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# Refining your approach to hypothyroidism treatment

Thyroid hormone supplementation can be complicated by a number of factors. These tips can help to ensure that you provide the best treatment possible.

## PRACTICE RECOMMENDATIONS

- ▶ *Prescribe levothyroxine 1.6 mcg/kg/d for healthy adult patients < 50 years of age with overt hypothyroidism.* **(B)**
- ▶ *Consider lower initial doses of levothyroxine in patients with cardiac disease (12.5-50 mcg/d) or subclinical hypothyroidism (25-75 mcg/d).* **(B)**
- ▶ *Titrate levothyroxine by 12.5 to 25 mcg/d at 6- to 8-week intervals based on thyroid-stimulating hormone measurements, comorbidities, and symptoms.* **(C)**
- ▶ *Closely monitor and provide thyroid supplementation to female patients who are pregnant or of reproductive age with concomitant hypothyroidism.* **(C)**

### 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

## CASE ▶

A 38-year-old woman presents for a routine physical. Other than urgent care visits for 1 episode of influenza and 2 upper respiratory illnesses, she has not seen a physician for a physical in 5 years. She denies any significant medical history. She takes naproxen occasionally for chronic right knee pain. She does not use tobacco or alcohol. Recently, she has started using a meal replacement shake at lunchtime for weight management. She performs aerobic exercise 30 to 40 minutes per day, 5 days per week. Her family history is significant for type 2 diabetes mellitus, arthritis, heart disease, and hyperlipidemia on her mother's side. She is single, is not currently sexually active, works as a pharmacy technician, and has no children. A high-risk human papillomavirus test was normal 4 years ago.

A review of systems is notable for a 20-pound weight gain over the past year, worsening heartburn over the past 2 weeks, and chronic knee pain, which is greater in the right knee than the left. She denies weakness, fatigue, nausea, diarrhea, constipation, or abdominal pain. Vital signs reveal a blood pressure of 146/88 mm Hg, a heart rate of 63 bpm, a temperature of 98°F (36.7°C), a respiratory rate of 16, a height of 5'7" (1.7 m), a weight of 217 lbs (98.4 kg), and a peripheral capillary oxygen saturation (SpO<sub>2</sub>) of 99% on room air. The physical exam reveals a body mass index (BMI) of 34, warm dry skin, and coarse brittle hair.

Lab results reveal a thyroid-stimulating hormone (TSH) level of 11.17 mIU/L (reference range, 0.45-4.5 mIU/L) and a free thyroxine (T4) of 0.58 ng/dL (reference range, 0.8-2.8 ng/dL). A basic metabolic panel and hemoglobin A1C level are normal.

What would you recommend?

**I**n the United States, the prevalence of overt hypothyroidism (defined as a TSH level > 4.5 mIU/L and a low free T4) among people ≥ 12 years of age was estimated at 0.3% based on National Health and Nutrition Examination Survey

TABLE 1

## Causes of primary hypothyroidism<sup>2-4</sup>

Disorder	Examples
Autoimmune thyroiditis	Atrophic autoimmune thyroiditis, Hashimoto thyroiditis
Congenital hypothyroidism	Thyroid aplasia or hypoplasia, thyroid hormone biosynthesis defect
Iatrogenic	Radioiodine therapy, total thyroidectomy
Iodine deficiency	Insufficient dietary iodine
Medications	Amiodarone, interferon, iodine, lithium, methimazole, propylthiouracil, rifampicin, sunitinib, thalidomide
Thyroiditis	Postpartum thyroiditis, silent thyroiditis, subacute thyroiditis

(NHANES) data from 1999-2002.<sup>1</sup> Subclinical hypothyroidism (TSH level > 4.5 mIU/L but < 10 mIU/L and a normal T4 level) is even more common, with an estimated prevalence of 3.4%.<sup>1</sup> Hypothyroidism is more common in females and occurs more frequently in Caucasian Americans and Mexican Americans than in African Americans.<sup>1</sup>

The most common etiologies of hypothyroidism include autoimmune thyroiditis (eg, Hashimoto thyroiditis, atrophic autoimmune thyroiditis) and iatrogenic causes (eg, after radioactive iodine ablation or thyroidectomy) (TABLE 1).<sup>2-4</sup>

### Initiating thyroid hormone replacement

Factors to consider when starting a patient on thyroid hormone replacement include age, weight, symptom severity, TSH level, goal TSH value, adverse effects from thyroid supplements, history of cardiac disease, and, for women of child-bearing age, the desire for pregnancy vs the use of contraceptives. Most adult patients < 50 years with overt hypothyroidism can begin a weight-based dose of levothyroxine: ~1.6 mcg/kg/d (based on ideal body weight).<sup>3</sup>

For adults with cardiac disease, the risk of over-replacement limits initial dosing to 25 to 50 mcg/d for patients < 50 years (12.5-25 mcg/d; ≥ 50 years).<sup>3</sup> For adults with subclinical hypothyroidism, it is reasonable to begin therapy at a lower daily dose (eg, 25-75 mcg/d) depending on baseline TSH level, symptoms (the patient may be asymptomatic), and the presence of cardiac disease (TABLE 2<sup>3,4</sup>). Consider treatment in patients

with subclinical hypothyroidism particularly when patients have a goiter or dyslipidemia and in women contemplating pregnancy in the near future. Elderly patients may require a dose 20% to 25% lower than younger adults because of decreased body mass.<sup>3</sup>

Levothyroxine is considered first-line therapy for hypothyroidism because of its low cost, dose consistency, low risk of allergic reactions, and potential to cause fewer cardiac adverse effects than triiodothyronine (T3) products such as desiccated thyroid extract.<sup>5</sup> Although data have not shown an absolute increase in cardiovascular adverse effects, T3 products have a higher T3 vs T4 ratio, giving them a theoretically increased risk.<sup>5,6</sup> Desiccated thyroid extract also has been associated with allergic reactions.<sup>5</sup>

Use of liothyronine alone or in combination with levothyroxine lacks evidence and guideline support.<sup>4</sup> Furthermore, it is dosed twice daily, which makes it less convenient, and concerns still exist that there may be an increase in cardiovascular adverse effects.<sup>4,6</sup> See TABLE 3<sup>7</sup> for a summary of available products and their equivalent doses.

### Maintaining patients on therapy

The maintenance phase begins once hypothyroidism is diagnosed and treatment is initiated. This phase includes regular monitoring with laboratory studies, office visits, and as-needed adjustments in hormone replacement dosing. The frequency at which all of these occur is variable and based on a number of factors including the patient's other medical conditions, use of other medications including over-the-counter agents, the



**Consider treatment in adults with subclinical hypothyroidism when they have a goiter or dyslipidemia and in women contemplating pregnancy in the near future.**

**>**  
Instruct patients to take levothyroxine either in the morning at least 30 to 60 minutes before eating or 3 to 4 hours after the last meal of the day.

**TABLE 2**

**Starting levothyroxine in adults<sup>3,4</sup>**

Patient	Recommended initial dose
Subclinical hypothyroidism (if treated)	1 mcg/kg/d or 25-75 mcg/d (dose may depend on weight and TSH value)
Overt hypothyroidism	
<i>Healthy adults</i>	
< 50 years old	~1.6 mcg/kg/d
≥ 50 years old	25-50 mcg/d
<i>Adults with cardiac disease</i>	
< 50 years old	25-50 mcg/d
≥ 50 years old	12.5-25 mcg/d
Myxedema coma or stupor	200-400 mcg IV initially, then 50-100 mcg/d orally

TSH, thyroid-stimulating hormone.

**TABLE 3**

**Types of thyroid supplementation<sup>7</sup>**

Drug, generic (brand)	Type of supplement	Equivalent dose
Levothyroxine (Synthroid, Levoxyl, Levothroid)	Synthetic T4	100 mcg
Liothyronine (Cytomel)	Synthetic T3	15-37.5 mcg
Liotrix (Thyrolar)	Synthetic T4 and T3 in 4:1 ratio	50-60 mcg T4 and 12.5-15 mcg T3
Desiccated thyroid extract (Armour Thyroid)	Desiccated pig or cow thyroid gland with T4 and T3	1 grain = 60 mg (~60 mcg T4)

T3, triiodothyronine; T4, free thyroxine.

patient's age, weight changes, and pregnancy status.<sup>3,4,8</sup> In general, dosage adjustments of 12.5 to 25 mcg can be made at 6- to 8-week intervals based on repeat TSH measurements, patient symptoms, and comorbidities.<sup>3</sup>

Once a patient is symptomatically stable and laboratory values have normalized, the recommended frequency of laboratory evaluation and office visits is every 12 months, barring significant changes in any of the factors mentioned above. At each visit, physicians should perform medication (including supplements) reconciliation and discuss any health condition updates. Changes to the therapy plan, including frequency or timing of laboratory tests, may be necessary if patients begin taking medications that alter the absorption or function of levothyroxine (eg, steroids).

**■ To maximize absorption,** providers should review with patients the optimal way to take thyroid hormones. Levothyroxine is approximately 70% to 80% absorbed under

ideal conditions, which means taking it in the morning at least 30 to 60 minutes before eating or 3 to 4 hours after the last meal of the day.<sup>3,9-13</sup> Of note, TSH levels may increase slightly in patients taking proton pump inhibitors, but this does not usually require a dose increase of thyroid hormone.<sup>11</sup> Given that some supplements, particularly iron and calcium, can interfere with absorption, it is recommended to maintain a 3- to 4-hour gap between taking those supplements and taking levothyroxine.<sup>12-14</sup> For those patients unable or unwilling to adhere to these recommendations, an increase in levothyroxine dose may be required in order to compensate for the decreased absorption.

**■ Don't adjust hormone therapy based on clinical presentation alone.** While clinical symptoms are important, it is not recommended to adjust hormone therapy based solely on clinical presentation. Common hypothyroid symptoms of dry skin, edema, weight gain, and fatigue may be caused by

other medical conditions. While indices including Achilles reflex time and basal metabolic rate have shown some correlation to thyroid dysfunction, there has been limited evidence to show that longitudinal index changes reflect subtle changes in thyroid hormone levels.<sup>3</sup>

The most recent guidelines from the American Thyroid Association recommend that, “Symptoms should be followed, but considered in the context of serum thyrotropin values, relevant comorbidities, and other potential causes.”<sup>3</sup>

### Special populations/circumstances to keep in mind

**Malabsorption conditions.** When a higher than expected weight-based dose of levothyroxine is required, physicians should review administration timing, adherence, and comorbid medical conditions that can affect absorption.

Several studies, for example, have demonstrated the impact of *Helicobacter pylori* gastritis on levothyroxine absorption and subsequent TSH levels.<sup>15-17</sup> In one nonrandomized prospective study, patients with *H pylori* and hypothyroidism who were previously thought to be unresponsive to levothyroxine therapy had a decrease in average TSH level from 30.5 mIU/L to 4.2 mIU/L after *H pylori* was eradicated.<sup>15</sup> Autoimmune atrophic gastritis and celiac disease, both of which are more common in those with other autoimmune diseases, are also associated with the need for higher than expected levothyroxine doses.<sup>17,18</sup>

A history of gastric bypass surgery alone is not considered a risk factor for poor absorption of thyroid hormone, given that the majority of levothyroxine absorption occurs in the ileum.<sup>19,20</sup> However, advancing age (> 70 years) and extreme obesity (BMI > 40) are independent risk factors for decreased levothyroxine absorption.<sup>20,21</sup>

**Women of reproductive age and pregnant women.** Overt untreated or undertreated hypothyroidism can be associated with increased risk of maternal and fetal complications including decreased fertility, miscarriage, preterm delivery, lower birth rates,

and infant cognitive deficits.<sup>3,22</sup> Therefore, the main focus should be optimization of thyroid hormone levels prior to and during pregnancy.<sup>3,4,8,22</sup> Thyroid hormone replacement needs to be increased during pregnancy in approximately 50% to 85% of women using thyroid replacement prior to pregnancy, but the dose requirements vary based on the underlying etiology of thyroid dysfunction.

One initial option for patients on a stable dose before pregnancy is to increase their daily dose by a half tablet (1.5 × daily dose) immediately after home confirmation of pregnancy, until finer dose adjustments (usually increases of 25%-60%) can be made by a physician. Experts recommend that a TSH level be obtained every 4 weeks until mid-gestation and then at least once around 30 weeks' gestation to ensure specific targets are being met with dose adjustments.<sup>22</sup> Optimal thyrotropin reference ranges during conception and pregnancy can be found in the literature.<sup>23</sup>

**Patients who have positive antibodies and normal thyroid function tests.** Patients who are screened for thyroid disorders may demonstrate normal thyroid function (ie, euthyroid) with TSH, free T4, and, if checked, free T3, all within normal ranges. Despite these normal lab results, patients may have additional test results that demonstrate positive thyroid autoantibodies including thyroglobulin antibodies and/or thyroid peroxidase antibodies. Thyroid autoimmunity itself has been associated with a range of other autoimmune conditions as well as an increased risk of thyroid cancer in those with Hashimoto thyroiditis.<sup>24</sup> Two studies showed that prophylactic treatment of euthyroid patients with levothyroxine led to a reduction in antibody levels and a lower TSH level.<sup>25,26</sup> However, no studies have focused on patient-oriented outcomes such as hospitalizations, quality of life, or symptoms. If the patient remains asymptomatic, we recommend no treatment, but that the patient's TSH levels be monitored every 12 months.<sup>27</sup>

**Elderly patients.** Population data have shown that TSH increases normally with age, with a TSH level of 7.5 mIU/L being the upper limit of normal for a population of healthy adults > 80 years of age.<sup>28,29</sup> Overall, studies



**Iron and calcium supplements can interfere with the absorption of levothyroxine, so a 3- to 4-hour gap between taking these supplements and levothyroxine is recommended.**



**Advancing age (> 70 years) and extreme obesity (BMI > 40) are independent risk factors for decreased levothyroxine absorption.**

have failed to show any benefit in treating elderly patients with subclinical hypothyroidism unless their TSH level exceeds 10 mIU/L.<sup>6,21</sup> The one exception is elderly patients with heart failure in whom untreated subclinical hypothyroidism has been shown to be associated with higher mortality.<sup>30</sup>

Elderly patients are at higher risk for adverse effects of thyroid over-replacement, including atrial fibrillation and osteoporosis. While there have been no randomized trials examining target TSH levels in this population, a reasonable recommendation is a goal TSH level of 4 to 6 mIU/L for elderly patients ≥ 70 years.<sup>4</sup>

#### CASE ►

As a result of the patient's elevated TSH level and symptoms of hypothyroidism, you start levothyroxine 150 mcg/d by mouth, counsel her on potential adverse effects, and schedule a follow-up visit with another TSH check in 6 weeks.

Follow-up laboratory studies 6 weeks later reveal a TSH level of 5.86 mIU/L (refer-

ence range, 0.45-4.5 mIU/L) and a free T4 level of 0.74 ng/dL (reference range, 0.8-2.8 ng/dL). Based on those results, you increase the dose of levothyroxine to 175 mcg/d.

At her follow-up visit 12 weeks after initial presentation, her TSH level is 3.85 mIU/L. She reports feeling better overall with less fatigue, and she has lost 5 pounds since her last visit. You recommend she continue levothyroxine 175 mcg/d after reviewing medication compliance with the patient and ensuring she is indeed taking it in the morning, at least 30 minutes prior to eating. With improved but not resolved symptoms, she agrees to follow-up with repeat TSH laboratory studies in 6 weeks to determine whether further dose adjustments are necessary. Given that she is of reproductive age and her TSH level is suboptimal for pregnancy, you caution her about heightened pregnancy/fetal risks with a suboptimal TSH and recommend that she use reliable contraception. **JFP**

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