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Subclinical hypothyroidism

By William Singer, MD

Hypothyroidism is a common condition with slowly progressive nonspecific symptoms. It is often diagnosed serendipitously and occurs most frequently in women over 50.[1] In addition to the marked female preponderance, there is a strong genetic component. There is also a large country-to-country variability due to differences in the iodine content of the diet.

Most often, hypothyroidism is caused by an autoimmune process. However, other, often transient causes need to be considered (Table 1). The diagnosis of primary hypothyroidism is made by the finding of an elevated thyroid stimulating hormone (TSH) level and a decreased free thyroxine (FT_4). Antibodies against the thyroid peroxidase enzyme (TPO), which catalyzes both the iodination and coupling of tyrosyl residues in the gland, are usually present. "Subclinical hypothyroidism" is a term that is applied to patients who have an elevated TSH, but a normal FT_4. This issue of *Endocrinology Rounds* reviews the prevalence of and the diagnostic evidence and treatment criteria for subclinical hypothyroidism in patients presenting with abnormal thyroid blood tests.

Prevalence

The prevalence of primary hypothyroidism has been estimated to be around 5%, although in women over 50, it is as high as 10% and, as noted above, in some countries considerably higher. In men, the prevalence is much lower. People of African origin have a much lower chance of developing thyroid dysfunction. The prevalence of subclinical hypothyroidism has been estimated to be up to 10 times higher than that of clinical hypothyroidism.[1]

Predictive factors

In a 20-year follow-up study in the north of England, it was found that both a mildly elevated TSH and elevated anti-TPO antibodies predicted the eventual development of hypothyroidism. When both were present, about 5% of the patients developed overt hypothyroidism per annum. However, when only an elevated TSH or an elevated anti-TPO was present, the process was much slower. In this group, however, about 28% had become hypothyroid by the end of the study period.[2] In a recent study, over 50% of patients with a TSH >6 or elevated antibodies had become hypothyroid within 10 years.[2] The development of

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Table 1: Causes of hypothyroidism

- Autoimmune thyroiditis (Hashimoto's)
- Late-phase of subacute thyroiditis
- Drugs – including amiodarone, lithium, anticonvulsants.
- Kelp and other seaweed preparations
- Radiation
- Hypothalamo-pituitary dysfunction

Table 2: Signs and symptoms of hypothyroidism

- Fatigue/low energy
- Cold intolerance
- Dry skin
- Polymenorrhea
- Hypertension
- Hyperlipidemia

hypothyroidism is a very slow process that may take decades to become overt.

Diagnosis

Hypothyroidism is usually detected serendipitously when an elevated TSH is found on routine testing. In patients with TSH levels that are <20 (normal range <5 - 6 mU/L), it is unusual to find a decreased FT_4 (FT_3 or triiodothyronine, drops much later, except in sick patients or those on 5'deiodinase-inhibiting drugs).

As mentioned above, for every patient with overt hypothyroidism, approximately 10 may have subclinical disease.[3] The symptoms and signs of subclinical hypothyroidism are not very different from those of clinical hypothyroidism in that they are rather vague and nonspecific (Table 2). In fact, it has been proposed that the milder forms be called "mild hypothyroidism," rather than "subclinical hypothyroidism."[4]

Patients with hypothyroidism may have associated lipid abnormalities (especially an elevated total cholesterol [TC] and low density lipoprotein [LDL] cholesterol), hypertension, musculoskeletal symptoms, coronary artery disease, depression, and other quality of life complaints. Clinical signs are nonspecific and include dry skin, an enlarged thyroid (size and function do not correlate in the thyroid), hypertension (which may or may not be related), and a delay in the contraction and relaxation phase of reflexes (this is usually not marked in the mild forms).

Effect of treatment

There is evidence that in both overt and subclinical hypothyroidism, beneficial changes can be brought about with thyroxine.[4] The question of whom to treat is difficult to determine. When do we treat a laboratory value? What evidence is there that we are actually helping the patient?

Cardiac function

Monzani et al[5] found that various myocardial functional parameters were adversely affected in 20 patients with subclinical hypothyroidism compared to age and gender-matched controls. These parameters were reversed by thyroxine replacement therapy with a high degree of statistical significance.

Hyperlipoproteinemia

The same group from the University of Pisa studied 49 patients with subclinical hypothyroidism and found that fasting TC, LDL cholesterol, and apolipoprotein-B were higher in subclinical hypothyroidism patients than in controls and correlated with their TSH level. Treatment with thyroxine resulted in reductions in both TC and LDL levels.[6] Similar findings were reported in 66 women with subclinical hypothyroidism where there was

Table 3: Common causes of transient hypothyroidism

- Postpartum thyroiditis
- Late phase sub-acute thyroiditis
- Kelp and other seaweed preparations
- Amiodarone
- Lithium carbonate

a significant drop in TC, LDL, and Apo B levels with thyroxine.[7]

In a meta-analysis comprising 173 patients, McDermott and Ridgway[4] found that in a majority of studies in patients with subclinical hypothyroidism, myocardial contractility and diastolic function improved with L-thyroxine treatment. They also quote an older uncontrolled Canadian study[8] that demonstrated progression of coronary artery disease in patients with elevated TSH levels.

Non-specific symptoms. (fatigue, etc)

Three randomized, controlled trials,[9-11] quoted by McDermott and Ridgway, demonstrated statistically significant improvement in 82 subclinical hypothyroid patients treated with L-thyroxine., based on responses to questionnaires. Similar benefits were reported in neuromuscular dysfunction that was often accompanied by electromyographic abnormalities.[11] However, other studies found little effect on these abnormalities with L-thyroxine treatment.[12,13] This is not surprising since these conditions have multiple causes and hypothyroidism is only one possibility.[3]

Who should be screened?

Various recommendations by different groups have been made about who should be screened in the population. These range from anyone over 20 years old to those over 60 years old. The consensus appears to be that all women over 50 years should have their TSH checked annually. Newborns, of course, are routinely checked. The TSH should be checked early in pregnancy or before conception because of the possible deleterious effects of hypothyroidism on fetal development. Women with elevated values have a much higher incidence of postpartum thyroid disease (hyper- or hypo-), which occurs between 6 weeks and 6 months after delivery. Furthermore, anyone with a history or family history of autoimmune disease, goiter, hyperlipidemia, hypertension, or other unexplained suggestive features, should be given the benefit of the doubt and have their TSH checked.

Who should be treated?

It is important to rule-out transient hypothyroidism due to late-phase subacute thyroiditis or the inappropriate ingestion of iodine-containing substances such as kelp (Table 3). In subacute thyroiditis, the presenting feature is hyperthyroidism early in the disease. However, once the gland is depleted of thyroid hormone after 6 to 12 weeks, hypothyroidism ensues and fatigue is the commonest symptom. At that time,

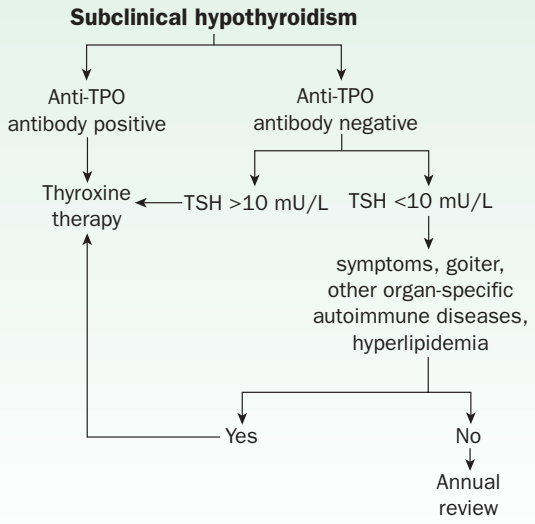
- the TSH is mildly or markedly elevated
- the FT_4 is low or low-normal
- anti-TPO antibodies are frequently present, and
- ^{131}I or ^{123}I neck uptake is elevated in the iodine-depleted gland.

These biochemical abnormalities are usually transient and require no treatment since they revert to normal in approximately 1 to 2 months.

Many vitamin preparations contain a sufficient amount of iodine to cause hypothyroidism (and occasionally hyperthyroidism) in susceptible people (usually those with a positive family history of thyroid disease). Kelp or other seaweed preparations can have the same effect, but these effects disappear 1 to 2 months after stopping these preparations.

Hypothyroidism due to long-acting radiological contrast media is no longer seen. However, approximately 20% of patients on amiodarone

Figure 1: An algorithm for the management of subclinical hypothyroidism.[9]



TPO = thyroid peroxidase

become hypothyroid (often only mildly, thus falling into the subclinical category) and in these patients, treatment with thyroxine is indicated in the absence of severe coronary artery disease. During the first few months on amiodarone, transient mild hypothyroidism may occur that does not require treatment.

About 20% of patients on lithium become hypothyroid (clinical or subclinical) and should be treated with thyroxine. These patients should be told that if they stop the lithium in the future, they will probably be able to stop the thyroxine as well.

The algorithm summarized in Figure 1 recommends that patients having a TSH >10 mU/L be treated and those with TSH values between 6 and 10 mU/L and elevated anti-TPO antibodies should be considered for treatment.[14] Patients with TSH values between 6 and 10 mU/L, but with negative antibodies, should only be treated if they happen to be pregnant or if other factors such as hypercholesterolemia, hypertension, or other suggestive symptoms are present. In practice, it is a good idea to repeat the TSH test after 2 or 3 months, especially if the value is borderline, and at the same time, measure anti-TPO antibodies before deciding on therapy that may be lifelong.

Negative effects of treatment with thyroxine

Negative effects are mostly due to overtreatment, especially in older patients where angina or other cardiac rhythm problems may be precipitated. This can be avoided by starting older patients on a low dose of thyroxine and increasing the dose gradually. In some patients with angina, the aim should not necessarily be to achieve normal biochemical values. L-thyroxine is inexpensive and therefore, the economic burden is small. However, the increased frequency of testing does come with an increased cost. Usually, when an optimal dose has been established, the frequency of testing need not exceed every 6 to 12 months, unless compliance is an issue.

Conclusions

- Patients with TSH levels >10 mU/L should be offered treatment with thyroxine, even if their antibodies are not elevated, provided transient or reversible causes of hypothyroidism have been ruled-out.
- Patients with TSH values between 6 and 10 mU/L *and* elevated TPO antibodies should be considered for treatment with thyroxine since the likelihood of developing overt hypothyroidism is approximately 5% per year.
- Patients with TSH values of <10 mU/L, but with negative antibodies, should not be offered treatment unless other factors are present such as pregnancy, hypertension, hyperlipidemia, heart disease, or other nonspecific symptoms such as fatigue that may be caused, at least in part, by the lack of thyroid hormone.

However, those not offered treatment need to have their TSH rechecked periodically.

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Abstracts of Interest

Subclinical hypothyroidism is mild thyroid failure and should be treated

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Subclinical hypothyroidism is defined as an elevated serum TSH level associated with normal total or free T4 and T3 values. The overall prevalence has been reported to range from 4–10% in large general population screening surveys and from 7–26% in studies of the elderly. Because of the frequency with which this condition is encountered, important questions have been raised regarding its clinical relevance and appropriate management. One of the myths that surrounds subclinical hypothyroidism is that the laboratory profile of an elevated serum TSH and normal free thyroid hormone levels really represents "compensated hypothyroidism." The reasoning behind this idea is that, since the circulating levels of thyroid hormones are within the normal range with only the serum TSH being elevated, the affected subject is really euthyroid because the increased TSH is stimulating and driving the thyroid gland to produce normal thyroid hormone levels. Certainly, elevated serum TSH levels do stimulate even a diseased thyroid gland to produce and release more thyroid hormone. However, as long as the serum TSH level remains elevated, the thyroid hormone levels are not truly normal for that individual. The clearance kinetics of thyroid hormones and TSH from the circulation actually make such a conclusion inescapable. Because the half-life of T4 is 7 d and that of T3 is 1 d, the serum TSH, which has a half-life of less than 1 h, would certainly be expected to return to normal if thyroid hormone levels were, indeed, normal for that individual. An elevated TSH in an individual patient, thus, means that the circulating thyroid hormone concentrations are insufficient, with a few rare exceptions (TSH-secreting tumors, thyroid hormone resistance syndromes). We, indeed, believe that subclinical hypothyroidism represents mild thyroid failure and is a clinically important disorder that has adverse clinical consequences and that should be treated in most, if not all, cases. We will support this position by reviewing the reported objective data regarding its natural history, its clinical manifestations, and the benefits of treatment.

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The treatment of subclinical hypothyroidism is seldom necessary

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Subclinical hypothyroidism (SH) is a common disorder with a prevalence ranging from 1–10% of the adult population in most community studies. The risk of developing SH increases with female gender, advanced age, and greater dietary iodine intake. The view that most subjects with SH should be treated with L-thyroxine has gained increasing

credence. A limited number of placebo-controlled randomized trials involving a small number of patients with SH have been performed and several of these studies show that L-thyroxine therapy may reduce symptoms of hypothyroidism. Other studies in subjects with SH have shown that L-thyroxine lowers low-density lipoprotein (LDL) cholesterol, improves cardiac function, and diminishes neuropsychiatric symptoms. A recent cross-sectional observational study noted an association between SH and atherosclerotic disease. On initial assessment then, it appears that the position advocating L-thyroxine therapy for most subjects with SH enjoys strong experimental support.

However, careful scrutiny of the entire spectrum of primary data bearing on the question of whether or not SH should be treated with L-thyroxine yields a legitimate contrary view. There are as many placebo-controlled randomized trials that observed no reduction in symptoms of SH as there are that note benefits of treatment. Other reports have noted the doubtful clinical significance and frequent statistical nonsignificance of L-thyroxine therapy on changes in LDL cholesterol, myocardial performance, and neuropsychiatric parameters. No association between SH and ischemic heart disease was shown in the Whickham survey, the most extensive longitudinal study of thyroid disease ever conducted. Such conflicting findings stem from inconsistencies of the reports in the variable definition of SH, the wide degree of thyroid failure examined, as well as the heterogeneous age, gender, and ethnicity of the subjects tested.

There is considerable evidence suggesting that the subjects with SH who would benefit most from L-thyroxine therapy are those with TSH levels exceeding 10 mU/liter. Such individuals constitute the minority of those with SH in all large-scale epidemiological studies that have stratified TSH levels. The majority of subjects with SH, however, have slight elevations of TSH ranging between 5 and 10 mU/liter, and they have minimal, often nonsignificant, metabolic abnormalities. They are either affected by mild incipient thyroid failure for which L-thyroxine therapy has not been shown to convey recognizable benefits, or they may simply represent "euthyroid outliers" in the 2.5% tail above the upper limit of the normal TSH reference range, in which case L-thyroxine treatment would be inappropriate. The available evidence also calls into question the need to treat men with SH, who are much less prevalent than women with SH, and who manifest almost no metabolic differences compared with men with normal TSH levels.

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