Subclinical Hypothyroidism: When to Treat, When to Watch

Dr Ross is professor of medicine at Harvard Medical School in Boston and a physician at Massachusetts General Hospital, also in Boston. He is co-editor of the thyroid disease section of UpToDate.

ABSTRACT: Subclinical hypothyroidism is defined as an elevated serum TSH level with a normal serum free T4 concentration. It is a laboratory diagnosis; hypothyroid symptoms—such as fatigue, inability to lose weight, memory impairment, hair loss, and depression—are nonspecific and are not included in the definition. If a patient’s serum TSH level is elevated and the serum T4 concentration is low, he or she has overt hypothyroidism.

The optimal approach to subclinical hypothyroidism continues to be debated. Experts disagree over screening for thyroid dysfunction, the threshold TSH level for treatment, and the upper limit of normal of the TSH reference range. Here I examine the often conflicting data—and I offer a practical strategy for patients you are likely to see in your practice (Table).

Subclinical hypothyroidism is common, with a prevalence of 4.3% in the National Health and Examination Survey (NHANES III).1 In population-based studies, the condition affects 7.5% to 8.5% of women and 2.8% to 4.4% of men.2,3 In women older than 60 years, the prevalence is as high as 15%.2 The prevalence is lower in African Americans and higher in patients with type 1 diabetes mellitus.

In patients with no history of thyroid surgery or radioiodine treatment, hypothyroidism almost always results from Hashimoto thyroiditis. The titer...
of anti-thyroid peroxidase (TPO) antibodies is proportional to the degree of lymphocytic infiltration and inflammation within the gland. Thus, hypothyroidism in patients with high titers of anti-TPO antibodies is more likely to progress from subclinical to overt disease. In one population-based survey with a 20-year follow-up, the progression to overt hypothyroidism was 2.6% per year among patients with an elevated TSH concentration and negative results on anti-TPO antibody testing and 4.3% per year among those with an elevated TSH concentration and positive results on anti-TPO antibody testing.4

SCREENING AND TREATMENT CONTROVERSIES

Controversy persists about screening for subclinical hypothyroidism and the TSH level at which treatment should be initiated. A 1998 position paper from the American College of Physicians questioned whether there were sufficient data to recommend treatment of patients with subclinical hypothyroidism.5 A 2004 publication from the US Preventive Services Task Force found that the data were insufficient to recommend for or against screening in adults.6 In 2002, a consensus development panel sponsored by the American Thyroid Association, the American Association of Clinical Endocrinologists, and the Endocrine Society found insufficient evidence to support screening and recommended against treating patients with a TSH concentration between 4.5 and 10 mIU/L.7 The conclusions of this panel were so controversial that the organizations involved formed a second panel of ex-

Table – Possible indications for treatment of subclinical hypothyroidism

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| Hypothyroid symptoms     | Placebo effect is 40% 
|                          | No improvement in symptoms seen in RCTs if TSH < 15 mIU/L 
|                          | Overtreatment may result                                                |
| Elevated lipid levels    | Improvement seen only when TSH > 10 mIU/L                                |
| At risk for atherosclerosis | Data suggest an association between subclinical hypothyroidism and markers for atherosclerosis 
|                          | Studies do not consistently show a reduction in cardiovascular disease or mortality; in a meta-analysis cardiovascular mortality, but not all-cause mortality was increased if TSH > 7.0 mIU/L 
|                          | No trials assess whether the benefits of treatment outweigh the risks of treatment in the elderly |
| Neuropsychiatric symptoms | Many studies testing the association with subclinical hypothyroidism have been poorly designed 
|                          | Depression in patients with subclinical hypothyroidism may be the result of a genetic predisposition |
| Overweight               | Modest increased BMI associated with TSH > 3.6 mIU/L 
|                          | No therapeutic trial shows weight loss                                  |
| Pregnancy                | Reduced IQ in offspring of women with subclinical hypothyroidism 
|                          | TPO antibodies and TSH > 2.5 mIU/L during pregnancy is associated with a poor pregnancy outcome 
|                          | Treatment is recommended in pregnant women for TSH > 4.5 mIU/L, or TSH > 2.5 mIU/L if she has positive TPO antibodies |
| High anti-TPO antibody titer | Without treatment, progression to overt hypothyroidism is likely |
| Goiter                   | Reduction of TSH may limit growth                                       |

RCT, randomized controlled trial; TSH, thyroid-stimulating hormone; BMI, body mass index; TPO, thyroid peroxidase.
Elevated cholesterol levels. A large cross-sectional study of 25,862 persons found that those with serum TSH concentrations of 5.1 to 10 mIU/L had higher serum cholesterol levels than those who were euthyroid (223 mg/dL vs 216 mg/dL). 11

The extensive literature on the effect of thyroxine treatment on lipid concentrations includes many conflicting results. A meta-analysis of several therapeutic trials revealed a 10-mg/dL reduction in low-density lipoprotein (LDL) cholesterol levels, but this occurred only in patients with total cholesterol levels of greater than 240 mg/dL at baseline. 12 The recommendation of the 2002 consensus panel 7 that only patients with TSH concentrations of greater than 10 mIU/L be treated is based on several studies that showed that treatment reduced serum total and LDL cholesterol levels in patients whose initial serum TSH concentrations were greater than 10 mIU/L. Non-randomized trials have shown that thyroxine therapy lowers serum lipoprotein (a) concentrations. 13,14

Atherosclerosis. Patients with subclinical hypothyroidism have abnormalities in parameters that are associated with atherosclerosis. Of note, all of these studies were published after the recommendations of the 2002 consensus panel were released. Moreover, all of these studies are of patients who have minimal elevations in serum TSH levels, with values generally less than 15 mIU/L.

Impaired endothelium-dependent vasodilatation is an early marker for atherosclerosis. This abnormality has been found in patients with subclinical hypothyroidism and was reversed by thyroxine treatment. 15 Platelet-activating factor (PAF) is a proinflammatory lipid mediator that has been implicated in atherogenesis. PAF-acetylhydrolase inactivates PAF; levels of PAF-acetylhydrolase have been found to be low in patients with subclinical hypothyroidism and increased to normal with treatment. 16 Elevated C-reactive protein levels also became normal with treatment in one study, 17 but not in another study. 18 Increased concentrations of osteoprotegerin, involved in the regulation of endothelium-dependent vasodilatation, have been noted in patients with subclinical hypothyroidism; the values normalized after treatment. 19 Finally, thyroxine therapy in patients with subclinical hypothyroidism resulted in an 11% reduction in carotid artery intima-media thickness. 20

Cardiovascular disease and mortality. The evidence is conflicting about whether subclinical hypothyroidism results in an increase in cardiovascular disease or cardiovascular mortality. In the Rotterdam Study of women older than 55 years, the risk of aortic atherosclerosis and myocardial infarction (MI) was increased by about 2-fold in participants who had subclinical hypothyroidism. 21 The Nagasaki study found a 2-fold elevation in the risk of angina and MI in men but not in women with subclinical hypothyroidism. 22 A study of patients with subclinical hypothyroidism who were between the ages of 70 and 79 years showed a 2.5- to 3-fold increased risk of congestive heart failure (for serum TSH higher than 7.0 mIU/L), but no increased risk of coronary or cerebrovascular disease or cardiovascular mortality. 23 The Busselton Health Study (Australia) revealed a 2- to 3-fold increase in the risk of coronary artery disease and a 1.5-fold increase in the risk of cardiovascular mortality in patients with subclinical hypothyroidism. 24

In contrast, the Cardiovascular Health Study—a prospective study of 3233 patients older than 65 years who were monitored for 12 to 13 years—found no differences in incidence of coronary artery disease, cerebrovascular disease, or cardiovascular mortality between euthyroid participants and those with subclinical hypothyroidism, 25 although there was an increase in heart failure if the TSH exceeded 10 mIU/L. 26 An analysis of the individual data from these and other studies found significant hazard ratios for coronary events to be 1.89 (CI, 1.28 to 2.80) for serum TSH levels from 10 to 19.9 mIU/L, and for cardiovascular mortality to be 1.42 (CI, 1.03 to 1.95) for serum TSH from 7.0 to 9.9 mIU/L and 1.58 (CI, 1.10 to 1.27) for serum TSH from 10 to 19.9 mIU/L; however, total mortality was not increased.
for TSH lower than 20 mIU/L.27 A study of patients aged 85 to 89 years showed lower cardiovascular mortality (hazard ratio, 0.77) in patients with subclinical hypothyroidism than in those who were euthyroid.28

Neuropsychiatric disease. Studies of neuropsychiatric disease and subclinical hypothyroidism are difficult to interpret because of such confounding variables as inadequate control groups and the inclusion of patients taking lithium, those with normal TSH levels and positive results on anti-TPO antibody tests, and those with normal TSH levels but abnormal responses to thyrotropin-releasing hormone. On the whole, these studies suggest an increased risk of depression and panic disorder and a poorer response to antidepressant treatment in patients with subclinical hypothyroidism.29,30 One study found an increased risk of depression in patients with positive titers of anti-TPO antibodies, but not in patients with elevated serum TSH concentrations and negative antibody titers.31 These results suggest a possible genetic basis for the association of hypothyroidism and depression. In the Framingham study, Alzheimer disease was more common in women, but not in men, with subclinical hypothyroidism.32 However cognitive function was unchanged by thyroid treatment in a randomized 1-year placebo-controlled trial of elderly patients with TSH between 6.0 and 8.5 mIU/L.33

Weight gain. In the Framingham trial, the 3.5-year weight gain among women with TSH values between 0.5 and 10 mIU/L was 2.3 kg for those in the highest quintile and 0.5 kg for those in the lowest quintile.33 No study has demonstrated weight loss with treatment of subclinical hypothyroidism.

Neuromuscular disease. A survey showed that 64% of patients with subclinical hypothyroidism had 2 or more symptoms of neuromuscular disease, compared with 14% of euthyroid controls; treatment with thyroxine ameliorated these symptoms.35 However, the patients in this survey knew their diagnosis, and treatment was not blinded or placebo-controlled. In another study older patients with TSH levels from 4.5 to 6.9 mIU/L had improved mobility (faster usual and rapid gait speed) and cardiorespiratory fitness.36

Poor pregnancy outcomes. Children born to mothers who had elevated serum TSH concentrations during the second trimester of pregnancy had a slightly lower IQ score at age 7 to 9 years than did children born to mothers with normal serum TSH concentrations (103 vs 107).37

The Argument for Therapy: A Critical Look at the Evidence

Those who favor treating most patients with subclinical hypothyroidism commonly cite 1 or more of the several randomized clinical trials. Among 8 trials38-45:

- Four of the seven that assessed for hypothyroid symptoms showed improvement with treatment.
- Two of the three that used psychometric testing results as an outcome measure found an improvement with treatment.
- Three of the seven that measured serum total and LDL cholesterol levels found lower levels with treatment. However, 3 of these studies included patients who met the strict biochemical criteria for subclinical hypothyroidism but had serum TSH concentrations as high as 30 to 55 mIU/L.38,40,41 and 2 studies used a fixed dose of thyroxine for treatment,39,45 which resulted in over-treatment in some patients. In 3 randomized controlled trials that included only patients whose TSH values were less than 15 mIU/L,42,44 there was no improvement in any parameter studied except for a reduction in total and LDL cholesterol levels in 1 study,42 while a fourth study that included patients with TSH up to 15.8 mIU/L, in which 10% of patients were given excessive doses of thyroxine, found improvement in lipids, fatigue, and endothelial function.43

Problems in Interpretation of Trial Results. Other studies point to the difficulty of interpreting many of these results, especially those whose end points are symptom scores. In a population-based study of almost 400 patients who had normal serum TSH concentrations while taking levothyroxine, participants had significantly distressed scores on both general health and thyroid-specific symptom questionnaires.46 One explanation for these findings may be a possible genetic predisposition to depression among patients with autoimmune thyroid disease.

It is also possible that levothyroxine therapy is suboptimal treatment for hypothyroidism in a subset of patients. While twelve randomized trials have compared combined treatment (triiodothyronine [T₃] and T₄ therapy) to therapy with T₄ alone, only 1 of these studies found that symptoms (as assessed by standardized questionnaires) abated with combined therapy. However, in another study, patients preferred combined therapy despite negative results on standardized symptom assessments.47 And a recent study from the United Kingdom suggests that 16% of patients have a polymorphism in the type 2 deiodinase that converts T₄ into T₃; those patients had improved symptoms (by standardized questionnaires) when treated with both T₄ and T₃.48

In one study that is commonly cited to support the treatment of subclinical hypothyroidism, patients were given doses of levothyroxine that were slightly lower or slightly higher than optimal doses (based on TSH levels). The investigators found
when to treat

when to watch

subclinical hypothyroidism

When to Treat, When to Watch

CLINICAL HIGHLIGHTS

- Considerable controversy persists regarding screening for thyroid dysfunction and treatment of subclinical hypothyroidism. Statements from the American College of Physicians, the US Preventive Services Task Force, the American Thyroid Association, the Endocrine Society, and the American Association of Clinical Endocrinologists have failed to reach a consensus.

- The upper limit of normal for serum TSH is age-related, with a value of 3.56 mIU/L for patients aged 20 to 29 years, increasing to 7.49 for patients over 80 years old.

- Subclinical hypothyroidism may be associated with modest weight increases; however, no study has demonstrated weight loss with treatment of the condition.

- When serum TSH concentrations are greater than 10 mIU/L, subclinical hypothyroidism is associated with increases in serum low-density lipoprotein cholesterol levels. In a meta-analysis, cardiovascular mortality, but not all-cause mortality was increased when serum TSH was greater than 7 mIU/L. Thus, thyroxine therapy should be considered if the serum TSH level is 7 to 10 mIU/L or higher.

- Consider a trial of thyroxine for symptomatic patients whose serum TSH level is below 10 mIU/L. If the patient perceives no benefit, therapy can be discontinued.

that patients preferred slightly higher doses of thyroid hormone. However, this study was not blinded. A double-blinded, randomized cross-over trial assessed 3 different levels of thyroxine treatment, which resulted in mean serum TSH concentrations of 2.8, 1.0, and 0.3 mIU/L, respectively. There were no differences in hypothyroid symptoms among the groups, and patients could not distinguish among the 3 levels of thyroid hormone replacement.

Placebos have a significant effect on hypothyroid symptoms. In one of the trials of combined T3 and T4 therapy, symptoms abated in 39% of patients who received placebo. In another study of patients with hypothyroid symptoms, thyroxine and placebo produced equal benefit despite the fact that the average serum TSH concentrations in the thyroxine-treated group were at the lower limit of the normal reference range. Because hypothyroid symptoms are readily amenable to the placebo effect, a large, double-blind, randomized, placebo-controlled trial is needed to accurately assess the efficacy of levothyroxine therapy on hypothyroid symptoms, cognitive function, and psychological well-being in patients with subclinical hypothyroidism.

RECOMMENDATIONS FOR SYMPTOMATIC PATIENTS

Let us return to the 76-year-old woman in the opening clinical scenario. Her TSH level is within the age-adjusted normal range for TSH. There is no evidence that treating her will improve her cognitive function or fatigue. I would not treat her with levothyroxine. Patients taking levothyroxine are commonly unintentionally over-treated; in one study 41% of patients over age 65 had subnormal serum TSH levels. Only one trial has assessed the risks of treatment; while that trial found a 10% mortality rate among treated patients and a 31% mortality rate among untreated patients, the study is hardly robust with only 20 patients treated, and only 2 deaths in the treatment group.

Measurement of TPO antibodies might be useful. If they are high, the patient should be more closely monitored, and if her TSH increased to values above 7.5 mIU/L, I would then consider treatment. If the TSH increased to values above 10 mIU/L, treatment is indicated.

If the patient was younger and had symptoms possibly related to subclinical hypothyroidism, I would offer a trial of levothyroxine, since in younger patients—eg, a premenopausal woman—the risks of overtreatment (atrial fibrillation, reduced bone density) are minimal.

RECOMMENDATIONS FOR ASYMPOMATIC PATIENTS

The evidence for treating patients with TSH values of less than 10 mIU/L is not compelling—except in women who are pregnant. At present, a TSH value of 7 to 10 mIU/L appears to be a reasonable threshold for routinely recommending treatment (based on the favorable response of LDL cholesterol levels to levothyroxine, and the higher risk of cardiovascular, but not all-cause mortality). Thus, I would not advise treating a patient whose TSH concentration is elevated—but below 7 to 10 mIU/L—if he or she exhibits no hypothyroid symptoms.

REFERENCES:


4. Vanderpump MP, Tunbridge WM, French JM, et al. The incidence of thyroid disorders in the com-
7. Surks MI, Ortiz E, Daniels GH, et al. Subclinical thyroid disease: review and guidelines for diagnosis and management. JAMA. 2004;291:228-238.