51 *Subclinical Hypothyroidism*

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Abstract: Subclinical hypothyroidism, the term was introduced in 1970's. This refers to cases of very mild thyroid dysfunction with normal serum levels of serum T4, T3 and mild elevated TSH (Thyrotropin). Over hypothyroidism develops in many cases of subclinical hypothyroidism mostly in females. Subclinical hypothyroidism has adverse impact on lipid profile and development of atherosclerosis. Most patients of subclinical hypothyroidism need follow-up and therapy with thyroxine.

INTRODUCTION

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 with 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.

It is not necessarily subclinical, since on close questioning many patients disclose mild, nonspecific symptoms. The term subclinical hypothyroidism was first introduced in 1970s coincident with the introduction of serum thyrotropin (TSH) measurement. Mild hypothyroidism may be a more appropriate term for this very common syndrome, which is defined by an isolated elevated serum thyrotropin level in the setting of normal serum thyroid hormone (free T4 and T3) levels, in the presence or absence of symptoms. The worldwide prevalence of subclinical hypothyroidism ranges from 1 to 10 %; the highest age- and sex-specific rates are in women older than 60 years of age, approaching 20 % in some reports.[1] 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). Goiter is twice as prevalent among patients with this condition as in the general population[1,2] (Tables 51.1 and 51.2).

Most patients have chronic autoimmune thyroiditis as defined by high serum Anti TPO antibodies (57-63%).[2] Radioiodine or surgical treatment of Graves' thyrotoxicosis is another major cause of subclinical hypothyroidism. Several drugs, specially iodine and iodine containing drugs, amiodarone and lithium cause subclinical hypothyroidism. External radiation may cause subclinical hypothyroidism.

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[3] involved almost 2800 randomly selected adults in whom thyroid function was assessed between 1972 and 1974. 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% per year, or 38 times that of women who had normal serum thyrotropin levels and no antithyroid antibodies).[17] 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 worthwhile in this population as well.

EFFECTS ON SERUM LIPID LEVELS

The effects of subclinical hypothyroidism on serum lipid levels remain controversial. Some 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/ dl and in the LDL cholesterol level of 10 mg/dl.[4,5] Changes in high-density lipoprotein (HDL) cholesterol were heterogeneous among the studies and were not statistically significant. Patients with higher cholesterol levels ≈ 240 mg/dl 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 < 240 mg per deciliter, the mean reduction in total cholesterol was only 0.7 mg/dl, which was not statistically significant. Small studies have suggested that patients whose serum thyrotropin level is less than 10 mU/L may have no reduction in cholesterol levels with thyroxine replacement. In 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) and a history of myocardial infarction, and the difference persisted after adjustment for body-mass index, systolic and diastolic blood pressure, smoking status, and total and HDL cholesterol levels. "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.[6]

EFFECT ON CARDIAC FUNCTION

In some studies (not all) resting pre-ejection period (PEP), left ventricular ejection time (LVET) was increased in SC hypothyroidism and improved on T4 therapy. Isovolumetric relaxation time was increased in some studies. The time to ventricular filling rate was high and became normal with treatment. Thus some patients with SC hypothyroidism have subtle abnormalities in systolic time intervals, diastolic function and myocardial contractility that may improve during treatment.[7]

EFFECTS ON SYMPTOMS, MOOD AND COGNITION

Several studies have suggested that mild symptoms of hypothyroidism are more prevalent in patients with subclinical hypothyroidism than in age-matched controls, but not all studies. There have been 3 published randomized, prospective, placebo-controlled trials of therapy for subclinical hypothyroidism. Two reported significant improvements in the symptoms of hypothyroidism, whereas the third 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 μ per liter) remained in the high-normal range after therapy. On the basis of the two trials with positive findings, one would need to treat approximately four patients for one to benefit.[8]

Patients with subclinical hypothyroidism have been reported to have higher scores on scales of anxiety or depression, although this finding has been inconsistent. In the studies in which cognitive function or memory was formally assessed before and after thyroxine therapy reported small but statistically significant improvements.

Limited data have suggested that therapy for subclinical hypothyroidism may decrease intraocular pressure, increase myocardial performance, and improve peripheral nerve function.

In women with subclinical hypothyroidism and ovulatory dysfunction, thyroxine therapy may restore fertility. Although difficulty-losing weight is often attributed to subclinical hypothyroidism, body weight is unlikely to decrease with thyroxine therapy.

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 over treatment, which could cause iatrogenic hyperthyroidism and ultimately lead to more serious abnormalities (e.g., osteopenia and atrial fibrillation) than leaving the subclinical hypothyroidism untreated. Indeed, in one large study, suppressed serum thyrotropin levels consistent with the occurrence of over treatment were found in 21% of patients who were taking thyroid hormone.[9] Rarely therapy may exacerbate angina pectoris or cardiac arrhythmia.

AREAS OF UNCERTAINTY

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.

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. 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.

Screening has yet to be shown to be cost effective, and the data suggesting that subclinical hypothyroidism during pregnancy may be associated with suboptimal intellectual performance in the offspring are based on relatively small numbers of cases.

GUIDELINES

Some professional organizations have also issued recommendations for the treatment of subclinical hypothyroidism (Fig. 51.1). The American College of Physicians finds insufficient evidence to recommend for or against treatment, whereas three other groups generally suggest initiating therapy in patients with subclinical hypothyroidism, especially if the patients have circulating antibodies against thyro-peroxidase. Potential exceptions include the elderly, patients with cardiac disease who have minimally elevated thyrotropin levels, and those with serum thyrotropin levels of less than 10 mu per liter and a negative test for antibodies against thyroperoxidase.

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 35 years of age, given the high prevalence, potential consequences, and ease of treatment of the disorder.[10]

Because undetected subclinical hypothyroidism during pregnancy may adversely affect the neuropsychological development and survival of the fetus and be associated with hypertension and toxemia, screening of pregnant women should be advocated at the first prenatal visit.

In addition, data suggesting that subclinical hypothyroidism is associated with ovulatory dysfunction and infertility may make screening worthwhile in this population as well.[10,11] Screening of men older than 65 years of age is also reasonable.

Thyroxine Therapy

Given the high rate of conversion of subclinical 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, though positive anti-thyroid-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.

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 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.

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.

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.

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