Subclinical Thyroid Disease
Clinical Applications

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Subclinical hypothyroidism and hyperthyroidism are diagnoses based on laboratory evaluation with few if any clinical signs or symptoms. Subclinical hypothyroidism is defined as an elevation in serum thyroid-stimulating hormone (TSH) above the upper limit of the reference range (0.45-4.5 mIU/L) with normal serum FT4 concentration; subclinical hyperthyroidism is defined as a decrease in serum TSH below the reference range with normal serum FT4 and T3 concentrations. Though these conditions represent the earliest stages of thyroid dysfunction, the benefits of detecting and treating subclinical thyroid disease are not well established. Most persons found to have subclinical thyroid disease will have TSH values between 0.1 and 0.45 mIU/L or between 4.5 and 10 mIU/L, for which the benefits of treatment are not clearly established; treatment may be beneficial in individuals with serum TSH lower than 0.1 mIU/L or higher than 10 mIU/L. This article illustrates approaches to managing patients with subclinical hypothyroidism and hyperthyroidism through 5 case scenarios that apply the principles of evidence-based medicine. Because of the substantial uncertainty concerning the consequences of untreated subclinical hypothyroidism and hyperthyroidism, as well as the benefit of initiating treatment, patient preferences are important in deciding on management of subclinical disease.

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In rare instances a slightly elevated serum TSH represents hypothalamic/pituitary disease. In these situations the TSH is extremely low when the TSH is only slightly elevated, in contrast to primary hypothyroidism in which the TSH increases exponentially with small decreases in serum FT4 concentration.

The normal range of free T4 (FT4) is 0.8 to 2.0 ng/dL (10-25 pmol/L); the normal range of thyroid-stimulating hormone (TSH) is 0.45-4.5 mIU/L.

Before making a treatment decision, guidelines recommend repeating the serum TSH and measuring FT4 within 2 to 12 weeks, depending on the clinical setting, to exclude transient forms of hypothyroidism. Transient hypothyroidism is most commonly caused by destructive thyroiditis (including painful subacute thyroiditis, silent subacute thyroiditis, or postpartum thyroiditis) or recovery from severe non-thyroidal illness. The clinician should assess the patient for symptoms and signs of hypothyroidism, including fatigue, lethargy, slow cerebration, diminished sweating, dry skin, cold intolerance, dry hair, weight gain, constipation, hoarseness, paresthesias, menstrual alterations, and muscle pain. The thyroid gland should be examined carefully. The patient should be asked about previous radioactive iodine treatment, thyroid surgery, levothyroxine treatment, a family history of thyroid disease, and her lipid profile, except for the serum TSH concentration of 7.9 mIU/L.

Three months later, the patient’s serum TSH was 6.8 mIU/L and FT4, 1.4 ng/dL (18 pmol/L); antithyroid peroxidase (TPO) antibodies were absent. She was referred to an endocrinologist for evaluation and treatment of subclinical hypothyroidism. The patient reported no symptoms of hypothyroidism. She was taking no medications other than oral contraceptives, her menses occurred regularly, and she was not intending to become pregnant. Her family history included one maternal aunt with hypothyroidism and a maternal grandmother with diabetes mellitus. Her examination findings were unremarkable and her thyroid gland was palpable but not enlarged.

Routine measurement of anti-TPO levels is controversial. Although antibody positivity predicts an increased risk of progressing to overt hypothyroidism (2.6% per year if negative, 4.3% if positive),2 it does not affect the effectiveness of treatment. Nonetheless, the increased rate of progression may tip the balance toward treatment in some cases. The presence of anti-TPO antibodies does predict an increased risk of miscarriage as well as postpartum thyroiditis.3

Having confirmed the diagnosis of subclinical hypothyroidism, deciding whether to initiate levothyroxine would depend on her serum TSH concentration, the presence of any signs or symptoms suggestive of hypothyroidism, her risk of progression to overt disease, and her preferences. There is no evidence that levothyroxine treatment in healthy, asymptomatic patients with TSH between 4.5 and 10 mIU/L results in significant improvements in either quality of life or clinical outcomes. Initiating treatment would prevent symptoms and signs of hypothyroidism should this patient eventually progress to overt hypothyroidism. The risk of progression to overt hypothyroidism is 2% to 5% per year. However, serum TSH decreases to the reference range in a similar percentage during the 2 to 4 years after elevated serum TSH is discovered.2 No risks of delaying detection of overt hypothyroidism have been demonstrated as long as individuals are carefully monitored.

In the absence of symptoms, the only other benefit of levothyroxine treatment in this patient would be possible improvement in cardiac function. Several small, unblinded studies suggest that subclinical hypothyroidism might be associated with subtle declines in cardiac contractility.4 However, evidence concerning the impact of subclinical hypothyroidism, treated or untreated, on clinical cardiac end points is limited. Because of the lack of clear clinical benefits, routine treatment with levothyroxine is not recommended in such patients. There is no compelling evidence that low-density lipoprotein (LDL) cholesterol is higher in individuals with serum TSH in the range of 4.5 to 10 mIU/L.
After discussing the risks and benefits of treatment, this patient elected not to be treated but to be followed with annual determination of serum TSH and to be alert for signs and symptoms of overt hypothyroidism.

If she were contemplating pregnancy, treatment with levothyroxine should be started, and serum TSH should be restored to the reference range. Although some data suggest that withholding treatment may result in an increased risk of fetal loss and neurodevelopmental complications in the offspring, there is no compelling evidence that levothyroxine decreases the risk of miscarriage or improves the neuropsychiatric complications. The requirement for levothyroxine in treated hypothyroid patients often increases during pregnancy and serum TSH should be monitored each trimester.

**Patient 2.** During an annual evaluation, a healthy 70-year-old woman complained of mild fatigue, dry skin, and constipation. Physical examination results were normal, including a nonpalpable thyroid gland and normal relaxation phase of deep tendon reflexes. The serum TSH was 8.1 mIU/L; serum total cholesterol, 215 mg/dL (5.57 mmol/L); high-density lipoprotein (HDL) cholesterol, 47 mg/dL (1.22 mmol/L); LDL cholesterol, 148 mg/dL (3.83 mmol/L); and triglycerides, 78 mg/dL (0.88 mmol/L). Repeat testing 2 months later revealed a serum TSH of 8.3 mIU/L and an FT₄ of 1.4 ng/dL (18 pmol/L).

Up to 20% of women older than 60 years have subclinical hypothyroidism; 75% of those have serum TSH between 4.5 and 10 mIU/L. Routine treatment with levothyroxine is not recommended because data are insufficient to link this degree of hypothyroidism with any adverse health outcomes, and no clear benefits of treatment have been demonstrated. However, because this patient has symptoms that may be associated with hypothyroidism, levothyroxine treatment may be considered. Although one study found patients with subclinical hypothyroidism to have more symptoms than euthyroid patients, other studies found no differences between patients and euthyroid controls.

There are no data clearly demonstrating that treatment will improve symptoms in patients with elevated serum TSH concentrations higher than 4.5 but lower than 10 mIU/L. While there appear to be no adverse effects of initiating levothyroxine treatment in this setting, inadvertent overtreatment occurs in about 20% (range, 14%-21%) of levothyroxine-treated patients, carrying the potential risks of osteoporosis and atrial fibrillation when serum TSH falls below 0.1 mIU/L. Treatment also involves the costs and inconvenience of taking a daily medicine for the rest of one’s life. Although follow-up diagnostic testing to adjust dosage is also necessary, periodic thyroid function tests are also necessary in individuals who are not treated.

**Patient 3.** A 58-year-old sedentary, obese man with well-controlled hypertension, type 2 diabetes mellitus, and hypercholesterolemia who presents for medical clearance before embarking on an exercise program is found to have a serum TSH of 12 mIU/L. Repeat testing 2 months later reveals a serum TSH of 14 mIU/L, FT₄ of 1.3 ng/dL (17 pmol/L), and total serum cholesterol of 235 mg/dL (6.09 mmol/L). Current medications included metformin, 850 mg twice each day, hydrochlorothiazide, 25 mg/d, and pravastatin, 20 mg/d. He reports occasional constipation and fatigue. His physical examination findings are unremarkable other than obesity (body mass index of 35).

Among patients with a serum TSH higher than 10 mIU/L and normal serum FT₄ who have signs and symptoms possibly consistent with hypothyroidism, there is suggestive evidence supporting treatment with levothyroxine. Potential benefits include a lowering of serum total and LDL cholesterol concentrations, an improvement

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TSH indicates thyroid-stimulating hormone; FT₄, free T₄; FT₃, free T₃.
in cardiac function, and a possible improvement in symptoms. However, the study suggesting that levothyroxine treatment reduced cholesterol levels among individuals with subclinical hypothyroidism did not compare treated with untreated groups, and the small, unblinded trials suggesting that treatment improved cardiac function examined intermediate end points of uncertain clinical significance. No blinded, randomized controlled studies have assessed the impact of levothyroxine on important clinical cardiac end points. Because the risk of progression to overt hypothyroidism may be higher in these patients than in patients with serum TSH between 4.5 and 10 mIU/L, treatment may prevent the manifestations and consequences of hypothyroidism in those who would have progressed.

After discussing the potential benefits of treatment on his serum cholesterol concentration, exercise tolerance, and constipation, the patient decided to begin treatment with levothyroxine.

**Patient 4.** A 36-year-old healthy woman was found to have a serum TSH concentration of 0.26 mIU/L, which is in the low (<0.45 mIU/L) but detectable (>0.1 mIU/L) range. She has no personal or family history of thyroid disease. She has one child and has monthly menstrual periods. Her examination results were unremarkable, and her thyroid gland was not palpable.

When the serum TSH concentration is found to be low but detectable, the assay should be repeated along with a serum FT4 and total or free T3 concentration within several months, sooner if any cardiac signs or symptoms are present such as atrial fibrillation or palpitations. If free thyroid hormone concentrations are within their reference ranges and serum TSH remains low, the following causes of low serum TSH should be excluded: treatment with levothyroxine, high-dose glucocorticoid or dopamine therapy, severe nonthyroidal illness, or pregnancy. Although a low serum TSH may also be due to hypothalamic or pituitary disease or anorexia nervosa, FT4 is usually low in these situations.

Patients with serum TSH levels between 0.1 and 0.45 mIU/L infrequently progress to overt hyperthyroidism, defined as serum TSH lower than 0.1 mIU/L and elevated concentrations of FT4 and/or FT3. However, the rate of progression varies according to the underlying etiology. Patients with large autonomously functioning adenomas (>3.0 cm diameter) or toxic multinodular thyroids are at greater risk for progression to overt hyperthyroidism, especially when exposed to high concentrations of iodine, most commonly after treatment with amiodarone or radiocontrast agents.

Routine treatment is likely not beneficial in young asymptomatic persons because there are no data that this condition is associated with adverse health outcomes. Additional studies such as a 24-hour radioiodine uptake and radionuclide thyroid scan to determine the etiology of the subclinical hyperthyroidism are usually not necessary in asymptomatic individuals with serum TSH concentrations in this range, if therapy is not being considered. In older patients, however, treatment should be based on clinical judgment because of a possible association of subclinical hyperthyroidism with increased cardiovascular mortality and osteoporosis and the higher risk of progression to hyperthyroidism.

**Patient 5.** An active 77-year-old woman with a history of myocardial infarction and osteoporosis feels well other than experiencing rare exertional angina. She takes atenolol and atorvastatin daily, alendronate weekly. Her pulse is 75/min and she is normotensive. Her thyroid gland is difficult to examine due to kyphosis but feels somewhat prominent. Thyroid function tests reveal serum TSH concentration lower than 0.01 mIU/L and FT4 and FT3 within the reference ranges. A thyroid ultrasound reveals a multinodular goiter. She has not received iodinated contrast material in the past year.

Although other causes of low serum TSH should be sought, subclinical hyperthyroidism due to a toxic multinodular goiter is the likely etiology. A 24-hour radioiodine uptake and radionuclide thyroid scan is the most efficient method to distinguish the various etiologies of hyperthyroidism. Hyperthyroidism due to the various forms of destructive thyroiditis is transient and self-limited; the 24-hour radioiodine uptake is close to zero when these conditions are present. In contrast, individuals with Graves hyperthyroidism have normal or elevated 24-hour radioiodine uptakes and a homogeneous pattern on radionuclide scan. Autonomous adenomas appear as “hot” nodules on scans. Individuals with toxic nodular goiters may have single or multiple hot areas but commonly have a heterogeneous pattern of uptake.

Thyroid autonomy in a single-nodule or multinodular goiter increases the likelihood of progression to subclinical or overt hyperthyroidism, especially if patients receive excess iodine such as radiocontrast dyes or amiodarone. However, nodules that do not concentrate radioactive iodine (“cold” nodules) also occur in this setting and in some individuals with Graves disease. These nodules may require a fine-needle aspiration biopsy.

Untreated subclinical hyperthyroidism with suppressed serum TSH (<0.1 mIU/L) carries the potential risks of atrial fibrillation, cardiovascular mortality, and osteoporosis. Because these risks are higher among patients older than 60 years, the balance is shifted toward treatment among older patients. There are no studies that compare the risk of atrial fibrillation in treated vs untreated patients, but bone density is higher in treated compared with untreated postmenopausal women with subclinical hyperthyroidism and decreased serum TSH. The risks of treatment include allergic reactions (rash, fever, arthralgias, agranulocytosis, hepatotoxicity, vasculitis) after antithyroid drug administration, and transient worsening hyperthyroidism, permanent hypothyroidism, or worsening Graves ophthalmopathy after therapy with iodohippurate sodium.21
Conclusion

The definition of subclinical thyroid dysfunction is based on serum TSH determination and is of necessity somewhat arbitrary. There is substantial uncertainty concerning the consequences of untreated subclinical hypothyroidism and hyperthyroidism, as well as the benefit of initiating treatment. Although treatment may be beneficial in individuals with serum TSH lower than 0.1 mIU/L or higher than 10 mIU/L, most persons found to have subclinical thyroid dysfunction will have values between 0.1 and 4.5 mIU/L or between 4.5 and 10 mIU/L, for which the benefits of treatment are not clearly established.

It is impossible to assess the merits of determination of serum TSH to screen for occult subclinical disease without addressing the merits of screening for occult overt thyroid disease, since both use the same test. Any attempt to screen for overt disease will likely yield a far greater number of cases of subclinical than overt disease. Unlike subclinical disease, the benefits of detecting and treating overt thyroid disease are established. Until clear therapeutic benefits are established for treating subclinical thyroid dysfunction, general population screening for these conditions is not recommended. However, the benefits of TSH determination to detect occult thyroid dysfunction will be greater among those populations at higher risk for developing overt disease, including women, older persons, and individuals with previous or family history of thyroid disease, type 1 diabetes mellitus, radioactive iodine treatment for hyperthyroidism, recurrent miscarriages, or administration of medications that may affect thyroid function, such as lithium carbonate or interferon. Vigorous case finding is recommended in these populations. Among those found to have subclinical disease, patient preferences are important in deciding on management.

REFERENCES