Subclinical Thyroid Disease

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The term *subclinical thyroid disease* is used to describe asymptomatic thyroid abnormalities found on imaging studies or laboratory tests. Thyroid nodules not palpable on physical examination but detected on imaging studies performed for other purposes are called *incidentalomas*. In the absence of risk factors for thyroid cancer, nodules that are less than 1 cm in diameter do not require biopsy. Subclinical hyperthyroidism is defined as suppressed serum sensitive thyrotropin (TSH) and normal serum thyroxine and triiodothyronine levels. This condition may adversely affect the heart and the bones and should be treated, especially in patients older than 60 years. Subclinical hypothyroidism, defined as mildly elevated serum TSH and normal serum thyroxine levels, is the most common thyroid dysfunction. In patients with subclinical hypothyroidism, thyroxine therapy should be given if the serum TSH level is higher than 10 mIU/L. For TSH values between 5 and 10 mIU/L, the decision for therapy should be individualized and depends on the level of TSH, presence of antithyroid antibodies, and clinical factors.

***Mayo Clin Proc*. 2001;76:413-417**

T_3 = triiodothyronine; T_4 = thyroxine; TSH = thyrotropin

With the advent of the serum thyrotropin (TSH) radioimmunoassay in the 1970s, the entity of mildly elevated TSH and normal serum thyroid hormone levels was recognized. Ultrasonography and other advanced imaging technologies facilitated the detection of occult nonpalpable thyroid nodules. The introduction of second- and third-generation sensitive TSH in the 1980s identified the entity of subclinical hyperthyroidism in which serum sensitive TSH is suppressed and serum thyroxine (T_4) and triiodothyronine (T_3) levels are normal.[1,2] Nonpalpable thyroid nodules and subclinical hypothyroidism are more common than the clinically overt forms of thyroid disease. Thus, technology is superior to clinical acumen in diagnosing early and subclinical thyroid abnormalities. However, the benefit of intervention for some of these subclinical conditions is controversial.

THYROID INCIDENTALOMAS

Nonpalpable thyroid nodules found with neck imaging, such as ultrasonography, magnetic resonance imaging, or computed tomography, performed for other reasons are termed *thyroid incidentalomas*. Nonpalpable thyroid nodules are common and can be detected with ultrasonography in 30% to 50% of the general population.[3] Ultrasonography can detect nodules as small as 2 mm; nodules smaller than 1 cm in diameter are usually not palpable. In 50% of patients with palpable nodules, ultrasonography shows the presence of other thyroid nodules. Biopsy specimens of nonpalpable incidental nodules should be obtained only if the nodule is larger than 1 cm, if there is a history of head and neck radiation or a family history of medullary cancer, or if ultrasonographic findings suggest malignancy, such as punctate calcifications. Nodules smaller than 1 cm are usually of no clinical importance in the absence of any of these factors, especially in older persons.[4] For nodules between 1 and 1.5 cm, biopsy or follow-up ultrasonography in 1 year is recommended, depending on the clinical setting.

SUBCLINICAL HYPERTHYROIDISM

Subclinical hyperthyroidism is diagnosed when serum sensitive TSH is suppressed below 0.1 mIU/L and serum free thyroxine and triiodothyronine levels are normal. Because of the wide range for normal peripheral thyroid hormone values, changes may occur while the levels remain in the reference range. However, a small increase in serum T_4 or T_3 results in suppression of sensitive TSH. Before the diagnosis of subclinical hyperthyroidism can be confirmed, serum T_3 should be measured to rule out T_3 toxicosis. Other causes of low serum sensitive TSH such as nonthyroidal illness (euthyroid sick syndrome), medications such as dopamine and exogenous glucocorticoids, recovery from hyperthyroidism, and hypothalamic pituitary disease should be ruled out.[5] Of note, in hypothalamic pituitary disease, the serum sensitive TSH level is

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A question-and-answer section appears at the end of this article.

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still detectable but may be abnormally low; however, thyroid hormone levels are also abnormally low or in the lower end of the reference range. In subclinical hyperthyroidism, serum T_4 and T_3 levels are usually above the mid normal range. In nonthyroidal illness, T_4 and T_3 levels are usually low, and serum TSH, although abnormally low, may be detectable with a third-generation sensitive TSH assay.

The most common cause of subclinical hyperthyroidism is excess thyroid hormone therapy. The prevalence of endogenous subclinical hyperthyroidism is between 0.6% and 1.1%. An autonomous functioning adenoma or multinodular goiter, early or mild Graves disease, silent or postpartum thyroiditis, subacute thyroiditis, and ingestion of pharmacologic amounts of iodine are other causes of subclinical hyperthyroidism.[5] Patients with subclinical hyperthyroidism are usually asymptomatic, but some may have subtle symptoms of hyperthyroidism, especially if free thyroxine is at the upper limit of the reference range.

In postmenopausal women who are not taking estrogen, prolonged subclinical hyperthyroidism manifested by suppressed serum sensitive TSH results in an exaggerated reduction of bone mineral density, more apparent in cortical bones (hip and forearm) than in trabecular bones. Bone loss has not been proved in men or in premenopausal women. Therefore, subclinical hyperthyroidism should be considered a risk factor for osteoporosis, especially in postmenopausal women who are not taking estrogen. No studies have shown that fracture incidence is increased in patients with normal serum thyroid hormone levels and suppressed serum sensitive TSH.[6]

In patients older than 60 years, the adverse effect of subclinical hyperthyroidism on the heart is of particular concern.[7] The risk of atrial fibrillation is increased 3 times in patients older than 60 years who have serum sensitive TSH levels lower than 0.1 mIU/L.[8] Some studies have also shown that such patients have an increased heart rate, premature atrial contractions, increased left ventricular mass index, and decreased left ventricular filling.[9]

No uniform national recommendations for the management of subclinical hyperthyroidism are available, and therapy should be individualized.[10] With replacement therapy, the thyroxine dose must be adjusted to obtain a normal serum sensitive TSH level. In patients with follicular cell–derived thyroid cancer who need suppressive thyroxine therapy, peripheral thyroid hormone levels should not exceed the upper limit of the reference range, and measures for the prevention of osteoporosis should be implemented. In patients with subclinical hyperthyroidism due to an autonomous functioning adenoma or multinodular goiter, spontaneous normalization of thyroid function is unlikely. Thus, surgery or radioiodine therapy is recommended, especially in older patients. In other types of subclinical hyperthyroidism, intervention or watchful waiting may be considered after T_3 toxicosis has been excluded. Before therapy is initiated, follow-up and repeated measurement are necessary because in 50% of patients with suppressed sensitive TSH, serum sensitive TSH levels may return to normal without intervention.[5,7] Intervention should be considered in symptomatic patients or in those with undetectable serum sensitive TSH levels and high to normal thyroid hormone levels. Before intervention, the cause of subclinical hyperthyroidism should be determined. In the absence of definite characteristics of Graves disease, suppressed sensitive TSH in the postpartum period usually indicates postpartum thyroiditis, a transient condition requiring only symptomatic therapy. Low uptake of radioiodine by the thyroid may distinguish silent thyroiditis from Graves disease. Occasionally, measurement of TSH receptor antibodies will be helpful in diagnosing Graves disease as the cause of subclinical hyperthyroidism.

SUBCLINICAL HYPOTHYROIDISM

The term *subclinical hypothyroidism* (also called *mild thyroid failure*) applies to mildly elevated serum TSH and normal levels of serum T_4. In the absence of other causes of elevated serum TSH, a combination of abnormally high serum TSH and normal or low-normal serum thyroid hormone levels is diagnostic of subclinical hypothyroidism.[11] One half of patients with serum TSH levels in the upper limit of the reference range (3-5 mIU/L) have an exaggerated response of TSH to thyrotropin-releasing hormone stimulation and may have early-stage subclinical thyroid disease. However, for clinical purposes, a thyrotropin-releasing hormone test is unnecessary, and the importance of such a diagnosis is questionable.

Subclinical hypothyroidism is usually asymptomatic and is found either on routine sensitive TSH screening or when nonspecific symptoms are being evaluated. On examination, the thyroid may be normal, nonpalpable, or diffusely enlarged.[12] The usual causes of subclinical hypothyroidism are thyroid autoimmunity and inadequately treated hypothyroidism. The presence of antithyroid antibodies indicates autoimmune thyroid disease. Other causes of subclinical hypothyroidism include previous therapy for hyperthyroidism; a history of neck radiation; treatment with cytokines, iodine, lithium, and amiodarone; and the hypothyroid phase of postpartum thyroiditis.[5] Causes of elevated serum TSH not associated with subclinical hypothyroidism include recovery phase of nonthyroidal illness, assay variability, presence of heterophile antibodies,

medications such as metoclopramide and domperidone, TSH-secreting pituitary adenomas, and thyroid hormone resistance.

Prevalence

Autoimmune thyroiditis is common. In autopsy series, the frequency of lymphocytic infiltration of the thyroid is as high as 20% to 30%. Thyroid antibody positivity in the white population of the United States is 16.8% for women and 10.2% for men. The prevalence for African Americans is much lower.

In the Whickham study, in an English town, 8% of women 35 years of age and older had subclinical hypothyroidism.[13] In that study, old age, female sex, and antithyroid antibody positivity were associated with higher risk of progression to overt hypothyroidism, and 40% of patients with subclinical disease developed clinical hypothyroidism after 20 years. The annual rate of progression to overt hypothyroidism was 2.1% in women with positive antithyroid antibody (antithyroperoxidase antibody or antithyroglobulin antibody) and normal serum TSH, 2.6% in women with mildly elevated TSH and negative antithyroid antibody, and 5% in women with both elevated serum TSH and positive thyroid antibody.[13]

Screening

Based on a computer model designed to assess cost-effectiveness, Danese et al[14] recommended screening with serum sensitive TSH every 5 years in patients older than 35 years. Cost-effectiveness in women and patients older than 50 years is more substantial.[14] Recent recommendations from the American Thyroid Association are similar.[15] The American College of Physicians recommends screening women who are older than 50 years but does not recommend screening younger women or asymptomatic men.[16] Consensus will be reached if more prospective randomized studies show benefits of therapy for subclinical hypothyroidism, the most common form of thyroid dysfunction. Recent evidence showed the adverse effects of subclinical hypothyroidism on neuropsychological development of the fetus, indicating the need for therapy for subclinical hypothyroidism in pregnant women.[17] These data point to possible benefits of screening and therapy for subclinical thyroid disease in early stages of pregnancy, preferably before anticipated conception.

Thyroxine Therapy

Several randomized trials of thyroxine therapy for subclinical hypothyroidism have been performed.[18-21] In one study, half the patients had fewer hypothyroid-related symptoms with therapy.[18] In another study, thyroxine therapy improved psychometric test results. One study showed only improvement in memory scores. Some of these studies included patients with TSH levels as high as 39 mIU/L, and in some, fixed high doses of thyroxine were used.[20] Thus, the reported benefits are difficult to interpret. A recent randomized study in patients with serum TSH levels between 5 and 10 mIU/L showed no clinical or metabolic benefit after 6 months of thyroxine therapy.[21] Thus, benefits of therapy for patients with serum TSH levels between 5 and 10 mIU/L remain to be determined. The most convincing argument for therapy is the high rate of progression to overt hypothyroidism.

The American College of Physicians stated that the available evidence is insufficient to make recommendations for or against the treatment of subclinical hypothyroidism.[16] However, the issue is still controversial. At present, some practical recommendations can be given. For patients with serum TSH levels higher than 10 mIU/L, no controversy exists, and treatment is recommended. This strategy is justified because the rate of progression to overt hypothyroidism is high, and low-density lipoprotein is reduced 8% with thyroxine therapy.[22] Thyroxine therapy for patients with subclinical hypothyroidism may improve quality of life, muscle function, mood, fertility, and cardiac function. For patients with TSH levels between 5 and 10 mIU/L, observation or treatment is recommended on an individual basis. Younger patients with a relatively large goiter and thyroid peroxidase–antibody positivity are usually treated. Symptomatic patients and patients with fertility problems should receive therapy. Tobacco use may be a risk factor for progression of subclinical hypothyroidism to clinical hypothyroidism and may be an indication for therapy. Bipolar disorder may be aggravated by subclinical hypothyroidism and is a possible indication for thyroxine therapy for subclinical thyroid failure. Because of concern about possible aggravation of coronary disease symptoms, patients with subclinical hypothyroidism who have only mild elevation of serum TSH and normal serum thyroxine levels are usually followed up with a repeated TSH measurement and treated if there is progression of subclinical thyroid disease. Children and adolescents, pregnant women, and women contemplating pregnancy should receive treatment. Of note, in women with hypothyroidism who are receiving thyroxine therapy, the dose of thyroxine replacement may need to be increased 30% to 40% during pregnancy.[17]

Observational data for possible adverse effects of subclinical hypothyroidism on the cardiovascular system are available.[22] A cohort study from Rotterdam showed that subclinical hypothyroidism in women older than 55 years with serum TSH levels between 4 and 10 mIU/L is a strong risk factor, independent of cholesterol level, for atherosclerotic disease and myocardial infarction.[23] The Colorado

Health Fair study showed that, with serum sensitive TSH levels between 5 and 10 mIU/L, there is a stepwise increase in serum cholesterol levels with increasing serum TSH.[24] Some evidence indicates that treatment of subclinical hypothyroidism may improve myocardial contractility.[25] Thus, if coronary disease is not a problem, cardiac function may improve with therapy.

In patients with subclinical hypothyroidism, a daily dose of 0.025 to 0.075 mg of levothyroxine is usually adequate to normalize serum sensitive TSH. The required dose varies with the level of serum TSH, serum thyroid hormones, and the age and weight of the patient. If the patient is already taking thyroxine, only a small increase is necessary. Serum sensitive TSH levels should be determined after 6 to 8 weeks of treatment to adjust the dose if necessary. Some thyroidologists aim for a serum sensitive TSH level between 1 and 3 mIU/L. Evidence for the need to increase the replacement thyroxine dose for patients who have sensitive TSH levels between 3 and 5 mIU/L is anecdotal.

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Questions About Subclinical Thyroid Disease

1. Which <u>*one*</u> of the following statements is <u>*not applicable*</u> when carotid ultrasonography reveals an 8-mm nodule on the right thyroid lobe of a 60-year-old man?
   a. History of neck radiation during childhood is an indication for fine-needle aspiration biopsy
   b. Biopsy should be performed based on current size of the nodule
   c. Family history of medullary cancer is an indication for fine-needle aspiration biopsy
   d. Most of these nodules have no clinical importance
   e. There is high likelihood that the left lobe also will have small nodules

2. A 70-year-old man has a 3-cm nodule in the right lobe of the thyroid, and the left lobe is not palpable. His serum sensitive TSH is 0.05 mIU/L, and his serum free thyroxine level is normal. Which *one* of the following statements is *false*?
   a. The most likely diagnosis is subclinical Graves disease
   b. T_3 level may be elevated
   c. Ultrasonography of the thyroid is unnecessary
   d. The patient has a high risk of atrial fibrillation
   e. A radioisotope thyroid scan is helpful for diagnosis
3. Which *one* of the following factors would be *least important* in deciding to initiate thyroxine therapy in a 35-year-old woman with a serum TSH level of 7 mIU/L?
   a. Relatively large thyroid
   b. Pregnancy
   c. Positive antithyroid antibodies
   d. Symptomatic coronary artery disease
   e. Bipolar disorder
4. Which *one* of the following is usually *not associated* with elevated serum TSH levels?
   a. Hypothyroid phase of postpartum thyroiditis
   b. Acute sepsis in a patient in the intensive care unit
   c. Thyroid hormone resistance
   d. Recovery from euthyroid sick syndrome
   e. Interfering antibodies in patient's serum
5. Which *one* of the following is the *most appropriate* dose for treating a 60-year-old man with a serum TSH level of 10 mIU/L and a normal serum thyroxine level?
   a. Levothyroxine, 0.1 mg/d
   b. Levothyroxine, 0.112 mg/d
   c. Levothyroxine, 0.05 mg/d
   d. Levothyroxine, 0.125 mg/d
   e. Combination of levothyroxine and triiodothyronine in low doses

Correct answers:
1. *b*, 2. *a*, 3. *d*, 4. *b*, 5. *c*