Subclinical Hypothyroidism: REFERENCES: EvidencE-based medicine: Relevant guidelines:

September 01, 2006
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ABSTRACT: Subclinical hypothyroidism is associated with elevated low-density lipoprotein (LDL) cholesterol levels and several factors related to atherosclerosis, including increased C-reactive protein levels and impaired endothelium-dependent vasodilatation. However, considerable controversy exists about screening for and treating this thyroid disorder. Thyroxine therapy lowers elevated LDL cholesterol levels in patients whose serum thyroid-stimulating hormone (TSH) concentrations are higher than 10 mIU/L; thus, most experts recommend treatment for such patients. However, there is no consensus regarding the management of patients with TSH levels of less than 10 mIU/L. Although the evidence supporting treatment of these patients is not compelling, it is reasonable to offer a therapeutic trial of thyroxine to those who have symptoms.

Key words: subclinical hypothyroidism, levothyroxine, thyroid screening

For several years, a 49-year-old woman has not "felt like herself." She complains of occasional muscle pain, impaired memory, and excessive fatigue (she usually falls asleep after dinner while watching television). She has also gained 35 pounds in the last 10 years. Thyroid tests reveal the following values:

• Thyroid-stimulating hormone (TSH), 5.6 mIU/L.
• Free thyroxine (T4), 1.2 ng/dL (normal 0.8 to 1.8 ng/dL).

Would you offer this patient treatment?

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).

PREVALENCE AND NATURAL HISTORY

Subclinical hypothyroidism is common. In population-based studies, the condition affects 7.5% to 8.5% of women and 2.8% to 4.4% of men. In women older than 60 years, the prevalence is as high as 15%. 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.

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. A 2004 publication from the US Preventive Services Task Force found that the data...
were insufficient to recommend for or against screening in adults.\textsuperscript{5} 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.\textsuperscript{6} The conclusions of this panel were so controversial that the organizations involved formed a second panel of experts. These experts disagreed with the findings of the first panel and recommended screening for thyroid dysfunction, especially among pregnant women; they also recommended treatment of "most patients" with subclinical hypothyroidism.\textsuperscript{7} Endocrinologists also disagree about the normal range for serum TSH levels. Although many laboratories have traditionally used 4 to 6 mIU/L as the upper limit of normal, the data used to calculate reference ranges have frequently included measurements in patients who had positive results on anti-TPO antibody tests or other evidence of early thyroid dysfunction. Careful analysis suggests that the true upper limit of normal for serum TSH concentration is closer to 2.5 mIU/L.\textsuperscript{8} Because endocrinologists cannot agree whether patients with TSH levels of 4.5 to 10 mIU/L require treatment, I believe it is not useful to diagnose subclinical hypothyroidism in the estimated 25 million persons whose TSH concentrations are between 2.5 and 4.5 mIU/L.\textsuperscript{9}\textbf{CLINICAL AND METABOLIC CONSEQUENCES OF SUBCLINICAL HYPOTHYROIDISM}

\textbf{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).\textsuperscript{10} 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.\textsuperscript{11} The recommendation of the 2002 consensus panel\textsuperscript{6} 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.\textsuperscript{12,13} \textbf{Atherosclerosis.} Recent preliminary studies suggest that 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.\textsuperscript{14} 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.\textsuperscript{15} Elevated C-reactive protein levels also became normal with treatment.\textsuperscript{16} 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.\textsuperscript{17} Finally, thyroxine therapy in patients with subclinical hypothyroidism resulted in an 11% reduction in carotid artery intima-media thickness.\textsuperscript{18}

\textbf{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.\textsuperscript{19} The Nagasaki study found a 2-fold elevation in the risk of angina and MI in men but not in women with subclinical hypothyroidism.\textsuperscript{20} 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, but no increased risk of coronary or cerebrovascular disease or cardiovascular mortality.\textsuperscript{21} 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.\textsuperscript{22} 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.\textsuperscript{23} 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.24

**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.25,26 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.27 These results suggest a possible genetic basis for the association of hypothyroidism and depression.

**Weight gain.** A recent population-based study from Denmark of more than 4000 women found a slightly higher 5-year weight gain in those whose serum TSH level was greater than 3.6 mIU/L (with a normal serum free T4 concentration) than was found in those whose serum TSH measured between 0.4 and 0.99 mIU/L.28 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.29 However, the patients in this survey knew their diagnosis, and treatment was not blinded or placebo-controlled.

**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).30

**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 these 7 trials31-37:

- Three of the six 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.
- Two of the six 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,31,33,34 and 1 study used a high fixed dose of thyroxine for treatment,32 which likely resulted in overtreatment. In the 3 randomized controlled trials that included only patients whose TSH values were less than 15 mIU/L,35-37 there was no improvement in any parameter studied except for a reduction in total and LDL cholesterol levels in 1 study.35

**Problems in interpretation of trial results.** Several 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.38 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. To investigate this possibility, 11 randomized trials 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.39

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 that patients preferred slightly higher doses of thyroid hormone.40 However, this study was not blinded. A recent 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.41

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.42 In another study of patients with hypothyroid symptoms,43 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 49-year-old woman in the opening clinical scenario. The patient wants to feel better, and she hopes to lose some weight. If she has a high titer of anti-TPO antibodies, the hypothyroidism is likely to progress. Because the response to placebo in patients with subclinical hypothyroidism is as high as 40%, it is likely she will feel better if thyroxine is prescribed. And although no short-term study has found that thyroxine therapy produces weight loss, the Danish study suggests that 5 years from now the patient might have gained an additional 10 pounds if she is not treated.  

I believe that treatment of a patient with symptomatic hypothyroidism can be justified on grounds such as these—even if the TSH concentration is less than 10 mIU/L. Arguments against treatment include the cost and the possibility of unintentional overtreatment, with the resultant risks of reduced bone density and atrial fibrillation. However, the cost of thyroxine therapy is modest. Moreover, treatment should be considered a therapeutic trial; if the patient perceives no benefit, thyroxine can be discontinued.**RECOMMENDATIONS FOR ASYMPTOMATIC PATIENTS**

The evidence for treating patients with TSH values of less than 10 mIU/L is not compelling—except in women who are pregnant. Recent preliminary data suggest that patients with subclinical hypothyroidism exhibit markers for atherosclerosis. Confirmation of this association and a better understanding of these data may provide a more compelling argument for treatment in the future. At present, a TSH value of 10 mIU/L appears to be a reasonable threshold for routinely recommending treatment (based on the favorable response of LDL cholesterol levels to levothyroxine). Thus, I would not advise treating a patient whose TSH concentration is elevated—but below 10 mIU/L—if he or she exhibits no hypothyroid symptoms.  


(Note: Because of the lack of consensus regarding the treatment of subclinical hypothyroidism [as discussed in the article], there are significant discrepancies between these 2 sets of guidelines and neither is regarded as authoritative.)

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