

# Hypothyroidism

## Clinical Challenges in Diagnosis and Treatment

Kara-anne Gregory Curl, MS, MPAS, PA-C

Although hypothyroidism is common, its typically vague symptoms of fatigue, lack of energy, and weight gain are shared with many other conditions.

Awareness of risk factors for hypothyroidism will aid in the differential diagnosis, and the patient's symptoms can help guide the clinician to the appropriate diagnostic workup. Thyroid function test results are necessary to confirm or rule out the diagnosis.

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### LEARNING OBJECTIVES

- Identify the signs and symptoms of and risk factors for hypothyroidism.
- Name the laboratory tests used to diagnose or rule out hypothyroidism.
- Describe current evidence-based and alternative treatments for hypothyroidism.
- Discuss appropriate long-term follow-up and monitoring of hypothyroidism.
- Instruct patients regarding optimal self-management of hypothyroidism.

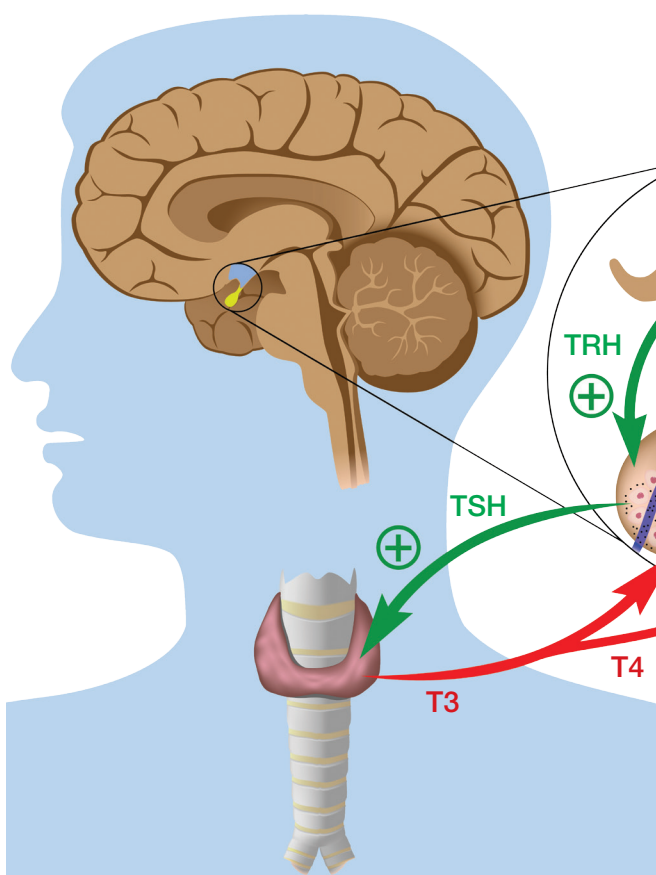
Approximately 4.6% of the US population ages 12 and older has been diagnosed with hypothyroidism, making it the most frequently diagnosed thyroid disorder.<sup>1</sup> Hypothyroidism is defined by an underproduction of thyroid hormones and can be either primary or secondary. *Primary hypothyroidism* is caused by the failure of the thyroid gland to produce adequate quantities of the hormones triiodothyronine (T3) and levorotatory thyroxine (T4). *Secondary (central) hypothyroidism* is a result of inadequate production of thyrotropin (TSH) by the pituitary gland; less often, it is caused by inadequate production of thyrotropin-releasing hormone by the hypothalamus. The great majority of patients with hypothyroidism have the primary form of the disease. In the US, the most common cause of hypothyroidism is chronic autoimmune thyroiditis (Hashimoto thyroiditis); worldwide, it is iodine deficiency.

Because hypothyroid symptoms are vague, the disease can be difficult to diagnose. Patients most often present with complaints of fatigue and lack of energy, raising suspicion for hypothyroidism; but true symptomatic, overt hypothyroidism is rather rare, occurring in only 0.3% of the population.<sup>2</sup>

*Subclinical hypothyroidism*, in which TSH levels are elevated but T3 and T4 levels are normal and the patient experiences few, if any, symptoms, is much more common. This makes the use of diagnostic laboratory tests essential; hypothyroidism cannot be diagnosed based on clinical presenta-

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**Kara-anne Gregory Curl** is an Adjunct Clinical Instructor of Medicine, Division of Endocrinology and Metabolism, with Medical Faculty Associates at George Washington University in Washington, DC. *The author has no significant financial relationships to disclose.*



The hypothalamic–pituitary–thyroid axis is a feedback loop that regulates metabolism. Thyrotropin-releasing hormone (TRH), produced by the hypothalamus, stimulates the pituitary gland to release thyrotropin (TSH). TSH causes the thyroid gland to release thyroid hormones (T3 and T4). These then suppress the production of TRH and TSH via a negative feedback loop (red arrows). If T3 and T4 levels dip, the hypothalamus and pituitary are stimulated to produce more TRH and TSH (green arrows).

tion alone. Signs and symptoms may include fatigue, lack of energy, cold intolerance, weight gain, thinning hair/hair loss, dry skin, constipation, menstrual cycle abnormalities, irritability, and depression. Bradycardia and hypotension are also possible. Physical examination may reveal depressed affect, eyelid edema, loss of lateral third of the eyebrow, thickened tongue, dry skin, and hyporeflexivity; however, most patients will have a benign and unrevealing physical examination.<sup>3</sup>

Hypothyroidism is more common in white people and in women and increases in incidence after age 60. Risk factors for hypothyroidism include

- Family history
- Autoimmune disorders (eg, type 1 diabetes, Addison disease)
- History of Graves disease treated with radioactive iodine or thyroidectomy
- Past external beam radiotherapy for head and neck malignancies
- Postpartum thyroiditis
- Turner and Down syndromes
- Multiple sclerosis
- Amiodarone or lithium use
- Iodine deficiency or previous residence in an iodine-deficient area.<sup>4</sup>

In addition, testing for hypothyroidism may be warranted in patients with any of the diagnoses in Table 1 (next page).

Because of its vague symptomatology, hypothyroidism can mimic many disease processes. How-

ever, the most pertinent include depression, anemia, and dementia/Alzheimer disease. Laboratory testing will almost always identify hypothyroidism.

## LABORATORY WORKUP

### Thyrotropin

The diagnosis of hypothyroidism is based on the results of the TSH test, which is the primary screening test for thyroid dysfunction.<sup>4</sup> TSH secretion is extremely sensitive to minor increases and decreases in T3 or T4, making it the most reliable laboratory test for the assessment of thyroid function. An elevated serum TSH level in the presence of hypothyroid symptoms is diagnostic of primary hypothyroidism. Other causes of elevated TSH, such as thyrotropin-secreting pituitary tumors, are rare, and their symptomatology is different.<sup>3</sup>

### Free Levorotatory Thyroxine

Though elevated TSH levels occur before T4 abnormalities are detected, T4 measurement can sometimes be useful in the diagnosis of hypothyroidism, especially in cases of possible central hypothyroidism. As a diagnostic test, measurement of serum free T4 (FT4) is preferable to total T4 because T4 binds to specific proteins in serum, making obtaining an accurate total T4 level subject to factors that alter binding. By contrast, FT4, the metabolically active form of the hormone, is not affected by binding factors. In primary hypothyroidism, FT4 is low or normal.<sup>4</sup>

Measurement of the FT4 level will also confirm the diagnosis of central hypothyroidism, if the FT4 is low when TSH is normal or low. As FT4 decreases, the TSH should elevate to compensate; in the presence of a low FT4, even a normal TSH is indicative of

**TABLE 1**  
Diagnoses That Prompt Testing for Hypothyroidism

Adrenal insufficiency
Alopecia
Anemia, unspecified deficiency
Cardiac dysrhythmia, unspecified
Changes in skin texture
Congestive heart failure
Constipation
Dementia
Diabetes, type 1
Dysmenorrhea
Hypercholesterolemia
Malaise and fatigue
Mixed hyperlipidemia
Myopathy, unspecified
Prolonged QT interval
Vitiligo
Weight gain

Source: Garber et al. *Endocr Pract.* 2012.<sup>4</sup>

hypothyroidism. In a patient with overt hypothyroid symptoms with a normal TSH, an FT4 should be ordered for further workup.<sup>4</sup>

### Triiodothyronine

Measurement of the serum T3 level, whether total or free, is of little clinical utility because it often remains normal, even as TSH and T4 levels change.<sup>4</sup>

Typical diagnostic test results in primary and secondary hypothyroidism are summarized in Table 2.

### Other Factors That May Affect Thyroid Function Test Results

The overall health status of the patient must be considered when evaluating the results of thyroid function tests because the results can be affected by other factors.

- Serum TSH may be low, often in combination with low FT4, in hospitalized patients with acute illness.
- TSH may increase to levels above normal during recovery from nonthyroid-related illness.
- Serum TSH typically falls (infrequently to below 0.1 mIU/L) during the first trimester of

pregnancy due to the stimulatory effects of human chorionic gonadotropin on the thyroid.<sup>5</sup> Levels typically return to normal in the second trimester.

- TSH and FT4 can be altered in the postpartum period secondary to postpartum thyroiditis. Levels will often resolve on their own without treatment.
- Patients with anorexia nervosa may have low TSH levels as well as low levels of FT4 secondary to pituitary and hypothalamic dysfunction.
- Mild TSH elevations may also be a normal manifestation of aging; TSH values above 3.0 mIU/L occur with increasing frequency with age.<sup>4</sup>

### Thyroid Peroxidase Antibodies

Testing the patient for thyroid peroxidase (TPO) antibodies, although not required to make the hypothyroidism diagnosis, may provide additional useful information. A positive TPO antibody result is significantly associated with hypothyroidism; in particular, TPO antibodies are more likely to be present in patients with autoimmune thyroiditis, helping to confirm the diagnosis.<sup>2,4</sup> However, positive antibody test results do not change clinical management decisions. Results will remain positive during treatment, and the continued presence of antibodies warrants no alteration in treatment or medication dose.

An elevated TPO antibody level does impart a risk for future transition to overt hypothyroidism, so this test is recommended for patients with subclinical hypothyroidism. In addition, for patients with other autoimmune diseases, such as type 1 diabetes or Addison disease, or with chromosomal disorders, such as Down or Turner syndromes, TPO antibodies suggest a propensity toward hypothyroidism. Current research also indicates that both pregnancy rates and pregnancy outcomes improve when TPO antibody-positive patients whose TSH levels are above 2.5 mIU/L are treated.<sup>5</sup>

### DIAGNOSIS

The diagnosis of hypothyroidism is made on the basis of laboratory test results, but symptomatology can help guide the clinician to the appropriate laboratory workup. Symptoms alone, when laboratory values are within normal limits or even at the high end of the normal range, do not support a hypothyroidism diagnosis. In such a case, a differential diagnosis should be pursued.

Since overt symptoms of hypothyroidism are

**TABLE 2**  
Typical Findings for Thyroid Function Tests

	TSH Level	Free T4 Level	T3 Level
<b>Primary Hypothyroidism</b>	Elevated	Low or normal	Normal or low
<b>Secondary Hypothyroidism</b>	Low or normal	Low	Normal or low

Abbreviations: TSH, thyrotropin; T4, levothyroxine; T3, triiodothyronine.  
Source: Garber et al. *Endocr Pract.* 2012.<sup>4</sup>

rare, clinicians may wonder if they should screen all their patients for hypothyroidism. Current recommendations, as set forth in the joint American Thyroid Association (ATA) and American Association of Clinical Endocrinologists (AACE) clinical practice guidelines, support “aggressive case finding” rather than universal screening because as yet, there is no consensus on screening guidelines.<sup>4</sup> The ATA recommends screening all adults at age 35 and then every five years thereafter.<sup>6</sup> In contrast, the AACE recommends routine TSH measurement in “older” patients, particularly women.<sup>7</sup>

There is, however, compelling evidence for testing patients with any of the following<sup>4</sup>

- An autoimmune disease
- Pernicious anemia
- A first-degree relative with autoimmune thyroid disease
- An abnormal thyroid examination
- Past radiation to the thyroid gland, including radioactive iodine therapy for hyperthyroidism
- Past external beam radiotherapy for head and neck malignancies
- History of thyroid surgery
- History of thyroid dysfunction
- One of the diagnoses listed in Table 1.

It is also suggested that patients with psychiatric disorders and patients taking amiodarone or lithium be screened.<sup>4</sup>

## TREATMENT

The standard evidence-based treatment for hypothyroidism is hormone replacement with levothyroxine.<sup>4</sup> This is a Grade A recommendation in the ATA/AACE joint guidelines. Levothyroxine is bioequivalent to T4 in the body and has a half-life of approximately six to seven days. It is stable and easily adjusted by monitoring TSH levels; adverse reactions or complications are minimal. The starting dose of

levothyroxine is 1.6 µg/kg/d for both primary and secondary (central) hypothyroidism.

Dose increases are made in 12.5 or 25 µg increments. In primary hypothyroidism, TSH levels should be monitored to determine the need for dose adjustments. FT4 need not be checked unless there is a discrepancy in the TSH levels.<sup>4</sup> In secondary hypothyroidism, TSH levels will always remain normal or low, and FT4 should be used to monitor therapy. Levels should be measured four to eight weeks after initiation of treatment or after subsequent dose adjustments.

## Overt Hypothyroidism (Primary or Secondary)

All patients with symptomatic, overt hypothyroidism and an elevated TSH level should be treated. Treatment is lifelong, and the goal is to reduce patient symptomatology, improve well-being, and prevent complications. The treatment target is a TSH level in the normal range, approximately 0.45 to 4.5 mIU/L on most laboratory assays. However, NHANES III data revealed that the mean serum TSH level in the normal population is 1.5 mIU/L.<sup>2</sup> Based on this fact and on their experience, many clinicians would argue that a more appropriate goal is a TSH target in the midnormal range, such as 0.5 to 2.5 mIU/L. There is little evidence to support a low- or subnormal TSH target in the treatment of hypothyroidism.<sup>4</sup>

## Subclinical Hypothyroidism

For patients with the more common subclinical hypothyroidism (an elevated TSH level without symptoms), the benefits of treatment are less clear. It is suggested that if the TSH level is > 10 mIU/L, even patients without symptoms should be treated because risk for overt hypothyroidism is high.<sup>8</sup> A TSH level > 10 mIU/L has also been shown to increase the patient’s coronary artery disease (CAD) risk.<sup>9</sup> For

individuals with TSH levels in the 4.5 to 10 mIU/L range who feel well and have no hypothyroid symptoms, the evidence is less clear. Treatment may be beneficial, but this has not been determined definitively.<sup>4</sup> A watch-and-wait approach may be taken with these patients; if symptoms develop, treatment should be considered.

Patients with subclinical hypothyroidism generally do not require full replacement doses (ie, a starting dosage of 1.6 µg/kg/d). A dosage of 25 to 75 µg/d is typically sufficient to achieve goal TSH levels. For patients older than 60 with no CAD and for all patients with CAD, lower starting dosages of 50 µg/d and 12.5 to 25 µg/d, respectively, are recommended.<sup>4</sup>

*“There is no benefit in treating symptomatic patients for hypothyroidism when thyroid test results are normal.”*

### Normal TSH, Positive TPO in Pregnancy

Current clinical evidence does not support treatment of patients who have normal TSH levels (2.5 to 4.5 mIU/L) but who are positive for TPO antibodies.<sup>4</sup> The exception is pregnant women or those considering pregnancy. Research suggests that the rates of spontaneous miscarriage and preterm labor are higher in TPO-positive women in this TSH range, so treatment may reduce these risks.<sup>4</sup>

### ADDITIONAL TREATMENT CONSIDERATIONS Overtreatment

The main complication of hypothyroidism treatment occurs when the patient receives more thyroid hormone than is required, which has been reported in 20% of cases.<sup>9</sup> The primary risks of overtreatment are osteoporosis and atrial fibrillation. Care should be taken especially in vulnerable populations such as the elderly, who are particularly susceptible to atrial fibrillation, and postmenopausal women, who are prone to accelerated bone loss. Targeting a TSH level in the midnormal range (0.5-2.5 mIU/L) will help the clinician avoid overtreatment complications; if symptoms persist, other causes should be sought.

For persistent symptomatology in the presence of normal thyroid test results, clinicians should consider other potential causes.

### Combination T4/T3 Treatment

Liothyronine is bioequivalent to T3 in the body. It is not recommended as a primary agent except in cases of thyroid suppression requiring quick reversal; its half-life is only approximately 18 hours. This short half-life makes it more difficult to monitor because T3 levels can vary substantially throughout the day.<sup>3</sup>

Recent media attention has focused on combination levothyroxine-liothyronine treatment for hypothyroidism, and patients may inquire about this treatment option. The healthy thyroid gland produces these hormones in a ratio of approximately 13:1; most of the active T3 in the body results from T4 to T3 conversion in the peripheral tissues.<sup>3</sup>

But is combination therapy an evidence-based treatment option for hypothyroidism? The ATA/AACE joint guidelines indicate that there is inadequate evidence to support the use of levothyroxine and liothyronine combinations to treat hypothyroidism. This recommendation was downgraded from Grade A to Grade B in the current guidelines.<sup>4</sup> This is because a

few studies suggest that some patients report feeling better on T4/T3 combinations, and it is possible that some patient subgroups may benefit from combination treatment.<sup>4</sup> There are no data that clearly identify these subgroups, and it is unknown precisely why some patients report improvement; further research is required.<sup>4</sup> Combination therapy is not recommended for pregnant women or those planning pregnancy because of the potential for harm to the fetus.<sup>4</sup>

Patients sometimes request a more “natural” treatment for hypothyroidism, and animal-derived desiccated thyroid is the one most often prescribed.<sup>4</sup> The two commonly used forms of desiccated thyroid are porcine in origin. Each is a levothyroxine-liothyronine combination in a ratio of approximately 4:1. While a recent randomized, double-blind, crossover study compared desiccated thyroid extract (DTE) to levothyroxine treatment and found that 48.6% of study subjects preferred DTE therapy, the authors concluded that “DTE therapy may be relevant for some hypothyroid patients” without defining the characteristics of those patients.<sup>10</sup>

In addition, because desiccated thyroid is derived from a tissue product, there can be variability in dosing that may make it challenging to reach treatment goals consistently. Inquiring vegan and vegetarian

patients would also need to be advised of the animal origin of desiccated thyroid.

### Treatment When Tests are Normal

Clinicians commonly encounter patients who request treatment for hypothyroid symptoms in the absence of laboratory evidence of hypothyroidism. Although hypothyroid symptoms are common, vague, and nonspecific and pinpointing their precise etiology may be difficult, there is no benefit in treating patients for hypothyroidism when thyroid test results are normal. In fact, treatment may be harmful, as there is substantial risk for subclinical or overt hyperthyroidism.<sup>4</sup>

### Generic vs Brand-Name Levothyroxine

Both generic and brand-name preparations of levothyroxine are available. Generic formulations are made by a variety of manufacturers, and formulations can vary in production; a brand name assures one manufacturer and consistency in production. It is difficult to accurately assess the bioequivalence and, therefore, the interchangeability, of the various manufacturers' generic formulations.<sup>4</sup> Differences in bioavailability of the drug may affect the dose the patient receives. Minor fluctuations may occur in thyroid function test results, which may or may not be clinically acceptable in an individual patient. Therefore, the current consensus encourages the use of a consistent levothyroxine preparation for individual patients to minimize variability from refill to refill.<sup>4</sup> For patients for whom medication cost is a key factor, generic formulations can be considerably less expensive than their brand-name counterparts.

### FOLLOW-UP TESTING

For primary hypothyroidism, the frequency of follow-up is dictated by symptoms and laboratory test values. Patients should be advised that symptoms will improve with treatment but that this improvement may not be noticeable for three to six months, even after TSH levels have reached the normal range.<sup>4</sup>

Thyroid function testing is typically repeated at four to eight weeks to assess initial dose titration; once an adequate replacement dose has been reached, testing may be repeated at six months and then annually thereafter unless symptoms arise.<sup>4</sup> In pregnant women, TSH and FT4 levels should be measured every four weeks during the first half of pregnancy and at least once between 26 and 32 weeks' gestation (levothyroxine dose requirements

## CROSSECTION

- In subclinical hypothyroidism, asymptomatic patients with TSH levels below 10 mIU/L do not require treatment; for those with higher levels (even if asymptomatic), treatment is suggested because of risk for overt hypothyroidism and coronary artery disease.
- When treating overt hypothyroidism, target a TSH level in the midnormal range (0.5 to 2.5 mIU/L) to avoid the health risks (osteoporosis and atrial fibrillation) of overtreatment.
- Educate patients on the importance of medication timing, because food and minerals can decrease levothyroxine absorption.

typically increase by 20% to 50% during pregnancy).<sup>4</sup>

Patients with secondary hypothyroidism should be referred for an endocrinology consultation for evaluation of their general pituitary or hypothalamic function.

### Changes in Dose Requirements

Dose requirements may change over time in any given patient. Underlying thyroid function may wane, and any absorptive issues secondary to other diseases, such as celiac disease, may alter dose requirements. In pregnancy, dose requirements increase but generally revert back to baseline postpartum.<sup>4</sup> Any addition or discontinuation of medications that affect plasma binding or metabolism will alter thyroid dosing.<sup>4</sup> Increasing age or weight loss may require decreases in dosing. After any dose adjustment, thyroid function test results should be reevaluated in four to eight weeks, with the same follow-up schedule for repeat testing as after initiation of hypothyroidism treatment.

### PATIENT EDUCATION

Patient education should focus on treatment and follow-up. Patients need to be told that treatment is lifelong, and it may be helpful to describe levothyroxine as a replacement for their thyroid hormone, rather than as a treatment of their thyroid disease. They should be reminded that they will need to undergo repeat thyroid function testing periodically to assess their dose. While their dose may need to be adjusted over time, typically TSH levels will stabilize and laboratory testing will only be necessary every 12 months.<sup>4</sup>

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Clinicians should also review with patients how and when to take levothyroxine. One tablet should be taken daily, with water, on an empty stomach, at least 30 to 60 minutes before eating or drinking or four hours after eating or drinking. Multivitamins or other supplements, especially those containing calcium and iron, should be taken at least four hours after taking levothyroxine. These are necessary requirements because both food and minerals can decrease absorption of the medication.<sup>4</sup>

Patients should also be informed that if they miss a dose of medication, two tablets may be taken the next day, but consistency in daily dosing is the goal. In patients with significant compliance problems, weekly dosing of levothyroxine results in similar safety, treatment outcomes, and TSH values as daily dosing.<sup>11</sup>

Finally, symptoms of both hypothyroidism and hyperthyroidism should be described and reviewed. Patients should be advised to notify their health care providers should any of these symptoms occur.

## CONCLUSION

Hypothyroidism is a common illness encountered in the primary care setting. Clinicians must be familiar with the signs and symptoms, as well as the risk factors for the disease, because many patients have minimal symptomatology. Appropriate laboratory testing will clarify the diagnosis.

Patients with symptomatic hypothyroidism confirmed on laboratory testing should be treated. The benefit of treatment in other subgroups is less clear and should be guided by current evidence-based guidelines. The mainstay of medical management for hypothyroidism is levothyroxine; other treatment options require further research. Well-informed patients are key to effective management of hypothyroidism. **CR**

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