REVIEW

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The case for more aggressive screening and treatment of mild thyroid failure

ABSTRACT

"Subclinical" (mild) thyroid failure is not benign: it tends to progress to overt thyroid failure and it has adverse clinical effects. We believe it should be screened for more aggressively in the general population, and treated with levothyroxine.

KEY POINTS

In nearly half of patients, mild thyroid failure progresses to overt hypothyroidism within 5 to 7 years; the risk of progression is especially high in elderly women and in patients with antithyroid antibodies.

Evidence is accumulating that levothyroxine therapy alleviates symptoms and prevents coronary artery disease when started early in mild thyroid failure.

Guidelines from the American Thyroid Association recommend measuring serum thyroid-stimulating hormone levels as part of routine health examinations in adults, but those from the American College of Physicians do not.

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WHAT DO YOU DO if a patient has a mildly elevated thyroid-stimulating hormone (TSH) level but normal levels of thyroid hormones and no obvious signs or symptoms of hypothyroidism?

Although many physicians would do nothing, we hope to change their minds. In this article we argue that this condition, variously called subclinical hypothyroidism or mild thyroid failure, is not benign and should be treated.

THE EARLY STAGE OF THYROID FAILURE

Like many disorders, hypothyroidism may become manifest earlier or later in its course. In the earliest and mildest form of hypothyroidism, the TSH level is slightly elevated, while the serum levels of total thyroxine (T_4), free T_4, total triiodothyronine (T_3), and free T_3 are normal (or more accurately, within their laboratory reference ranges)—albeit probably lower than when the patients were truly euthyroid (**FIGURE 1**).

The normal range for TSH is approximately 0.3 to 4.0 μIU/mL, depending on the laboratory. In the early stages of thyroid failure, if the thyroid gland has any remaining reserve, mild elevations in TSH (between 4 and 10 μIU/mL) can stimulate it enough to maintain relatively normal serum T_4 and T_3 levels.[1–7]

HYPOTHYROIDISM IS COMMON

Hypothyroidism is common. Various surveys[8–14] found the prevalence to be from as low as 1% to as high as 14%, depending on the TSH level used as the criterion and the population studied. The prevalence was higher in:

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Screen for thyroid function during pregnancy

- Whites than in blacks
- Women than in men
- Older people than in younger people.

Other risk factors for hypothyroidism include:

- High iodine intake (urinary iodide > 1 mg/G creatinine)[8,9]
- Antithyroid antibodies (either antithyroperoxidase or antithyroglobulin)
- Family history of thyroid disease
- Hypercholesterolemia
- Diabetes
- Pregnancy or postpartum status.

Mild thyroid failure (defined as TSH > 4.5 µIU/mL with normal T_4 levels) accounted for 38% of cases of thyroid failure in a study by Flatau et al.[13] The overall prevalence of hypothyroidism was 14% in this population (1,110 men and women ages 65 to 92).

Pregnant women at special risk

Pregnancy often brings an increased demand for thyroid hormone, and if the thyroid gland is already mildly compromised it may not be able to meet that demand.

Glinoer et al[15] reported that the risk of progression from normal to frankly elevated TSH levels during pregnancy approached 50% in women with positive antithyroid antibody titers.

The detection and treatment of mild thyroid failure during pregnancy is beneficial not only to the health of the mother, but also to the subsequent neurophysiologic development of the offspring.[16–19] Experts around the world now recommend thyroid function screening during pregnancy.[20–22]

After delivery, hypothyroidism may be a prominent presentation of postpartum thyroiditis, and although usually transient, it may last for months. It is best managed by temporary levothyroxine therapy.

Diabetes is associated with autoimmune thyroid disease, and postpartum thyroid dysfunction occurs in 25% of pregnant diabetic women.[23]

CAUSES OF MILD THYROID FAILURE

As in overt primary hypothyroidism or myxedema, the most common cause of mild thyroid failure is chronic autoimmune (Hashimoto) thyroiditis.[24]

Other causes include conditions and treatments that affect thyroid hormone production, such as thyroid ablation with radioactive iodine, antithyroid drugs, external beam radiation, partial thyroidectomy, and drugs such as lithium.

Amiodarone, antitussives, radiographic contrast agents, and health supplements such as kelp tablets are rich in iodine and may cause mild hypothyroidism, particularly in patients with underlying thyroid disease.[1]

THE ARGUMENT FOR TREATING MILD THYROID FAILURE

We base our argument for treating mild thyroid failure on three lines of evidence:

- Without treatment, mild thyroid failure tends to progress to overt thyroid failure
- Thyroid replacement therapy may ameliorate symptoms that had not previously been attributed to hypothyroidism
- Thyroid replacement therapy may reduce the cardiovascular risks of ongoing atherogenesis.

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Mild thyroid failure tends to progress to overt hypothyroidism

Follow-up studies indicate that, without treatment, mild thyroid failure progresses to overt hypothyroidism within 5 to 7 years in approximately half of cases.[11,25,26]

The highest rate of progression is in women older than 65 years with TSH values greater than 10 μIU/mL and with detectable serum antithyroid antibodies.[11]

We generally attribute the increased prevalence of thyroid failure with age to Hashimoto disease, in which cytotoxic antibodies destroy thyroid follicular cells over time, causing a progressive decline in thyroid function. A study of outpatients[25] reported that 80% of geriatric patients with an antimicrosomal antibody titer greater than 1:1,600 and a TSH level greater than 4 μIU/mL developed frank hypothyroidism in 4 years.

Elevations in TSH may be transient, however. In a study in children and adolescents, autoimmune thyroiditis evolved to frank hypothyroidism in only 1 of 18 patients during a mean follow-up of 5.8 years.[27] One explanation for transient mild to moderate hypothyroidism could be TSH receptor-blocking antibodies.[28–30]

Moreover, some experts postulate that insults to the thyroid gland such as partial thyroidectomy or neck radiation can lead to "euthyroidism with reset thyrostat,"[31] in which TSH levels are elevated but T_4 and T_3 levels are normal. In this view, the condition is permanent and does not necessarily progress to frank thyroid failure. We believe that this is a matter of semantics and that such patients simply have mild thyroid failure.

Thyroid replacement may ameliorate symptoms

Part of the reason physicians have been reluctant to treat mild thyroid failure is the belief that patients do not have any symptoms. But although the symptoms may be so mild as to be overlooked, some presenting complaint must have prompted the physician to order thyroid function tests in the first place.

Furthermore, Cooper et al[32] found that nearly half of patients with mild thyroid failure improved with levothyroxine therapy but not with placebo. However, a retrospective study at a primary care geriatric clinic[33] showed no association between TSH levels and hypothyroid symptoms.

Peripheral nerve dysfunction. Misiunas et al[34] reported significant peripheral nerve dysfunction (manifested as shortening of motor and sensory amplitudes) in patients with TSH levels over 20 μIU/mL. On the other hand, Ozata et al,[35] in a study of patients with a mean TSH level of 18.05 μIU/mL, found that neither peripheral nerve conduction velocity nor brain auditory evoked potentials were affected.

Memory. A study in 37 middle-aged or older patients with elevated serum TSH levels[36] found statistically significant improvement in composite psychometric memory scores with levothyroxine therapy.

Monzani et al[37] administered two neurobehavioral tests, the Crown and Crisp Experiential Index (CCEI) and the Wechsler Memory Scale (WMS), to 50 control subjects and 14 patients with subclinical hypothyroidism before and after levothyroxine therapy (0.1–0.15 mg/day). At baseline, the patients with subclinical hypothyroidism showed significant memory impairment on the WMS; the CCEI showed significant impairment in total score, which specifically included anxiety, depression, somatic complaints, and hysteria. The WMS and CCEI scores were both significantly improved by levothyroxine treatment.

Baldini et al[38] compared the effects of levothyroxine therapy in patients with either mild thyroid failure or euthyroid goiter and found that, although psychometric tests showed no differences in affective function, patients with mild thyroid failure had a significant decrement in memory skills, which improved with levothyroxine therapy.

Fatigue, muscle dysfunction. Beyer et al[39] studied 10 patients with overt hypothyroidism and 13 patients with mild thyroid failure and noted a positive correlation between levels of the muscle enzyme creatine phosphokinase and TSH, even in patients with mild thyroid failure.

Monzani et al[40] measured lactate and pyruvate levels at rest and during exercise in 12 patients with mild thyroid failure and in 10 normal, matched controls. With exercise, blood lactate levels rose significantly higher in

Most patients with elevated TSH but normal T_4 develop overt hypothyroidism

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the patients with mild thyroid failure, and the increment was related to the duration of thyroid failure rather than the degree of TSH elevation. The authors concluded that mild thyroid failure was associated with impaired energy metabolism that could account for fatigue with exercise and early muscle dysfunction.

In more recent studies, muscle fatigue, weakness, paresthesias, and muscle cramps improved with levothyroxine therapy.[41]

Depression. The evidence supporting a link between mild thyroid failure and depression (similar to the risk in frank hypothyroidism[42]) includes a report[43] of a series of depressed patients, 10% of whom met the criteria for mild thyroid failure.

Haggerty et al[44] reported a 56% lifetime frequency of depression in patients with mild thyroid failure vs 20% in euthyroid patients.

Bipolar disorder. Haggerty et al[45] observed that patients with bipolar manic-depressive disorder have a higher prevalence of autoimmune thyroid disease (positive antithyroid antibodies), and that the depression may respond to levothyroxine therapy.

High intraocular pressure. An unexpected observation, by Centanni et al,[46] was that patients with mild thyroid failure had substantially higher intraocular pressures than controls, but that the pressures returned to normal in nearly all patients after only 2 months of levothyroxine therapy.

In one study, muscle fatigue, weakness, and cramps improved with levothyroxine treatment

Therapy may reduce cardiovascular risk

Lipids. In profound hypothyroidism, elevations in LDL cholesterol are associated with an increased risk for atherosclerotic coronary artery disease.

The data are far from definitive about the impact of mild thyroid failure on lipids, however. Several studies[32,47–52] showed little if any elevation in total cholesterol, LDL, or lipoprotein A levels in people with mild thyroid failure, or no changes in these levels after levothyroxine therapy.

On the other hand, the bulk of the data seem to indicate the opposite.[14,53–65] An extensive meta-analysis[62] concluded that levothyroxine therapy for mild thyroid failure could reduce total cholesterol levels by a mean of 15 mg/dL. Another meta-analysis,[64] covering 247 patients in 13 studies, concluded that thyroxine therapy was associated with a reduction in mean total cholesterol and LDL levels. The greatest benefit was in patients with the greatest degree of pre-therapy hyperlipidemia.

Larger, well-controlled, prospective studies may be required to better delineate the lipid abnormalities in mild thyroid failure and their response to therapy.

Coronary artery disease was associated with mild thyroid failure in some[66,67] but not all studies.[68]

The Whickham study[51] showed no association between mild thyroid failure and coronary artery disease, but mild thyroid failure was linked to electrocardiographic abnormalities.

Perk and O'Neill[69] performed serial coronary angiography to study the association between levothyroxine dose (based on TSH levels) and coronary artery disease progression. They found that 5 of 7 patients receiving adequate levothyroxine doses showed no progression of coronary plaque, whereas all 6 patients taking inadequate doses of levothyroxine (0.1 mg or less) showed progression over 8 to 24 months.

Hak et al[70] examined 1,149 elderly women and found that 10.8% met their criteria for mild thyroid failure (a normal free T_4 level and TSH > 4.0 μIU/mL). The patients with mild thyroid failure had a greater incidence of aortic atherosclerosis (odds ratio 1.7) and myocardial infarction (odds ratio 2.3). A positive antibody titer increased the odds ratio for aortic atherosclerosis to 1.9 and for myocardial infarction to 3.1.

Heart function. Profound hypothyroidism can cause significant left ventricular (LV) dysfunction,[71] diastolic hypertension, increased systolic time intervals, pericardial effusion, and bradycardia.

However, the effects of mild thyroid failure are less evident. Early efforts to study its impact on myocardial contractility have concentrated on measuring systolic time intervals and LV ejection fraction.[32,50,72,73]

The systolic time interval is the interval between electromechanical systole and the ejection period, as measured by Doppler carotid ultrasonography and electrocardiography. Although this measurement is not as sensitive as radionuclide ventriculography, multiple studies have used it to estimate LV function.

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An increased systolic time interval has been reported in about 50% of patients with mild thyroid failure,[71] and significant reductions of the interval were observed after levothyroxine therapy.[72]

Although a subsequent study failed to show any changes in the mean systolic time interval, significant improvement was noticed in a subgroup of treated patients with the highest TSH values.[32]

Studies that used LV ejection fraction as an estimate of LV function suggest that some patients with mild thyroid failure have impaired myocardial contractility. One study reported a suboptimal increase in LV ejection fraction during exercise,[73] while another observed a decrease in LV ejection fraction at rest.[74]

A more recent study using Doppler echocardiography[75] reported a beneficial effect of levothyroxine therapy on LV diastolic dysfunction in mild thyroid failure.

POPULATION SCREENING

The American Thyroid Association[76] recommends that serum TSH levels be measured as part of routine health examinations in adults (especially women) every 5 years starting at age 35. This recommendation is based on a cost-utility analysis[77] that found screening for mild thyroid dysfunction to be as cost-effective as screening for breast cancer or hypertension.

On the other hand, the American College of Physicians[78] does not recommend general population screening for mild thyroid failure, contending that it is not cost-effective and that the potential benefits of early detection and treatment might be outweighed by the associated costs of therapy, follow-up testing, and the theoretical risks of mislabeling such patients.

Given the known associations and risk factors for thyroid failure and the greater prevalence with age, screening for mild thyroid failure should be most beneficial and cost-effective in specific groups:

- The elderly (especially those with functional physical or cognitive impairment)
- Women (especially if pregnant, postpartum, or postmenopausal)
- Patients with a family history or personal past medical history of thyroid disorders or treatment
- Patients with diabetes mellitus, cardiovascular dysfunction, hypercholesterolemia, or other endocrinopathy
- Patients with signs of underlying mild thyroid failure such as unexplained bradycardia, depression, or sleep apnea.

DIAGNOSING MILD THYROID FAILURE

The serum TSH level is the cornerstone of the diagnosis of mild thyroid failure and should be measured in all patients at risk.

The free T_4 level should be measured next to confirm hypothyroidism. Secondary (pituitary or hypothalamic) hypothyroidism should be strongly suspected with the finding of a low free T_4 level and a TSH level in the low-normal or normal range.

Antithyroid antibody titers confirm autoimmune thyroid disease and predict progression to frank hypothyroidism, especially in the elderly.

Rule out false and transient TSH elevations

Measure serum TSH in all patients at risk

Causes of **transient TSH elevation** must be ruled out before committing a patient to a lifetime of levothyroxine therapy. Hospitalized patients often have slightly elevated TSH levels,[79] and transient elevations occur during the recovery phase of subacute thyroiditis or during the evolution of other illnesses. Critically ill patients who have euthyroid sick syndrome in the recovery phase may have TSH values from 5 to 20 μIU/mL.[80]

False TSH elevations. Heterophilic antibodies may interfere with the TSH assay, resulting in false elevations.[81] Antiemetics and antipsychotics may also elevate TSH by interfering with the dopaminergic (TSH-inhibitory) pathway. Antiretroviral therapies such as protease inhibitors and nucleoside analogue reverse transcriptase inhibitors may cause significant false elevations in 8% to 12% of patients.

Other causes of TSH elevation. Patients with primary adrenal insufficiency or TSH-producing adenomas may give an erroneous impression of thyroid failure because of associated high TSH levels.[82–84]

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TREATMENT RECOMMENDATIONS

The risk-benefit ratio of therapy in mild thyroid failure is difficult to establish, because no placebo-controlled longitudinal interventional trials have shown therapy to have unequivocally demonstrable effects on specific metabolic markers of thyroid state and positive overall benefit by outcomes analysis. Conceivably, the metabolic abnormalities in mild thyroid failure are either too mild or too transient to significantly affect such variables as free water excretion, creatine kinase levels, and metabolic rate.[32]

In the absence of this information, what do we recommend?

First, we focus on identifying any previous insult to the thyroid, such as radioactive iodine, antithyroid drugs, or surgical intervention. Drugs such as iodine and lithium have a greater likelihood of inducing hypothyroidism in patients with a marginally compensated gland. Because antithyroid antibodies predict progression to overt hypothyroidism, an antibody titer may be helpful. We recommend a trial of levothyroxine therapy in antibody-positive patients. A negative antibody titer should not exclude consideration for therapy, however, especially if the patient has signs and symptoms suggesting thyroid failure, and particularly since a small fraction of patients with Hashimoto disease are seronegative.[85]

The goal of therapy is to maintain TSH levels within the normal biological range (generally between 0.5 and 1.5 μIU/mL, as opposed to the laboratory reference range, which is typically 0.3 to 5.0 μIU/mL). This can be achieved using the dose of 1.6 to 1.7 μg/kg of ideal body weight.[86]

In elderly patients and patients with coronary artery disease, an initial low dose (eg, 25 μg/day) should be used. The dose can be cautiously titrated upward, as patient age and underlying cardiovascular status permit, until the goal of optimal replacement is achieved. In general, we start with an initial daily dose of 25 to 50 μg and increase by 25 to 50 μg at 4-to-6-week intervals until the TSH level is normalized, or down to the range of 0.5 to 1.5 μIU/mL.

Cautions. Special caution should be exercised in patients with ischemic heart disease and mild hypothyroidism. In these cases, a more conservative approach to starting therapy is indicated to prevent dysrhythmias, worsening angina, or even precipitation of myocardial infarction.

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