

Current Screening and Management of Hypothyroidism

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Thyroid dysfunction is prevalent in the general population, and hypothyroidism is especially common among older women. Although hypothyroidism can result from a defect anywhere in the hypothalamic-pituitary-thyroid axis, it is caused by direct abnormalities of the thyroid (primary hypothyroidism) in the vast majority of cases. The main focus of this review will be screening for and management of this condition, with special considerations for the perimenopausal and postmenopausal patient population.

Pathophysiology and Epidemiology

Worldwide, the majority of cases of hypothyroidism result from iodine deficiency, but in iodine-sufficient areas of the world autoimmune thyroiditis is the most common cause of primary hypothyroidism, followed by iatrogenic hypothyroidism secondary to thyroidectomy or radiation. Other causes of primary hypothyroidism are listed in Table 1.¹ There are two forms of chronic thyroiditis; a goitrous form characterized by lymphocytic infiltration (classic Hashimoto's disease) and an atrophic form with minimal residual thyroid tis-

sue at the later stages of the disease. In affected patients hypothyroidism results from cell- and antibody-mediated destruction of thyroid tissue. The classic biochemical manifestation of overt hypothyroidism is a high concentration of thyroid-stimulating hormone (TSH) and a low level of free thyroxine (fT4) in serum; most patients with these abnormalities are symptomatic. Subclinical hypothyroidism refers to the finding of an elevated TSH level with a normal fT4 level in an asymptomatic patient.

The prevalence of overt hypothyroidism varies from 0.1% to 2% and is about 8 times more common in women than in men.^{2,3} It is also more common in adult women who had small body size at birth and during childhood.⁴ In addition, the prevalence of hypothyroidism increases with age, making this a very common

diagnosis in the older patient population.⁵ Subclinical hypothyroidism is found in about 5% of adults and about 15% of women over age 65.⁶⁻⁸

Clinical Presentation

Symptoms and signs of hypothyroidism vary depending upon the severity and duration of the condition. In most cases of autoimmune primary hypothyroidism there is gradual loss of thyroid function over several years, resulting in the development of subtle and nonspecific symptoms and signs that may be erroneously attributed to other etiologies, especially in perimenopausal and postmenopausal women, and in the elderly. In such cases, the typical manifestations of hypothyroidism may take months or years to appear, as opposed to iatrogenic hypothyroidism following surgery, in which the manifestations of frank hy-

Table 1. Causes of Primary Hypothyroidism

- Chronic autoimmune thyroiditis
- Iatrogenic (thyroidectomy, radiation)
- Infiltrative diseases of the thyroid
- Transient hypothyroidism (painless, subacute or postpartum thyroiditis)
- Iodine deficiency
- Drug-induced (thionamides, lithium, iodine and iodine-containing compounds including amiodarone, cytokines, sulfonamides)
- Congenital causes

hypothyroidism rapidly ensue over a course of several weeks.

Many of the clinical manifestations of hypothyroidism reflect a generalized slowing of metabolic processes or an accumulation of matrix substances in tissues (Table 2).^{1,9} Women with hypothyroidism may complain of fatigue, weight gain, cold intolerance, dry skin, hair loss, cognitive impairment, depression, decreased appetite, constipation and/or menstrual irregularities. They may also describe periorbital edema, muscle weakness, stiffness, arthralgias and/or galactorrhea. Physical examination may reveal a goiter in hypothyroid women in whom the etiology is Hashimoto's thyroiditis, while women with other forms of hypothyroidism may have little palpable thyroid tissue.

Screening and Diagnosis

The value of screening for hypothyroidism in asymptomatic patients is controversial. While various clinical practice guidelines have been published by different professional groups over the past 2 decades to address this issue, with conflicting recommendations,¹⁰⁻¹⁶ most professional organizations agree that screening postmenopausal women for subclinical hypothyroidism may be justified. A 2004 consensus committee comprised of representatives of the American Thyroid Association, the Endocrine Society and the American Association of Clinical Endocrinologists recommended against population-based screening but suggested that aggressive case finding is appropriate in women over age 60 and in others at high risk for thyroid dysfunction, including those with a history of previous thyroid dysfunction, a personal history of autoimmune disease or a family history of thyroid disease.¹⁶ A follow-up joint consensus statement favored routine screening in adults, including pregnant women and those contemplating pregnancy.¹⁷

Table 2. Clinical Manifestations of Primary Hypothyroidism

General	Fatigue Cold intolerance, hypothermia Weight gain Hoarseness
Integument	Cool, dry skin Nonpitting edema Brittle nails Coarse hair Hair loss
Ophthalmic	Periorbital edema
Hematologic	Anemia
Cardiovascular	Decreased heart rate and cardiac output Hypertension Hypercholesterolemia Pericardial effusion
Respiratory	Dyspnea on exertion Hypoventilation Sleep apnea
Gastrointestinal	Constipation
Reproductive	Menstrual irregularities Decreased fertility Increased risk for miscarriage Hyperprolactinemia, galactorrhea
Neurologic	Depression Slow movements or speech Cognitive impairment Peripheral neuropathy Ataxia Encephalopathy Myxedema madness Myxedema coma
Musculoskeletal	Carpal tunnel syndrome Arthralgias Stiffness Myopathy
Metabolic abnormalities	Hyponatremia

These recommendations are limited by the lack of definitive data, and clinicians are currently encouraged to exercise their clinical judgment and consider patient preferences when determining the need for testing and treatment.

Determination of the serum TSH level is the most sensitive and cost-effective initial test for diagnosing thyroid dysfunction. An elevated TSH is the hallmark of primary hypothyroidism. If on repeated measure serum

TSH is still outside the reference range, a serum fT4 level should be checked. The majority of patients with autoimmune hypothyroidism will have measureable, and often high, titers of antibodies reacting with thyroid peroxidase or thyroglobulin. In women with subclinical hypothyroidism, measurement of serum anti-thyroid peroxidase antibodies may be useful to predict the likelihood of progression to overt hypothyroidism.^{8,13,16}

When pituitary or hypothalamic disease is the cause of hypothyroidism (secondary hypothyroidism), the TSH level will not be a useful tool for the detection of hypothyroidism. In these cases, serum fT4 must be relied upon to make the diagnosis.

Unfortunately, a screening TSH level in an asymptomatic patient will not be covered by many third-party payers, including Medicare; however, perimenopausal and postmenopausal women, as well as elderly patients, often have potential symptoms of hypothyroidism. Thus, measurement of a serum TSH level is easily justifiable in this patient population. Diagnoses (ICD-9 codes) that would allow obtaining a serum TSH value include fatigue (780.79), weight gain (783.1), menstrual disorder (626.9), cold intolerance (780.99), hair loss (704), depression (311), cognitive impairment (331.83) and hyperlipidemia (272.4).

Management of Overt Hypothyroidism

Hypothyroidism is a permanent condition requiring lifelong therapy in most patients. The goal of therapy is to normalize the TSH level to 1-2 mU/L and restore euthyroidism.¹⁸ The treatment of choice is synthetic levothyroxine (L-T4), which should be taken on an empty stomach. This is preferred over other thyroid formulations since T4, which is a prohormone with a 7-day half-life, is converted to triiodothyronine (T3), the active form, in peripheral tissues based on the patient's metabolic needs. Once-daily administration of L-T4 achieves uniform circulating levels of T4 and T3 without significant fluctuations.

Some women remain symptomatic despite adequate L-T4 replacement therapy and normalization of the serum TSH level, which raises the question of whether adding T3 (Cytomel) to L-T4 therapy may be beneficial. At present, combination L-T4

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and T3 therapy remains controversial. Although some studies have suggested that combination therapy may improve mood and neuropsychological function,¹⁹ a systematic review of 9 controlled clinical trials and a meta-analysis of 11 randomized studies failed to show a clear advantage to combination therapy, concluding that the administration of L-T4 alone should remain the treatment of choice for hypothyroidism replacement therapy.^{20,21} Despite the extensive literature demonstrating that patients do well clinically on L-T4 monotherapy, most clinicians have at least anecdotally seen benefits from L-T4 and T3 combination therapy for some patients, with a recent study suggesting a genetic basis for this.^{22,23}

There are concerns about the use of other thyroid preparations, such as desiccated thyroid (eg, Armour Thyroid) and mixtures of T3 and L-T4 (eg, Thyrolar). These are generally not recommended for the treatment of hypothyroidism since the potency and bioavailability of these preparations can vary.²⁴ Furthermore, patients may experience wide fluctuations in their serum T3 levels due to the rapid gastrointestinal absorption and relatively short half-life (approximately 1 day) of T3. The pharmacokinetic profile of T3 along with the excessive amount contained in most commercially available preparations makes its routine use and adjustment particularly difficult. Finally, serum T4 levels tend to

be relatively low in patients treated with combination L-T4 and T3 therapy, which may lead to inappropriate dose changes.

The average replacement dose of L-T4 in adults is about 1.6 mcg/kg/day. The full dose can be started in young, healthy patients. Women between the ages of 50 and 65 should be started on a lower dose (50 mcg/day) because of possible coronary artery disease (CAD) in this population. Patients over age 65, patients with CAD and those with risk factors for CAD should be started on 25 mcg daily, allowing tissues to adjust to the new oxygen requirements. This can be increased by 25 mcg/day every 2 to 4 weeks until the TSH level normalizes, provided there are no adverse effects.¹⁸ Patients usually begin to improve within a couple of weeks of starting L-T4 replacement therapy, although complete recovery may take up to several months in severe hypothyroidism.

Several L-T4 preparations are currently available, and there has been considerable controversy regarding their bioequivalence.²⁵ It is preferable to maintain patients on the same formulation whenever possible since there may be differences in the bioavailability that can lead to differences in treatment effects. This is critical for patients who are especially susceptible to incorrect titration of levothyroxine therapy, including the elderly, pregnant women and those with a history of atrial fibrillation, ischemic heart disease or thyroid cancer.²⁶ When using generic brands of levothyroxine, there is the potential for interchange of preparations by a given pharmacy. It is recommended to recheck the TSH level 6 weeks after changing brands or switching generic preparations to determine if retitration of the dose is necessary.

Adverse effects of L-T4 replacement therapy are unusual as long as the patient is not over- or underdosed.

Patients may rarely develop an allergy to the dye in the tablets, in which case multiples of the white 50-mcg tablets can be substituted for the dose.

Management of Subclinical Hypothyroidism

There is considerable debate about whether or not subclinical hypothyroidism should be treated.^{27,28} The natural history of this condition suggests that although some may have their serum TSH level revert to normal without therapy,²⁹ a significant proportion of patients with subclinical hypothyroidism progress to overt hypothyroidism, especially if their serum TSH concentration is >10 mU/L and their serum anti-thyroid peroxidase (TPO) antibody level is high.^{8,30} Furthermore, there is compelling evidence that subclinical hypothyroidism may have adverse clinical consequences, especially after menopause. An association between subclinical hypothyroidism and elevated total and low-density lipoprotein cholesterol levels has been shown; these levels improved after treatment with L-T4.³¹ In addition, several studies have shown that subclinical hypothyroidism is associated with cardiovascular disease, although this finding has not been consistent in all studies. The Rotterdam study found that subclinical hypothyroidism (defined as a TSH level >4 mU/L) is an independent risk factor for atherosclerosis and myocardial infarction in postmenopausal women,³² while a prospective study following up individuals 65 years of age or older for more than 10 years did not show an effect of subclinical hypothyroidism on cardiovascular outcome or mortality.³³

In view of the above, it seems prudent to treat subclinical hypothyroidism with low doses of levothyroxine in menopausal women, keeping in mind that overtreatment of these patients could actually precipitate symptoms of occult

Table 3. Compounds Interfering with L-T4 Absorption

- Iron sulfate
- Calcium carbonate
- Cholestyramine
- Sucralfate
- Antacids (aluminum hydroxide)
- Omeprazole
- Sertraline
- Raloxifene
- Soy supplements
- Dietary fiber
- Coffee

CAD and contribute to increased rates of bone loss and osteoporosis. One study showed that adding L-T4 therapy prevented the beneficial effects of estrogen replacement therapy on bone mineral density,³⁴ suggesting that other forms of antiresorptive bone therapy may be needed in such cases. Treatment is also indicated in those who have a goiter or nonspecific symptoms suggestive of hypothyroidism such as fatigue, constipation or depression.

Special Considerations

After identification of the proper maintenance dose, annual monitoring of the TSH level is adequate unless there is a change in the patient's clinical status. A decrease in the dose may be needed with aging,³⁵ weight loss or during androgen therapy.³⁶ An increase in the dose may be required if the thyroid disease worsens or in patients in whom thyroid hormone absorption is diminished due to gastrointestinal disorders or certain compounds (Table 3).^{1,37,38} Other factors that contribute to increased L-T4 requirements include weight gain, increased excretion of L-T4 (eg, nephrotic syndrome) and increased rate of metabolism (eg, use of rifampin or antiepileptic medications). When

medications that affect the metabolism of L-T4 are initiated, serum TSH should be measured about 6 weeks later to confirm that the L-T4 dose is still adequate. Drugs that may interfere with L-T4 absorption should be taken several hours after the L-T4 dose.

In women on oral estrogen therapy, the serum thyroid-binding globulin (TBG) concentration is increased, which, in turn, may increase the need for L-T4. Serum TSH should be measured about 12 weeks after starting estrogen therapy in women receiving L-T4 therapy to determine if the L-T4 dose needs to be adjusted.³⁹ Transdermal estrogen therapy does not affect TBG levels and, hence, is not expected to alter L-T4 requirements in postmenopausal women on L-T4 therapy.⁴⁰ Tamoxifen, a selective estrogen-receptor modulator (SERM), has also been reported to increase TBG levels in postmenopausal women, but its effect on other thyroid function tests remains controversial.^{41,42} It is important to keep in mind that euthyroid postmenopausal women on estrogen replacement therapy and premenopausal women on oral contraceptives will have elevated total T4 and T3 levels with normal free T4 and free T3 levels.

Because many symptoms of hypothyroidism are nonspecific, women may believe that they are inadequately treated when they feel tired or gain weight. In one study, most of the patients preferred a dose that caused very mild hyperthyroidism.⁴³ However, in a cross-over randomized trial, patients could not distinguish between small changes in L-T4 therapy that resulted in TSH values ranging from 0.3 mU/L to 2.8 mU/L.⁴⁴ Therefore, it is necessary to educate patients about the potential adverse effects of overly aggressive therapy with L-T4, such as cardiac arrhythmias and increased bone loss. It is reasonable to aim for serum TSH values in the lower half of the normal range

if patients have possible symptoms suggestive of hypothyroidism.

Summary and Conclusions

Hypothyroidism is common, especially among older women. There is increasing evidence that subclinical hypothyroidism may have serious clinical sequelae in postmenopausal women. Hence, aggressive case-finding should be pursued in this patient population. Women with TSH levels ≥ 10 mU/L should be treated, and therapy should be considered for women with subclinical hypothyroidism and TSH levels < 10 mU/L, especially in the presence of potential symptoms, a goiter, anti-TPO antibodies or dyslipidemia. L-T4 therapy should be administered cautiously to avoid the potential adverse effects of iatrogenic subclinical hyperthyroidism. Finally, it is important to recognize the physiologic changes that occur with the concomitant use of oral estrogen or SERMs and L-T4 replacement therapy. ■

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