Clinical Practice

This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

Subclinical Hypothyroidism

David S. Cooper, M.D.

A 59-year-old woman is found to have a serum thyrotropin level of 7 mU per liter on routine screening. Her only symptoms are mild fatigue, which has been present for more than 10 years, and difficulty losing weight. The results of the physical examination are normal, except for the finding of a small, firm thyroid with a slightly irregular surface. The serum cholesterol level is 220 mg per deciliter (5.69 mmol per liter), the low-density lipoprotein (LDL) cholesterol level is 140 mg per deciliter (3.62 mmol per liter), and a test for antibodies against thyroperoxidase is positive. Should treatment with thyroxine be initiated?

The Clinical Problem

There is a broad clinical spectrum of hypothyroidism. The lethargic, myxedematous patient with severe hypothyroidism is a familiar inhabitant of medical textbooks but is rarely seen in today's clinics. In contrast, physicians frequently encounter patients with very mild thyroid dysfunction. Unlike patients with overt hypothyroidism, these patients have normal serum levels of thyroxine and triiodothyronine and only mildly elevated serum thyrotropin levels. Such patients are often identified through routine screening or in the course of an evaluation of common nonspecific symptoms or hypercholesterolemia.

Although subclinical hypothyroidism is the term most frequently used to describe this condition and will be used in this discussion, it is not necessarily apt, since on close questioning many patients disclose mild, nonspecific symptoms. Mild hypothyroidism may be a more appropriate term for this very common syndrome,[1] which is defined by an isolated elevated serum thyrotropin level in the setting of normal serum thyroid hormone levels, in the presence or absence of symptoms. The worldwide prevalence of subclinical hypothyroidism ranges from 1 to 10 percent; the highest age- and sex-specific rates are in women older than 60 years of age, approaching 20 percent in some reports.[2,3] In a recent survey, the prevalence of subclinical hypothyroidism in men over the age of 74 years (16 percent) was almost as high as it was in women of the same age (21 percent).[3] Up to 75 percent of patients have only mildly elevated serum thyrotropin values (5 to 10 mU per liter),[2,3] and 50 to 80 percent of patients have positive tests for antibodies against thyroperoxidase, depending on the age, sex, and serum thyrotropin levels. Goiter is twice as prevalent among patients with this condition as in the general population.[2]

Patients with treated hyperthyroidism, a history of neck irradiation, postpartum thyroiditis, and certain autoimmune disorders, especially type 1 diabetes, are at increased risk for subclinical hypothyroidism. Subclinical hypothyroidism may also develop in patients who are being treated with the iodine-containing antiarrhythmic agent amiodarone, lithium, or immune-response modulators, such as interferon alfa, but most patients have no obvious risk factors. Other causes of elevated levels of serum thyrotropin and normal levels of serum free thyroxine that must be considered in the differential diagnosis include intermittent noncompliance with thyroxine therapy, recovery from severe nonthyroidal illness, chronic renal failure, primary adrenal failure, high thyrotropin levels as an artifact due to circulating heterophilic antibodies against thyrotropin, and mutations causing inactivation of the thyrotropin receptor. However, these causes are usually distinguishable from subclinical hypothyroidism on clinical and laboratory grounds.

Strategies and Evidence

Screening

Because the majority of persons with subclinical hypothyroidism have few symptoms or none at all, routine population screening has been advocated.[4] Population screening has not been endorsed unanimously (Table 1), because the benefits of subsequent therapy have not been established in prospective clinical trials. Using a decision and cost-effectiveness model, it was calculated that screening women older than 35 years of age every five years would cost about $9,200 per quality-adjusted year of life. Half of this benefit accrued from the prevention of overt hypothyroidism and its attendant morbidity, 30 percent from improved symptoms of subclinical hypothyroidism, and a smaller benefit from a decrease in serum cho-

From the Division of Endocrinology, Sinai Hospital of Baltimore and Johns Hopkins University School of Medicine, Baltimore. Address reprint requests to Dr. Cooper at the Division of Endocrinology, Sinai Hospital of Baltimore, Baltimore, MD 21215, or at dcooper@lifebridgehealth.org.

TABLE 1. RECOMMENDATIONS OF EIGHT ORGANIZATIONS REGARDING SCREENING OF ASYMPTOMATIC ADULTS FOR THYROID DYSFUNCTION.

ORGANIZATION	SCREENING RECOMMENDATIONS
American Thyroid Association[5]	Women and men >35 yr of age should be screened every 5 yr
American Association of Clinical Endocrinologists[6]	Older patients, especially women, should be screened
College of American Pathologists[7]	Women ≥50 yr of age should be screened "if they seek medical care"; all geriatric patients should be screened on admission to the hospital and at least every 5 yr
American Academy of Family Physicians[8]	Patients ≥60 yr of age should be screened
American College of Obstetrics and Gynecology[9]	Women in "high-risk groups" (those with autoimmune disease or a strong family history of thyroid disease) should be screened starting at 19 yr of age
American College of Physicians[10]	Women >50 yr of age with an incidental finding suggestive of symptomatic thyroid disease should be evaluated
U.S. Preventive Services Task Force[11]	Insufficient evidence for or against screening
Royal College of Physicians[12]	Screening of the healthy adult population unjustified

lesterol levels and the prevention of future heart disease. In the model, the costs of screening were greatly influenced by the cost of the thyrotropin assay. Potential savings derived from decreases in the cost of evaluating and treating nonspecific symptoms, as well as possible elimination of the need for expensive lipid-lowering therapy.

Because undetected subclinical hypothyroidism during pregnancy may adversely affect the neuropsychological development[13] and survival[14] of the fetus and be associated with hypertension and toxemia,[15] screening of pregnant women has been advocated.[13] In addition, data suggesting that subclinical hypothyroidism is associated with ovulatory dysfunction and infertility may make screening worthwhile in this population as well.[16]

Effects of Therapy

The potential benefits and risks of therapy for subclinical hypothyroidism have been debated for two decades. The possible advantages of treating subclinical hypothyroidism generally fall into three categories. First, progression to overt hypothyroidism, with its attendant morbidity, would be prevented by thyroxine therapy. Second, thyroxine therapy may improve the serum lipid profile and thereby potentially decrease the risk of death from cardiovascular causes. Finally, treatment may reverse the symptoms of mild hypothyroidism, including psychiatric and cognitive abnormalities.

Prevention of Progression to Overt Hypothyroidism

The Whickham survey involved almost 2800 randomly selected adults in whom thyroid function was assessed between 1972 and 1974.[2] After 20 years of follow-up, a high risk of overt hypothyroidism was found in women who had both elevated serum levels of thyrotropin and antithyroid antibodies at base line (4.3 percent per year, or 38 times that of women who had normal serum thyrotropin levels and no antithyroid antibodies).[17] Moreover, a high serum thyrotropin level alone or antithyroid antibodies alone at base line also conferred an increased risk of overt hypothyroidism (2.6 percent per year and 2.1 percent per year, respectively). The number of patients who would need to be treated to prevent one case of overt hypothyroidism ranged from 4.3 to 14.3,[18] depending on the age and the serum thyrotropin level at base line. This range is similar to that for other accepted preventive medical strategies, such as statin therapy for hypercholesterolemia.[19]

Effects on Serum Lipid Levels

The effects of subclinical hypothyroidism on serum lipid levels remain controversial. Some,[20] but not other,[21] cross-sectional studies have demonstrated that serum levels of total cholesterol and LDL cholesterol are higher in patients with subclinical hypothyroidism than in euthyroid controls. A recent meta-analysis of the effect of therapy for subclinical hypothyroidism on serum lipid levels demonstrated a mean reduction in the total cholesterol level of 7.9 mg per deciliter (0.2 mmol per liter) and in the LDL cholesterol level of 10 mg per deciliter (0.26 mmol per liter).[22] Changes in high-density lipoprotein (HDL) cholesterol were heterogeneous among the studies and were not statistically significant. Patients with higher cholesterol levels (≥240 mg per deciliter [6.21 mmol per liter]) and patients with subclinical hypothyroidism as a result of inadequately treated overt hypothyroidism had greater reductions in cholesterol levels. In patients with newly diagnosed subclinical hypothyroidism whose total cholesterol level was less than 240 mg per deciliter, the mean reduction in total cholesterol was only 0.7 mg per deciliter (0.02 mmol per liter), which was not statistically significant. Small studies[23] have suggested that patients whose serum thyrotropin level is less than 10 mU per liter may have no reduction in cholesterol levels with thyroxine replacement, but the meta-analysis did not directly address this issue.

Two population-based studies have added to our uncertainty in this area. In the first, based on a 20-year follow-up of the Whickham cohort, the rates of death from all causes or from cardiovascular causes were not significantly higher in subjects who had subclinical hypothyroidism at base line than in those with euthyroidism at base line (risk ratio for death from cardiovascular causes, 1.26 for men; 95 percent con-

fidence interval, 0.5 to 2.66; and 1.07 for women; 95 percent confidence interval, 0.58 to 1.87).[24] In the second study, a cross-sectional cohort study of middle-aged Dutch women, those with subclinical hypothyroidism were approximately twice as likely as euthyroid control women to have "atherosclerosis" (defined by a finding of calcification of the aorta on a chest film) (odds ratio, 1.9; 95 percent confidence interval, 1.2 to 3.1) and a history of myocardial infarction (odds ratio, 2.3; 95 percent confidence interval, 1.3 to 4.2), and the difference persisted after adjustment for body-mass index, systolic and diastolic blood pressure, smoking status, and total and HDL cholesterol levels.[25] Over a follow-up period of 4.6 years, women with subclinical hypothyroidism had an insignificantly greater risk of myocardial infarction. Remarkably, at base line, women with subclinical hypothyroidism had age-adjusted serum cholesterol levels that were lower than those of the euthyroid control women. The authors suggested that "nontraditional" coronary risk factors such as elevated lipoprotein(a) or homocysteine levels might explain the higher rate of atherosclerosis in subclinical hypothyroidism, but published data are few and conflicting.

Effects on Symptoms, Mood, and Cognition

The questions of whether persons with subclinical hypothyroidism have symptoms, and the extent to which the putative symptoms are reversible with thyroid hormone therapy, remain unanswered. Several studies have suggested that mild symptoms of hypothyroidism are more prevalent in patients with subclinical hypothyroidism than in age-matched controls,[3,21,26] but not all studies have found this to be true.[27]

There have been three published randomized, prospective, placebo-controlled trials of therapy for subclinical hypothyroidism.[28-30] Two[28,29] reported significant improvements in the symptoms of hypothyroidism, whereas the third[30] found no benefit of therapy. Overall, the percentage of patients whose condition improved ranged from 0 to 28 percent of those treated. In the trial that found no treatment benefit, however, the mean serum thyrotropin level (4.6 mU per liter) remained in the high-normal range after therapy.[30] On the basis of the two trials with positive findings, one would need to treat approximately four patients for one to benefit.

Preliminary findings of two small placebo-controlled trials have provided further information on the effects of therapy.[31,32] In a study involving women whose base-line serum thyrotropin level was between 5 and 10 mU per liter,[31] thyroxine therapy had no effect on symptoms, whereas this therapy was associated with a significant improvement in symptoms among women in the other study,[32] whose mean serum thyrotropin level was 12.7 mU per liter at base line.

Patients with subclinical hypothyroidism have been reported to have higher scores on scales of anxiety or depression,[33,34] although this finding has been inconsistent.[27,35] In the four studies in which cognitive function or memory was formally assessed before and after thyroxine therapy, all four reported small but statistically significant improvements.[29,30,33,35] Limited data have suggested that therapy for subclinical hypothyroidism may decrease intraocular pressure,[36] increase myocardial performance,[37] and improve peripheral-nerve function.[38] In women with subclinical hypothyroidism and ovulatory dysfunction, thyroxine therapy may restore fertility.[16] Although difficulty losing weight is often attributed to subclinical hypothyroidism, body weight is unlikely to decrease with thyroxine therapy.[28]

Arguments against Treatment

The arguments against treatment are its expense and the likelihood that some, or even most, patients will not benefit. There is also a danger of overtreatment, which could cause iatrogenic hyperthyroidism and ultimately lead to more serious abnormalities (e.g., osteopenia and atrial fibrillation) than leaving the subclinical hypothyroidism untreated.[39] Indeed, in one large study, suppressed serum thyrotropin levels consistent with the occurrence of overtreatment were found in 21 percent of patients who were taking thyroid hormone.[3]

AREAS OF UNCERTAINTY

Aside from the results of two computer simulations,[4,40] we do not know whether screening the general population, pregnant women, or even the groups at highest risk is cost effective. Recognizing and treating subclinical hypothyroidism will prevent overt hypothyroidism, but only a minority of patients will subsequently have overt hypothyroidism when serum thyrotropin levels alone are elevated or antithyroid antibodies alone are present (e.g., 33 percent and 27 percent, respectively, in the Whickham study after 20 years of follow-up).[17] The potentially positive effects of therapy on heart disease must be tempered by the negligible changes in serum cholesterol levels observed with thyroxine therapy in many studies and the lack of effect on the risk of death from cardiovascular causes in patients with untreated subclinical hypothyroidism in the Whickham cohort.[24] Benefits in terms of decreased symptoms or other systemic effects are generally moderate and may not enhance a patient's quality of life.

With respect to the screening of pregnant women, the timing and the best tests are controversial.[41] For example, some studies have suggested that the maternal serum free thyroxine level is more sensitive than the serum thyrotropin level in predicting the likelihood of adverse intellectual outcomes in the offspring.[41] Screening has yet to be shown to be cost effective, and the data suggesting that subclinical hy-

pothyroidism during pregnancy may be associated with suboptimal intellectual performance in the offspring are based on relatively small numbers of cases.

GUIDELINES

Table 1 summarizes the recommendations of a number of groups that have considered the question of screening asymptomatic adults for thyroid dysfunction. In this context, screening is distinct from case finding, which involves thyroid-function testing in a person with symptoms consistent with the presence of hypothyroidism or a person with elevated serum cholesterol levels.

Some professional organizations have also issued recommendations for the treatment of subclinical hypothyroidism. The American College of Physicians finds insufficient evidence to recommend for or against treatment,[10] whereas three other groups[6,12,42] generally suggest initiating therapy in patients with subclinical hypothyroidism, especially if the patients have circulating antibodies against thyroperoxidase. Potential exceptions include the elderly,[6] patients with cardiac disease who have minimally elevated thyrotropin levels,[6] and those with serum thyrotropin levels of less than 10 mU per liter and a negative test for antibodies against thyroperoxidase.[12] These patients could instead be closely followed.

CONCLUSIONS AND RECOMMENDATIONS

Screening

Although screening is controversial, I believe that it is warranted every five years in women older than

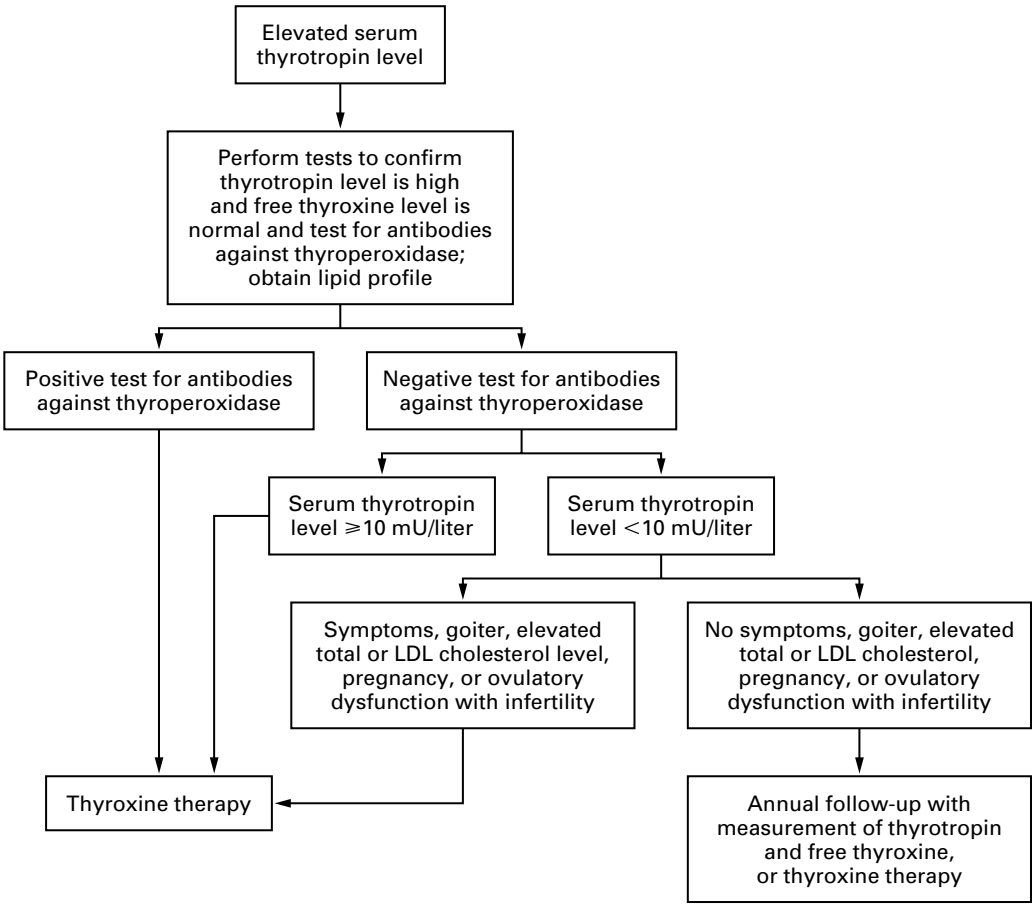

Figure 1. An Algorithm for the Management of Subclinical Hypothyroidism.

An elevated serum thyrotropin level should be confirmed. If the serum level of free thyroxine is low, then the patient has overt hypothyroidism and should be treated with thyroxine. Testing for antibodies against thyroperoxidase and obtaining a lipid profile are important in subsequent decision making. If the results of these tests are not abnormal, there are no symptoms or goiter, and the serum thyrotropin level is less than 10 mU per liter, therapy is optional. Women who are pregnant or who have ovulatory dysfunction and infertility should be treated regardless of the presence or absence of symptoms, antibody status, or serum lipid levels. LDL denotes low-density lipoprotein.

35 years of age, given the high prevalence, potential consequences, and ease of treatment of the disorder.[1] The importance of the recognition of hypothyroidism in pregnant women[13-15] argues in favor of routine screening at the first prenatal visit. Screening of men older than 65 years of age is also reasonable.

Thyroxine Therapy

Given the high rate of conversion of subclinical hypothyroidism to overt hypothyroidism in the presence of circulating antithyroid antibodies, it makes sense to treat asymptomatic persons with positive antibody tests even if they have normal serum lipid levels. However, because an elevated serum thyrotropin level is associated with an increased risk of overt hypothyroidism even in the absence of antithyroid antibodies, positive antithyroid-antibody titers should not be the sole criterion for therapy. It is also reasonable to treat subclinical hypothyroidism in pregnant women and in women who have ovulatory dysfunction with infertility (Fig. 1).

A therapeutic trial for subclinical hypothyroidism is warranted if patients have symptoms consistent with the presence of mild hypothyroidism, hypercholesterolemia, or a goiter. Although the overlap in symptoms between patients with subclinical hypothyroidism and euthyroid persons makes it difficult to predict who will have a response to treatment, some patients have a remarkable improvement in their symptoms with thyroxine therapy. The positive findings in some small clinical trials[28,29,32] also support the use of therapy in symptomatic patients, and thyroxine replacement can always be discontinued if there is no apparent benefit.

An initial dose of thyroxine of 0.05 to 0.075 mg per day is usually sufficient to normalize the serum thyrotropin level.[28-30] Patients with coronary artery disease should receive lower initial doses (e.g., 0.0125 to 0.025 mg daily). Serum thyrotropin levels should be measured four to six weeks after therapy is begun, after any change in the dose, and then annually once the levels become stable. Thyroxine requirements may increase over time if there is progressive thyroid failure.

Once an elevated serum thyrotropin level is detected and confirmed, the costs of annual follow-up with clinical assessment and laboratory testing are relatively similar whether or not patients are treated with thyroxine. Without treatment, only 5 percent of elevated serum thyrotropin levels will revert to normal values one year later in older persons.[43] I believe that the evidence supports the use of treatment for most patients, as long as therapy is monitored with the use of annual measurements of serum thyrotropin.[44]

With respect to the patient described in the clinical vignette, I would initiate therapy with thyroxine at a dose of 0.05 mg daily. Although this treatment would be unlikely to have substantive effects on the serum cholesterol level, it should prevent overt hypothyroidism and may decrease the patient's fatigue. I would monitor her symptoms and serum total and LDL cholesterol levels and measure her serum thyrotropin annually, in order to achieve a serum thyrotropin level between 0.5 and 3 mU per liter.[17,44]

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