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Strategies for improved management of hypothyroidism

Management is clear-cut—yet many patients don't reach treatment goals. To optimize quality of life, master the fine points of T4 replacement and address the impact of comorbidities.

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PRACTICE RECOMMENDATIONS

› *Prescribe levothyroxine (LT4) to maintain thyroid-stimulating hormone (TSH) at 4 to 7 mIU/L in select patients with primary hypothyroidism for whom that range of the serum TSH level can be considered appropriate (ie, those older than 65 years and those who have underlying coronary artery disease or another debilitating chronic disorder).* (A)

› *Counsel all women of childbearing age with primary hypothyroidism that they need to have their dosage of LT4 increased as soon as pregnancy is suspected.* (A)

› *Keep in mind that treating hypothyroidism is not always necessary in older patients who have subclinical disease and a serum TSH level < 10 mIU/L.* (A)

Strength of recommendation (SOR)

(A) Good-quality patient-oriented evidence

(B) Inconsistent or limited-quality patient-oriented evidence

(C) Consensus, usual practice, opinion, disease-oriented evidence, case series

The hormones thyroxine (T4) and triiodothyronine (T3), produced by the thyroid gland, are crucial for maintaining metabolism. A deficit of thyroid hormone production—hypothyroidism—is a common endocrine disorder seen in primary care.

Although the diagnosis and management of hypothyroidism are considered straightforward, many patients with hypothyroidism do not achieve optimal treatment goals or see an improvement in their quality of life. In this article, we address the questionable utility of screening; outline the diagnostic approach, including the central role of laboratory testing; and explain why treatment requires a precise approach to address the range of patient types.

Epidemiology and classification

Estimates are that almost 5% of Americans 12 years or older have hypothyroidism; older people and women are more likely to develop the condition.[1] In the US National Health and Nutrition Examination Survey (NHANES III) of 13,344 people *without* known thyroid disease or a family history, hypothyroidism was found in 4.6% (overt [clinical] in 0.3% and subclinical in 4.3%); 11% had a high serum thyroid peroxidase antibody level, which increases their risk of hypothyroidism, and is treated the same as hypothyroidism of other causes; and, overall, lower serum thyroid-stimulating hormone (TSH) levels were seen in Blacks, compared to Whites and Mexican Americans.[1]

Primary hypothyroidism accounts for > 95% of cases of hypothyroidism, representing a failure of the thyroid gland to produce sufficient hormone. It has been shown that, in iodine-replete countries such as the United States, the prevalence of spontaneous hypothyroidism is 1% to 2%, and it is 10 times more common in women.[2,3]

Central hypothyroidism is caused by insufficient stimulation of the thyroid gland by TSH, due to pituitary (*secondary*

Many patients with hypothyroidism do not achieve optimal treatment goals or see an improvement in their quality of life.

hypothyroidism) or hypothalamic (*tertiary hypothyroidism*) disease and is estimated to occur in 1 in every 20,000 to 80,000 people in the general population.[4]

How does hypothyroidism manifest?

Signs and symptoms. Manifestations of hypothyroidism range from life-threatening to minimal or no clinical signs and symptoms (**TABLE W1**, available at mdedge.com/familymedicine). Signs and symptoms of low thyroid function vary by the degree of hypothyroidism at presentation.

Common signs and symptoms of low thyroid function include fatigue, weight gain, dry skin, brittle hair, hair loss, morning stiffness, muscle aches, joint pain, cold intolerance, diffuse headache, constipation, difficulty concentrating, low libido, depression, and menstrual irregularities. On physical examination, a patient might present with bradycardia, hypotension, hypothermia with slow speech or movement, coarse facial appearance, goiter, diffuse hair loss, cold hands and feet, and a prolonged Achilles tendon reflex.[5] Skin findings, such as keratosis pilaris, palmoplantar keratoderma (thickening of the skin), and pityriasis rubra pilar, can be associated with autoimmune hypothyroidism.[6,7]

Carpal tunnel syndrome, plantar fasciitis, infertility or miscarriage, dyspepsia, and small intestinal bacterial overgrowth can be associated with hypothyroidism; thyroid function should therefore be assessed in patients who have any of these conditions, along with other signs and symptoms of low thyroid function.[8,9] A patient with severe hypothyroidism might present with hemodynamic instability, pericardial or pleural effusion, and myxedema coma.[10]

Clues in the history and from the lab. A history of radiation to the head, neck, or chest area and a history or family history of autoimmune disorders are risk factors for autoimmune thyroid disease.[11,12] Laboratory findings can include markers of oxidative stress, such as elevated levels of low-density lipoprotein cholesterol and serum malondialdehyde.[13-15]

Screening and diagnosis

Screening. The US Preventive Services Task Force has asserted that evidence is insufficient by which to evaluate the benefits and risks of routine screening for thyroid dysfunc-

IMAGE: STEVE OH AND MYRIAM OH

tion in nonpregnant, asymptomatic adults.[16] According to the American Thyroid Association and the American Association of Clinical Endocrinologists, screening should be considered in high-risk patients, including those who take medication that affects thyroid function or the results of thyroid hormone assays (**TABLE W2**, available at mdedge.com/familymedicine).[17-20]

Screening inpatients is challenging and usually not recommended unless thyroid disease is strongly suspected. This is because changes in the levels of thyroid hormones, binding proteins, and the TSH concentration can occur in severe nonthyroidal illness; in addition, assay interference by antibodies and other substances can affect thyroid hormone measurement.[21]

Testing strategy. Generally, screening and diagnosis of hypothyroidism are based primarily on laboratory testing, because signs and symptoms are nonspecific (**FIGURE 1**[5]). A serum TSH level is usually the initial test when screening for thyroid dysfunction. A normal serum TSH value ranges from 0.5-5.0 mIU/L.

When an abnormal serum TSH level is found, further tests can be performed to investigate, including a serum free thyroxine (FT4) test. (Our preference is to order TSH and FT4 assays simultaneously to facilitate and confirm the diagnosis.) An FT4 test measures the amount of unattached, or free, thyroxine in blood by immunoassay. A normal FT4 value usually ranges from 0.7-1.9 ng/dL.

The combination of a high TSH level and a low FT4 level could be an indication of an underactive thyroid gland (ie, clinical or overt hypothyroidism). Milder, subclinical hypothyroidism is characterized by a higher-than-normal TSH level but a normal FT4 level.[22] Central (secondary) hypothyroidism is characterized by a low serum FT4 level and a serum TSH level that can be below the reference range, low normal, or even slightly high.[4]

These measurements must be interpreted within the context of the laboratory-specific normal range for each test. Third-generation serum TSH assays are more sensitive and specific than serum FT4 measurements for hypothyroidism. FT4 is usually measured by automated analogue immunoassay, which generally provides reliable results; abnormal binding proteins or other interferences occur in some patients, however, resulting in reporting of a falsely high, or falsely low, FT4 level. In such cases, FT4 by direct dialysis, or total T4, can be measured for further evaluation. In primary care, you are most likely to encounter primary hypothyroidism; secondary (central) hypothyroidism is much rarer (< 5% of cases).[4]

A patient with severe hypothyroidism might present with hemodynamic instability, pericardial or pleural effusion, or myxedema coma.

The ins and outs of treatment

For most patients, hypothyroidism is a permanent disorder requiring lifelong thyroid hormone replacement therapy—unless the disease is transient (ie, painless or subacute thyroiditis); reversible, because it is caused by medication; or responsive to medical intervention that addresses the underlying autoimmune condition.[19] Goals of treatment (**FIGURE 2**[5,23]) are to:

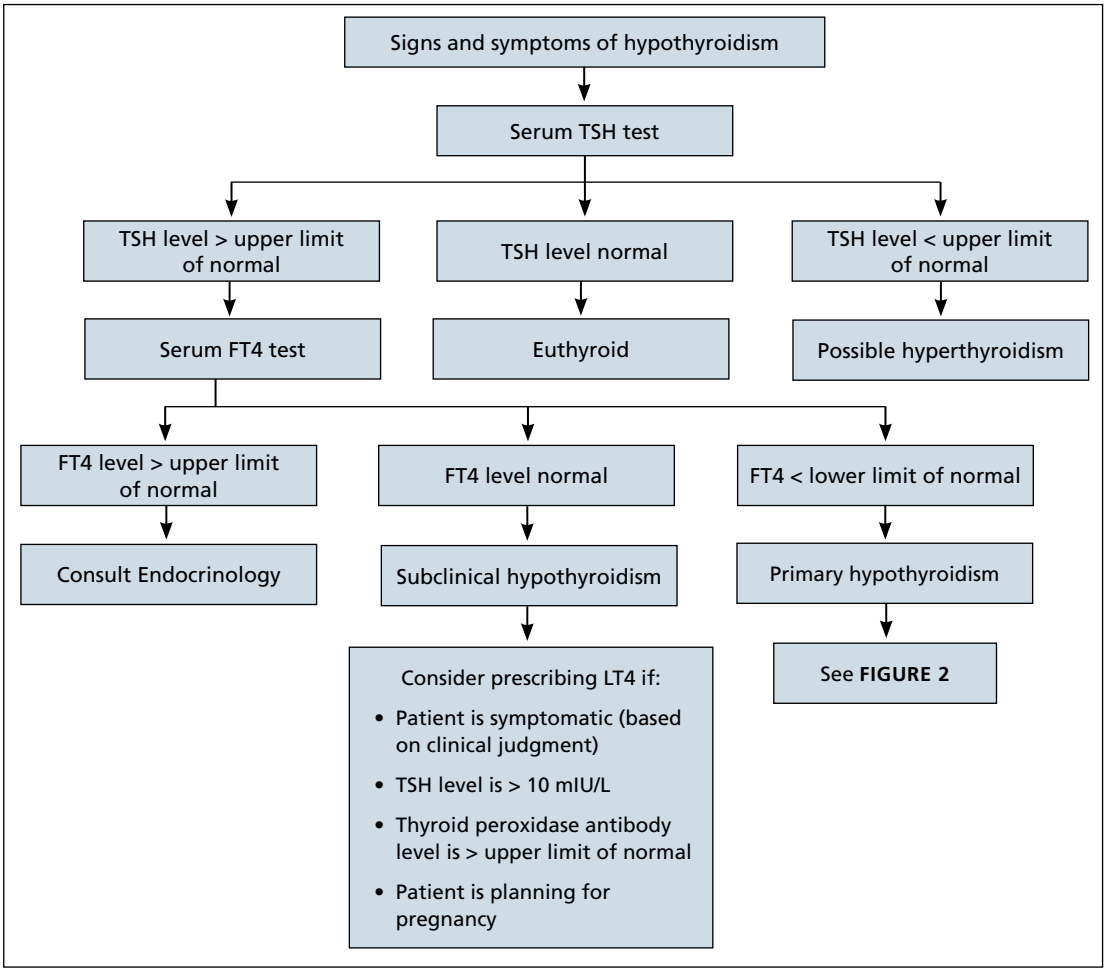
- normalize the TSH level to 0.5-5.0 mIU/L (the main goal), with an age-related shift toward a higher TSH goal in older patients (and an upper limit of normal of 7.5 mIU/L in patients who are ≥ 80 years of age)[20]
- restore the euthyroid state
- relieve symptoms
- reduce any goiter
- avoid overtreatment (iatrogenic thyrotoxicosis).

Desiccated thyroid extract (DTE), developed in the late 1880s and made from the dried thyroid gland of pigs, sheep, or cows, was the earliest treatment for hypothyroidism. The use of DTE has declined since the introduction of synthetic thyroxine (T4, or levothyroxine [here, referred to as LT4]), which is now the standard treatment.[20-22] LT4 is deiodinated in peripheral tissues to form T3, the active thyroid hormone; this process accounts for 80% of total T3 production daily.[24]

LT4 formulations. LT4 is commercially available in tablet, soft-gel, and liquid preparations. Most patients are treated with the tablet; the soft-gel capsule or liquid is an option for patients who absorb the tablet poorly (because of atrophic gastritis, celiac disease,

FIGURE 1

Evaluation of suspected hypothyroidism[5]



FT4, free thyroxine; LT4, levothyroxine; TSH, thyroid-stimulating hormone.

or gluten sensitivity or because they are post bariatric surgery). Increasing the dosage of the tablet form of LT4, with ongoing TSH monitoring, is more cost effective than moving to an alternative preparation.

If a switch of LT4 formulation is made (ie, from one manufacturer to another), test the serum TSH level to ensure that the therapeutic goal is being reached. Also, in our experience, it is best to prescribe a brand-name preparation of levothyroxine, not a generic, whenever possible, due to the variability in generic formulations and the potential presence of other (inert) ingredients.[25]

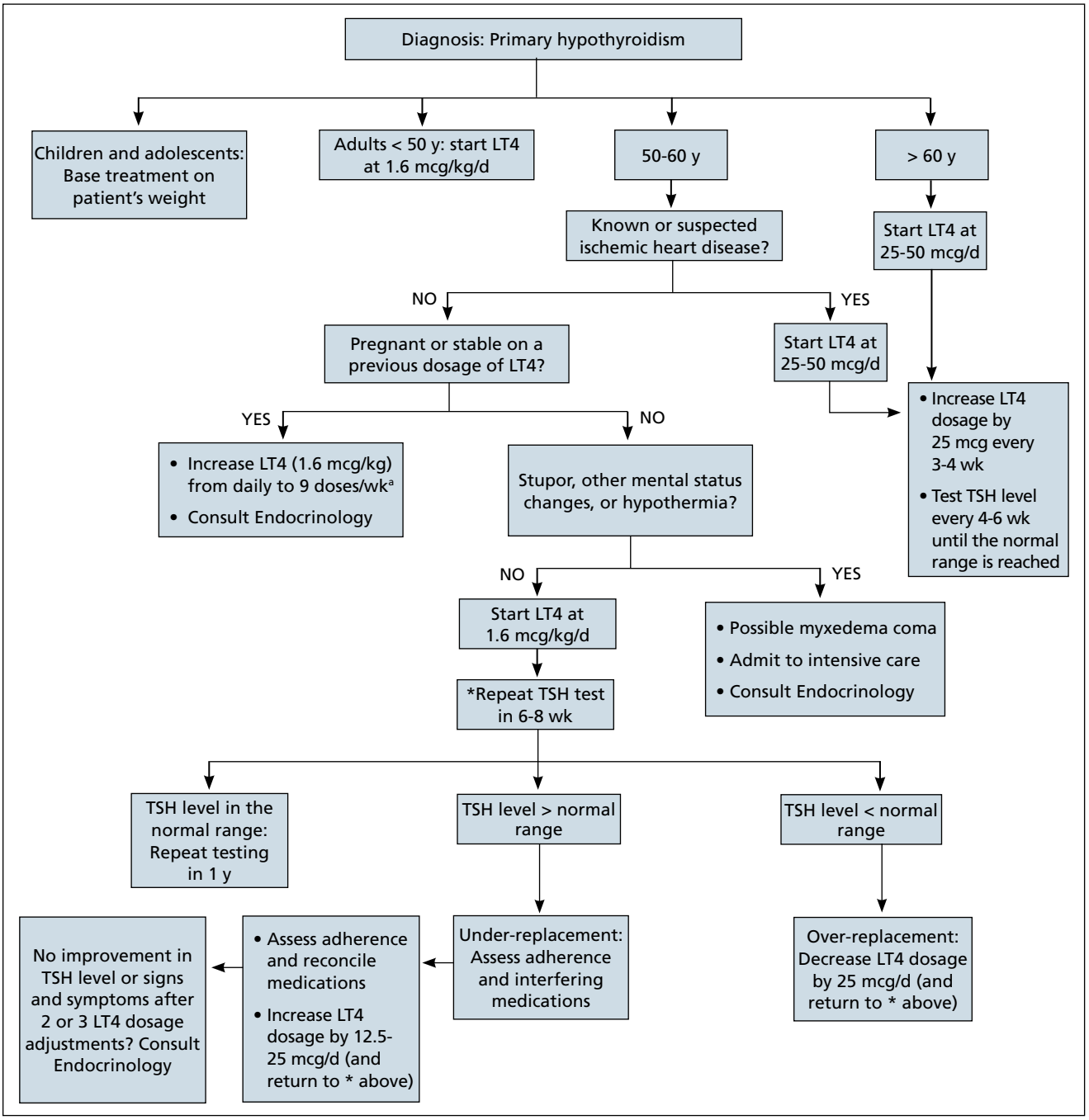
Dosing (TABLE 3[20,23]). The average full replacement dosage of LT4 for a young, healthy adult is approximately 1.6 mcg/kg/d. Older patients (> 65 years) or those with coronary artery disease (CAD) should be started on a lower dosage (25-50 mcg/d) and titrated to goal accordingly.

LT4 (tablets, soft-gel capsules, or liquid) should be administered on an empty stomach, with water only, 30 to 60 minutes before breakfast. Medications that interfere with LT4 absorption (eg, bile acid resins, calcium carbonate, ferrous sulfate) should be taken several hours after LT4. For patients who cannot take LT4 in the morning, taking it at bedtime (≥ 2-3 hours after the last meal) is acceptable.

Monitoring and titrating. Hypothyroid symptoms usually improve after 2 or 3 weeks of LT4 treatment; in severe hypothyroidism, complete recovery might take months. Ap-

FIGURE 2

Treatment of primary hypothyroidism[5,23]



LT4, levothyroxine; TSH, thyroid-stimulating hormone.

[a] By taking 1 dose per day every day of the week and a second dose on any 2 consecutive days of the week.

proximately 6 weeks after LT4 therapy is initiated, serum TSH should be measured. After assessing whether administration of LT4 at the starting dosage is appropriate, that dosage can be increased, or decreased, every 4 to 6 weeks until the TSH goal is reached. Once the patient is maintained at a given dosage, measure serum TSH once a year—more often

TABLE 3

LT4 dosing guidelines in hypothyroidism[20,23]

Population	Dosing of LT4
Nonpregnant patients	Starting dosage: 1.6 mcg/kg/d
Pregnant patients	At the earliest knowledge of pregnancy, increase the dosage (1.6 mcg/kg) from daily to 9 doses/wk[a]; refer to Endocrinology
Older patients or patients with known or suspected cardiac disease	Initial dosage: 25-50 mcg/d; increase by 25 mcg every 3-4 wk until full replacement dosage is reached
Patients with subclinical hypothyroidism	**TSH level < 10 mIU/L** Initial dosage: 50 mcg/d; increase by 25 mcg/d every 6 wk until TSH level is in normal range **TSH level ≥ 10 mIU/L** 1.6 mcg/kg/d

LT4, levothyroxine; TSH, thyroid-stimulating hormone.
[a] By taking 1 dose per day every day of the week and a second dose on any 2 consecutive days of the week.

TABLE 4

Equivalent doses of LT4, LT4 + LT3, and desiccated thyroid extract[34]

	Capsules								
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
LT4 (mcg)	88	100	112	125	137	150	175	200	250
LT4 + LT3 (mcg)	63/7.5	75/7.5	82/7.5	88/10	100/10	112/10	125/12	150/15	175/20
Desiccated thyroid extract (mg)	60	67.5	75	82.5	90	105	120	135	165

LT4, levothyroxine; LT3, liothyronine.
Adapted from Shakir et al. *J Clin Endocrinol Metab*. 2021.[34]

if there is an abnormal result or a change in the patient's health status.[23]

Adverse effects of LT4 therapy are rare, unless over-replacement occurs. Rarely, patients have an allergy to the dye or an excipient (filler) in the tablet.[26-28] The white, 50-mcg tablets can be given safely to patients with dye sensitivity. For those who have an allergy to an excipient (except gelatin) or gluten intolerance, the LT4 soft-gel capsule or liquid preparation (Tirosint) can be prescribed.

Pure LT4, in a capsule made from vegetable sources, can be ordered through a compounding pharmacy for patients who are allergic to animal products.

Anemia, especially iron-deficiency anemia, can cause intolerance to LT4 therapy; in such patients, lowering the starting dosage and treating anemia are indicated.[29]

Persistent symptoms (despite a normal TSH level). Because many hypothyroid symptoms are nonspecific, patients might come to think that their LT4 dosage is inadequate if they feel tired or gain weight. Persistent hypothyroid symptoms despite a normal serum TSH level might be due to (1) the inability of LT4 therapy to restore tissue thyroid hormone levels to normal or (2) other variables unrelated to hypothyroidism, including disorders associated with inflammation or autoimmune disease, certain medications, diet, lifestyle, and environmental toxins.

These patients might benefit from a detailed history to identify other causes and a switch to either LT4 + liothyronine (LT3; synthetic T3) combination therapy or DTE[26,30-33] (**TABLE 4**[34]), although a beneficial effect of LT4 + LT3 therapy was not seen in several studies.[35,36] Over-replacement with LT4 should be discouraged, due to concerns about thyrotoxicosis and its complications (eg, atrial fibrillation, accelerated bone loss).

CONTINUED

Consider screening for hypothyroidism in patients who take medication that affects either their thyroid function or the results of thyroid hormone assays.

DTE and LT4 + LT3. Use of DTE has decreased since the 1970s, when LT4 became the therapy of choice. Subsequently, anecdotal evidence emerged that some patients did not feel well on LT4 and preferred to return to DTE.[32,33]

Several clinical trials addressed the question of whether residual symptoms could be resolved through LT4 + LT3 combination therapy[31-39] (**TABLE 4**[34]), but evidence of any consistent superiority of combination therapy was not demonstrated.[35-39] In selected cases, patients might prefer the combination approach.[31,33,39] The quality of life of hypothyroid patients was found to be similarly improved with LT4 or DTE, but the latter was associated with modest weight loss (approximately 4 lbs); nearly 50% of study patients preferred treatment with DTE over LT4.[33] A follow-up study did not confirm weight loss with DTE, however.[34]

When LT4 monotherapy and LT4 + LT3 combination therapy were compared, results were mixed[31-39]; responsiveness to therapy containing LT3 might therefore depend on multiple variables, including genetic background, nutritional and lifestyle factors, stress, presence of comorbidities and autoimmune disorders, and other unidentified or poorly defined variables.[40-48]

Although combination therapy and DTE are not generally recommended over LT4 monotherapy, they might offer better options for patients who are still symptomatic when being treated with LT4 only: In a randomized, double-blind, crossover study that compared LT4 with DTE and with LT4 + LT3, one-third of the most highly symptomatic patients who had low scores on mood, cognitive, and quality-of-life assessments improved significantly after they were switched to combination therapy or DTE.[34]

The 2014 American Thyroid Association guidelines[24] do not support routine use of LT4 + LT3 in hypothyroid patients who have residual symptoms after LT4 monotherapy; however, a therapeutic trial of LT4 + LT3, while maintaining a normal serum TSH, is reasonable in selected patients. Candidates for DTE or LT4 + LT3 might include patients who do not feel well on LT4 monotherapy, are post thyroidectomy or post radioiodine therapy, or have a low serum T3 level. DTE and combination therapy are discouraged in older patients, patients who have underlying CAD, and pregnant patients.

Special treatment circumstances

A number of patient variables have the potential to alter management strategies for hypothyroidism.[18,20,23,40,49-53]

Age, comorbidity. Older patients (> 65 years) and patients with cardiopulmonary disease or CAD should be treated with LT4, 25 to 50 mcg/d, initially; that dosage can be titrated upward by 12.5 to 25 mcg/d every 4 to 6 weeks until the TSH goal is reached—preferably, in the range of 4 to 8 mIU/L. An increase in the dosage of LT4 might be required in the presence of malabsorption (eg, gastrointestinal disorders, celiac disease) and in nephrotic syndrome.[18,20,23]

Body weight. A *decrease* in the dosage of LT4 might be indicated in the setting of significant weight loss (> 10% body weight).[23]

Co-pharmacy. An increase in the dosage of LT4 might be required when other drugs (eg, phenytoin, phenobarbital, rifampin, and carbamazepine) have led to an increased rate of thyroid hormone metabolism. A *decrease* in the dosage of LT4 might be necessary after initiation of androgen therapy.[23]

Pregnancy. Women with pre-existing hypothyroidism require an increase of 25% to 50% in their LT4 dosage during pregnancy to maintain a TSH level in the recommended pregnancy reference range. Thyroid function should be monitored every 4 to 6 weeks to ensure that the TSH target for each trimester is reached (first trimester, 0.1-4 mIU/L; second trimester, 0.2-4 mIU/L; third trimester, 0.3-4 mIU/L). Postpartum, LT4 can be reduced to the prepartum dosage; TSH should be checked every 4 to 6 weeks to maintain the TSH goal.[23]

Estrogen therapy. Hypothyroid women who are receiving estrogen therapy might require an increase in their LT4 dosage because serum thyroxine-binding globulin levels are increased by estrogens or through other mechanisms that have not been identified.[23]

TABLE 5

Recommendations for managing subclinical hypothyroidism[59-62]

Symptoms of subclinical hypothyroidism can be nonspecific and might not always improve when treated with LT4.

Age (y)	Thyroid-stimulating hormone level (mIU/L)	Test for level of thyroperoxidase antibody or thyroglobulin antibody (or both)?	Is treatment with LT4 recommended?[a]
Any age	≥ 10	N/A	Yes
< 65	7.0-9.9	N/A	Yes
< 65	4.0-6.9	Yes	Yes
> 65	7.0-9.9	Yes	Yes[b]
> 65	4.0-6.9	N/A	No

LT4, levothyroxine; N/A, not applicable.

[a] The presence of a goiter or presence of thyroid antibodies, or both, can also be considered when selecting LT4 treatment. In women of childbearing age who are planning to conceive and have a history of infertility, LT4 treatment is recommended.

[b] When there are convincing symptoms of hypothyroidism.

Surgical candidacy. Observational studies show few adverse outcomes in surgical patients with mild (subclinical) hypothyroidism or moderate hypothyroidism; however, the risk of adverse surgical outcome might be increased in patients with severe hypothyroidism. For patients in whom surgery is planned and who have:

- *subclinical hypothyroidism* (elevated TSH and normal FT4), we recommend that surgery—urgent or elective—*not* be posptoned but proceed.
- *moderate (overt) hypothyroidism* who require urgent surgery, we recommend not postponing surgery, even though minor perioperative complications might develop. Such patients should be treated with LT4 as soon as the diagnosis for which surgery is required has been made. Alternatively, when moderate hypothyroidism is discovered in a patient who is being evaluated for elective surgery, we recommend postponing surgery until the euthyroid state is restored.
- *severe hypothyroidism* (myxedema coma [discussed in a bit]; severe clinical symptoms of chronic hypothyroidism, such as altered mental status, pericardial effusion, or heart failure; or a very low level of T4), surgery should be delayed until hypothyroidism has been treated. When emergency surgery is required for a severely hypothyroid patient, they should be treated with LT4 as soon as the diagnosis for which surgery is indicated has been made. When emergency surgery must be performed in a patient with myxedema coma, we recommend treatment with LT4 + LT3, rather than LT4 alone, often administered intravenously because LT4 is poorly absorbed in these patients.

Nonadherence. For patients who do not take LT4 regularly or do not respond to efforts to improve adherence, LT4 can be given weekly, instead of daily, although this interval is not ideal. Weekly dosing should not be used in older patients with CAD.[23]

Thyroid cancer. Patients who are post total thyroidectomy for thyroid cancer need to take LT4 to treat hypothyroidism and to prevent recurrence of thyroid cancer. The goal TSH level should be based on the cancer stage and risk of recurrence and should be monitored by an endocrinologist.

Myxedema coma. This medical emergency has high mortality. Myxedema coma occurs when severe hypothyroidism leads to any, or a combination, of the following: diminished mentation; hypothermia; bradycardia; hyponatremia; hypotension; cardiovascular, respiratory, and gastrointestinal dysfunction; and renal insufficiency. LT4, LT3, and glucocorticoids should be administered intravenously and the patient moni-

tored closely—preferably in consultation with an endocrinologist.

When to seek consultation

A patient with hypothyroidism should be referred to Endocrinology if they are < 18 years of age, pregnant, unresponsive to therapy, or have cardiac disease, coexisting endocrine disease, suspected myxedema coma, goiter or thyroid nodules, or a structural thyroid abnormality.

What we know about nutrition and hypothyroidism

Although it is commonly recognized that iodine is essential for production of thyroid hormone, other nutritional factors might contribute to proper production of thyroid hormones, including:

- adequate intake of iron, tyrosine, selenium, zinc, and vitamins E, B_2, B_3, B_6, C, and D[44,45]
- selenium and zinc, which increase conversion of T4 to T3 and might be important in the management of hypothyroid patients[40,46]
- vitamin A, zinc, and regular exercise, which have been shown to improve cellular sensitivity to thyroid hormones.

Low iron stores can contribute to persistent symptoms and poor quality of life in patients with hypothyroidism, despite their being treated according to guidelines.[29,47]

Despite what is known about these nutritional connections, there is insufficient evidence that improving nutrition can reverse hypothyroidism.

Prevention

Prevention of hypothyroidism should take into account variables that affect or inhibit thyroid function, such as stress, infection (eg, Epstein-Barr virus), excessive fluoride intake, toxins (eg, pesticides, solvents, mercury, cadmium, and lead), autoimmune disease (eg, celiac disease), and food sensitivity.[54,55] Oxidative stress can also cause thyroid impairment.[40-48,54-58]

Otherwise, there are, at present, no effective strategies for preventing thyroid disorders.

Increasing the dosage of the tablet form of LT4 (while monitoring the TSH level), is more cost effective than moving to an alternative preparation, such as a softgel or liquid.

Subclinical hypothyroidism: Elusive management target

Subclinical hypothyroidism is defined as a normal serum FT4 level in the presence of an elevated serum TSH level. The prevalence of subclinical hypothyroidism varies from 3% to 15%, depending on the population studied; a higher incidence has been noted in women and older people.[59] In the NHANES III,[1] which excluded people with previously diagnosed thyroid disease, the incidence of subclinical hypothyroidism was 4.3%.

Causes of subclinical hypothyroidism are the same as those of overt hypothyroidism, and include Hashimoto disease. The combination of an elevated TSH level and a normal FT4 level is associated with disorders characterized by protein-binding variations (eg, pregnancy, genetic disorders, drugs), TSH-secreting pituitary adenoma, class II and III obesity (respectively, body mass index, ≥ 35 but < 40 and ≥ 40), and assay variability.[49,51]

Lab diagnosis: Fraught with difficulty

The serum TSH level and either the total T4 level or the FT4 level should be measured to make a diagnosis of subclinical hypothyroidism. Most laboratories use a 1-step analogue immunoassay to determine free thyroid hormones; protein-binding variations can thus affect measurement of FT4.

Several scenarios that can result in inaccurate measurement of FT4 by radioimmunoassay include genetic disorders that affect binding proteins; pregnancy; use of certain drugs, including heparin, furosemide, antiepileptic agents, salicylate, ferrous sulfate, and cholesterol-binding resins; and some medical conditions, including cardiac surgery, critical illness, and renal failure. Variables that inhibit proper production of thyroid hormones—stress, infection, fluoride (an iodine antagonist), toxins (pesticides, mercury, cadmium, lead) and autoimmune conditions, such as celiac disease—should be considered when attempting to determine the cause of subclinical hypothyroidism.

Liquid chromatography–mass spectrometry measurement of thyroid hormones might be more accurate than immunoassay.[53] Measuring serum total T4 and FT4 by dialysis, free from interfering proteins, might

also be useful when measurement of FT4 by immunoassay is affected by binding-protein variations.

Features of subclinical hypothyroidism

Most patients who have subclinical hypothyroidism and a serum TSH level < 10 mIU/L are asymptomatic. Some might have nonspecific symptoms of hypothyroidism, however, such as reduced quality of life, poor cognitive function, and poor memory—symptoms that do not typically correlate with the serum TSH level.

It has been suggested that some elderly people *normally* have a higher level of serum TSH, and that they might have even a prolonged lifespan.[51] Additionally, it has been shown that, in nonpregnant adult patients with subclinical hypothyroidism and a serum TSH level of 4.5 to 10 mIU/L, treatment with LT4 was not associated with improvement in thyroid-related symptoms or general quality of life.[52]

Treat, or don't treat, subclinical hypothyroidism?

It is well accepted that the goal of therapy in hypothyroid patients is to normalize the serum TSH level; however, the American Thyroid Association and the American Association of Clinical Endocrinology recommend starting LT4 in patients with a serum TSH level ≥ 10 mIU/L (**TABLE 5**).[59-62] The principal reason for not treating subclinical hypothyroidism is the lack of benefit in reducing the risk of cardiovascular morbidity and mortality when the TSH level is between 7.5 and 10 mIU/L.[62]

Routine treatment of patients with a serum TSH level of 4.5 to 10 mIU/L remains controversial. When TSH is 7.0 to 9.9 mIU/L, treatment is recommended for (1) patients < 65 years and (2) for older patients (> 65 years) only when there are convincing hypothyroid symptoms because of concern about unintended overtreatment.

When the TSH level is anywhere above the upper limit of normal to 6.9 mIU/L, treatment is recommended for patients < 65 years old, patients who have a high titer of thyroid peroxidase antibodies, and patients with goiter—but not for patients > 65 years (and, especially, not for octogenarians) because their upper limit of normal could be as high as 6 to 8 mIU/L, especially if they are otherwise healthy.

Treatment should be considered for women with subclinical hypothyroidism who are trying to conceive or experiencing an infertility problem.

For patients with subclinical hypothyroidism who are not being treated, monitor thyroid function every 6 to 12 months by testing TSH and FT4. JFP

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Prescribe a brand-name preparation of levothyroxine whenever possible; generic formulations might have variable potency or contain other ingredients.

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TABLE W1

Signs and symptoms of hypothyroidism

Signs	Symptoms
Bradycardia	Arthralgias
Coarse facies	Cold intolerance
Cognitive impairment	Constipation
Delayed relaxation phase of deep-tendon reflexes	Depression
Diastolic hypertension	Dry skin
Edema	Fatigue
Elevated C-reactive protein level	Menorrhagia
Elevated creatine kinase level	Myalgia
Elevated low-density lipoprotein	
Elevated triglycerides	
Eyebrow thinning	
Goiter	
Hair thinning or loss	
Hoarseness	
Hyperprolactinemia	
Hyponatremia	
Hypothermia	
Infertility	
Low-voltage electrocardiogram	
Macroglossia	
Normocytic anemia	
Pericardial or pleural effusion	
Periorbital edema	
Proteinuria	
Voice changes	
Weight gain	

TABLE W2

Risk factors for hypothyroidism[17-20]

Autoimmune disease
• Adrenal insufficiency
• Celiac disease
• Gastric atrophy
• Multiple autoimmune endocrinopathies
• Type 1 diabetes mellitus
Down syndrome
Family history of thyroid disease
Goiter
Medications
• Amiodarone
• Biotin
• Immune checkpoint inhibitors
• Interferons
• Interleukin-2
• Lithium
• Phenobarbital
• Rifampin
• Tyrosine kinase inhibitors
Radioiodine therapy
Thyroidectomy
Turner syndrome