels are significantly elevated and T_4 and T_3 levels are very low in most cases; however, the diagnosis of myxedema coma cannot be based on the degree of TSH elevation or T_4/T_3 deficiency. Two proposed Myxedema Coma Scoring Systems have been published to facilitate accurate diagnosis (54–56) (**Table 4**), but even these validated tools cannot replace sound clinical judgment.

The first treatment goal is to rapidly replace the depleted thyroid hormone pool. The normal total-body T_4 pool is about 1000 mcg (500 mcg in the thyroid and 500 mcg in the rest of the body). No RCTs have compared different thyroid hormone replacement strategies because the condition is rare. At my institution, we favor intravenous LT_4 given as a 300- to 500-mcg loading dose (bolus)

Table 4. **Myxedema Coma: Clinical Feature Scoring System***

Feature	*Score*
Temperature	
>35 °C	0
32–35 °C	10
<32 °C	20
CNS symptoms	
None	0
Somnolence/lethargy	10
Obtundation	15
Stupor	20
Coma/seizures	30
Gastrointestinal	
Anorexia/pain/constipation	5
Decreased motility	15
Paralytic ileus	20
Precipitating event	
Present	10
Cardiovascular	
Heart rate ≥60 beats/min	0
Heart rate 50–59 beats/min	10
Heart rate 40–49 beats/min	20
Heart rate <40 beats/min	30
Other electrocardiographic changes	10
Pericardial/pleural effusion	10
Pulmonary edema	15
Cardiomegaly	15
Hypotension	20
Metabolic disorders	
Hyponatremia	10
Hypoglycemia	10
Hypoxemia	10
Hypercarbia	10
Decreased glomerular filtration rate	10
Precipitating events for myxedema coma	
Cold exposure	–
Infection, trauma, surgery	–
Stroke	–
Myocardial infarction	–
Pulmonary embolism	–
Diabetic ketoacidosis	–
Medications (CNS suppressant)	–
Score	
≤24	Myxedema coma unlikely
25–59	Suggestive of myxedema coma
≥60	Myxedema coma likely

CNS = central nervous system.
** From reference 54.*

the first day, followed by daily intravenous LT_4 at 75% of the estimated oral dose (home dose or 1.6 mcg/kg per day) until oral intake is resumed, with full-dose oral LT_4 daily thereafter. Intravenous LT_3 in 5-mcg doses every 4–6 hours can be considered if there is no clinical response to intravenous LT_4 after several days. Combination intravenous LT_4/LT_3 therapy is recommended by some experts, with a lower intravenous LT_4 loading dose (200-300 mcg) and a 10-mcg intravenous LT_3 loading dose, followed by intravenous LT_4, 100 mcg/d, plus LT_3, 10 mcg every 8–12 hours (32, 56). Other critical measures are to administer stress doses of glucocorticoids, support vital functions and oxygenation, and treat any identified precipitating conditions.

Treatment... LT_4 replacement is the cornerstone of therapy for hypothyroidism. A full replacement dose of 1.6 mcg/kg per day based on ideal body weight is appropriate for young and otherwise healthy adults. Lower doses (25-50 mcg/d) with gradual titration upward are recommended for elderly patients and those with known or suspected cardiac disease. Serum TSH should be checked at 6- to 8-week intervals to guide dosage titrations until serum TSH levels are within the reference range. Clinical manifestations of hypothyroidism resolve in most 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 the hospital with rapid intravenous repletion of the large thyroid hormone deficit, stress glucocorticoid therapy, maintenance of vital functions, and treatment of any identified precipitating causes.

CLINICAL BOTTOM LINE

Practice Improvement

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

The ATA (7, 32), the AACE (7), the U.K. Royal College of Physicians (1, 7), the Latin American Thyroid Society (8), the U.S. Preventive Services Task Force (9), and the ETA (44, 47) have all published guidelines for screening, evaluation, and management of persons with hypothyroidism that emphasize evidence-based and patient-centered clinical decision making.

In the Clinic
Tool Kit

Hypothyroidism

Patient Information

https://medlineplus.gov/hypothyroidism.html
Patient information and handouts on hypothyroidism from the National Institutes of Health's MedlinePlus.

www.niddk.nih.gov/health-information/endocrine-diseases/hypothyroidism
Patient resources on hypothyroidism from the National Institute of Diabetes and Digestive and Kidney Diseases.

www.thyroid.org/hypothyroidism

www.thyroid.org/hipotiroidismo
Frequently asked questions on hypothyroidism in English and Spanish from the American Thyroid Association.

Information for Health Professionals

www.liebertpub.com/doi/full/10.1089/thy.2014.0028
American Thyroid Association 2014 guidelines for treatment of hypothyroidism.

www.aafp.org/afp/2012/0801/p244.html
Guideline on diagnosis and treatment of hypothyroidism from the American Academy of Family Physicians.

https://annals.org/doi/10.7326/M15-0483
U.S. Preventive Services Task Force 2015 recommendation statement on screening for thyroid dysfunction.

www.karger.com/Article/FullText/491388
2018 European Thyroid Association guidelines on the diagnosis and management of central hypothyroidism.

www.liebertpub.com/doi/pdf/10.1089/thy.2016.0457
American Thyroid Association 2017 guidelines for diagnosis and management of thyroid disease during pregnancy and the postpartum period.

WHAT YOU SHOULD KNOW ABOUT HYPOTHYROIDISM

What Is Hypothyroidism?

The thyroid is a small gland in the front of your neck. It makes hormones that control how the body uses energy. Hypothyroidism is a common condition that occurs when the thyroid gland does not make enough hormone for your body's needs. There can be several causes, including:

- Hashimoto thyroiditis (an autoimmune condition where your body attacks the thyroid)
- Radiation treatment for head and neck cancer
- Treatment for an overactive thyroid
- Surgical removal of the thyroid
- Too little iodine (a mineral the body needs) in the diet
- Certain medicines

What Are Common Symptoms?

- Feeling tired all the time
- Rough, dry skin
- Constipation
- Feeling cold frequently
- Weight gain
- Puffy eyes

These symptoms are common to many other conditions. Sometimes, people have no symptoms at all. In older patients, the most common symptoms are feeling tired and weak. Because of this, blood testing is always needed to diagnose hypothyroidism.

Am I at Risk?

Hypothyroidism is more common in women than in men and increases with age. It occurs more often in people with autoimmune diseases, Down syndrome, and Turner syndrome. You may also be at higher risk if you have any of the following:

- A goiter (swelling of the thyroid gland in the front of your neck)
- Certain medical conditions, such as type 1 diabetes and celiac disease
- A history of head and neck radiation therapy
- A personal or family history of thyroid disease
- Use of certain medications

How Is It Diagnosed?

- Your doctor will ask about your symptoms and medical history and examine you. The physical examination will include feeling your neck, where the thyroid gland is.
- You will have blood tests to measure your thyroid hormone levels.

Supplements containing biotin (commonly used for cosmetic skin, nail, and hair conditions) can affect blood test results. If you take these supplements, stop at least 3 days before having a blood test.

How Is It Treated?

Hypothyroidism is treated with thyroid hormone replacement, with the goal of improving symptoms and preventing complications. Thyroid hormone should be taken by mouth every day, preferably at bedtime. Symptoms usually get better within a few weeks of starting the medicine. Hypothyroidism is a permanent condition, so you will need to take medicine to replace thyroid hormone for the rest of your life.

It is important to take this medicine with lots of water and space it out from meals (1 hour before or 4 hours after) and any vitamin supplements containing iron, calcium, or soy so that your body can best absorb it.

After starting the medicine, you will have regular follow-up visits with your doctor. These visits will ensure that your symptoms are improving and that your hormone levels are in range. Follow-up blood tests every 6–8 weeks will show if your dose needs to be adjusted to get your levels within the correct range. Once your levels are in the correct range, they will only need to be checked every 3–6 months. The amount of medicine you need may change over time as your age and health status change.

Questions for My Doctor

- If I don't take thyroid hormone replacement medicine, what will happen?
- What are the risks and side effects of the treatment?
- What should I do if I miss a dose or two of the treatment?
- What are the differences between generic and brand-name hormone replacement?
- How often should I have follow-up visits?
- If I am pregnant or planning to become pregnant, what considerations should I be aware of?
- Will I need to see any other doctors?

For More Information

ACP℠
American College of Physicians
Leading Internal Medicine, Improving Lives

American Thyroid Association
www.thyroid.org/hypothyroidism

MedlinePlus
https://medlineplus.gov/hypothyroidism.html

Patient Information

Appendix Table. **Elements of Follow-up for Hypothyroidism**

Issue	*Method of Evaluation*	*Frequency*	*Notes*
History			
Weakness	Question	Every visit	Improvement expected
Lethargy	Question	Every visit	Improvement expected
Fatigue	Question	Every visit	Improvement expected
Cold intolerance	Question	Every visit	Improvement expected
Impaired memory	Question	Every visit	Improvement expected
Adherence	Question	Every visit	Adherence essential
Other drugs	Question	Every visit	May interfere with LT_4
Physical examination			
Dry skin	Palpation	Every visit	Improvement expected
Coarse skin	Palpation	Every visit	Improvement expected
Periorbital puffiness	Inspection	Every visit	Improvement expected
Laboratory			
TSH level	Measure by second- or third-generation TSH assay	Every 6–8 wk until normal, 3–6 mo later, then annually	Maintain within reference range (0.45–4.5 mU/L)

LT_4 = L-thyroxine; TSH = thyroid-stimulating hormone.