CHAPTER

185 Subclinical Hyper and Hypo Thyroidism - When to Treat

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SUBCLINICAL HYPOTHYROIDISM

Subclinical hypothyroidism is defined as an increased serum TSH in the presence of a normal serum FT4 concentration. Increased refers to values above and normal to values within population-based reference ranges of these hormones. It is however not so simple to diagnose accurately subclinical hypothyroidism in day-to-day practice applying this biochemical definition. Diagnosis of subclinical hypothyroidism is hampered by uncertainty about what constitutes appropriate reference intervals, and by biologic variation in especially TSH. The upper limit of the TSH reference interval was 4.12 mU/L in the National Health and Nutrition Eamination Survey III (NHANES III) for a large reference population that was free of thyroid disease and representative of the U.S. population, in which subjects were excluded who had thyroid antibodies or were taking thyroid medications or other medications affecting thyroid measurements.

Table 1: Abnormalities reported in some but not all studies on subclinical hypothyroidism

Symptoms	• hypothyroid symptoms • impaired well-being and quality of life • impaired cognitive functions (working memory) • mood disturbances
Signs	• impaired left ventricle diastolic and systolic function • hypertension • increased systemic vasular resistance • increased central arterial stiffness • impaired endothelium function • increased carotid intima-media thickness • impaired muscle energy metabolism • impaired peripheral nerve conduction latency and amplitude • impaired stapedial reflex
Biochemistry	• high serum total and LDL cholesterol • high HOMA index (insulin resistance) • high serum C-reactive protein • low factor VIIa • high serum lactate during exercise • low serum IGF-1, high serum leptin

It is highly relevant after the biochemical diagnosis to establish a etiological diagnosis to evaluate which condition is responsible for the elevated TSH. The list of possible causes is very long. The most common causes of subclinical hypothyroidism are chronic autoimmune thyroiditis (Hashimoto's disease), previous 131I therapy or thyroidectomy, and inappropriate dosage of thyroxine or antithyroid drugs. Loss-of-function mutations in the gene encoding for the TSH receptor are relatively common in isolated hyperthyrotropinemia, especially in children and adolescents. Other causes of an elevated TSH are interference of heterophilic TSH antibodies in TSH immunoassys, nonthyroidal illness syndrome (recovery phase), impaired renal function, untreated adrenal insufficiency (Addison's disease) and obesity.

The prevalence of subclinical hypothyroidism in the general population is rather high in the order of 4% to 8%; it is higher in iodine-replete areas than in iodine-deficient areas.The higher prevalence of subclinical hypothyroidism in females than in males and in older than in younger subjects is in agreement with the higher prevalence of thyroglobulin and thyroid peroxidase (microsomal) antibodies in women and in elderly people.

The natural history of subclinical hypothyroidism is reported in many studies, although it remains difficult to predict whether the increased TSH levels will return spontaneously to within the normal range, will remain stable, or will increase to higher values with development of overt hypothyroidism. In general it can be said that the higher the initial TSH, the higher the risk of progression; the presence of TPO antibodies potentiates the risk. Spontaneous normalization of increased TSH values in subclinical hypothyroidism is a well-known phenomenon, but the reported frequency of normalization differs markedly between studies from 4% up to 52%. Progression to overt hypothyroidism ranges from 7.8% to 17.8% in various studies. Table 1 depicts some of the abnormalities reported in some studies.

TREATMENT

Many studies on the effect of levothyroxine treatment in subclinical hypothyroidism have yielded inconsistent results (Table 2). The Cochrane meta-analysis did not observe statistically significant improvement in

Table 2: Quality of Evidence on the Strength of Association and Risks/Benefits of Levothyroxine Treatment of Subclinical Hypothyroidism for Patients With a Serum TSH Level of 4.5 to 10.0 mIU/L[a]

Clinical condition	Strength of association	Benefits of treatment
Progression to overt hypothyroidism	Good	Variable[b]
Adverse cardiac end points	Insufficient[c]	No evidence
Elevation in serum total cholesterol and LDL-C levels	Insufficient[c]	Insufficient
Cardiac dysfunction	Insufficient[c]	Insufficient
Systemic hypothyroid symptoms	No clear evidence	Insufficient
Psychiatric symptoms	No clear evidence	Insufficient

[a]LDL-C = low-density lipoprotein cholesterol; TSH = thyroid-stimulating hormone; [b]Thyroid hormone therapy normalizes the serum TSH level at any TSH concentration. Overt hypothyroidism occurs earlier in untreated patients with a serum TSH level of >10 mIU/L than in those with a serum TSH level of 4.5 to 100 mIU/L; [c]Available data do not distinguish between serum TSH concentrations of 4.5 to 10 mIU/L and of more than 10 mIU/L. Adapted from *JAMA?* with permission of the American Medical Association. Copyright © 2004, All rights reserved.

symptoms, mood or quality of life; one study showed a statistically significant improvement in cognitive function. A placebo-controlled randomized clinical trial in the UK demonstrated significant improvement in tiredness upon levothyroxine treatment The Cochrane meta-analysis evaluated many parameters of systolic and diastolic heart function. Significant improvement after L-T4 treatment was observed for some parameters, like isovolumic relaxation time, index of myocardial performance, cycle variation index and left ventricular ejection time; systemic vascular resistance was not improved. Some studies report a lower systolic and diastolic blood pressure upon L-T4 treatment of subclinical hypothyroidism. One study reports a 6% reduction in supine mean arterial pressure. Recent studies also indicate regression of the increased carotid intima-media thickness upon L-T4 treatment. With respect to serum lipids, an early non-systematic review concluded that normalization of serum TSH in subclinical hypothyroidism decreases serum cholesterol on average by 0.4 mmol/l.

A RCT demonstrated increased cardiopulmonary exercise performance after L-T4 therapy in comparison to no treatment. L-T4 treatment of subjects older than 70 yr with subclinical hypothyroidism did not document any benefit in terms of functional mobility. A non-RCT shows normalization of reduced glomerular filtration rate and increased serum Cystatin-C levels upon L-T4 treatment of subclinical hypothyroidism. A RCT in iron-deficient subjects with subclinical hypothyroidism demonstrated greater increase in hemoglobin levels upon treatment with L-T4 plus iron than in treatment with iron alone. L-T4 treatment of subclinical hypothyroidism in pregnant women improves maternal and fetal outcomes of pregnancy, and is recommended. A RCT in infertile women reports improved outcomes of in vitro fertilization upon L-T4 treatment as compared to placebo treatment.

Whether or not subclinical hypothyroidism should be treated was and still is hotly debated; there are strong defenders as well as strong opponents to levothyroxine treatment. A 2004 scientific review by a panel of experts concluded that data supporting associations of subclinical thyroid disease with symptoms or adverse clinical outcomes or benefits of treatment are few, and that the consequences of subclinical thyroid disease are minimal ; consequently, the panel recommended against routine treatment of subclinical hypothyroidism, albeit recognizing the possible need for treatment in selected individual cases. The 2007 Cochrane meta-analysis also could find no evidence supporting treatment. Subsequent meta-analyses of long-term follow-up population-based studies seem to indicate that subclinical hypothyroidism is indeed associated with a modest risk on cardiovascular morbidity and mortality (although this may be age-dependent), but proof that levothyroxine treatment decreases the risk is lacking. This would require appropriately powered, randomized,placebo- controlled, double-blinded interventional trials with long follow-up. The debate whether or not to treat, thus continues.Given the current state of affairs with a lack of controlled trials reporting on long-term outcome, the decision whether or not to treat has to be taken in the face of uncertainty. This is not rare in medical practice, and the physician copes with such problems by an individualized approach taking into account best available circumvential evidence and clinical judgment.

It is recommended to confirm the existence of subclinical hypothyroidism in a second blood sample taken about 3-6 months later. This recommendation in current guidelines is given in view of the high chance of spontaneous normalization of the elevated TSH value.It might be useful to already order assay of TPO-Ab and serum lipids in the second sample, because it may be relevant for further management in case subclinical hypothyroidism turns out to be persisitent. If subclinical hypothyroidism is confirmed, a strong case can be made for levothyroxine treatment when TSH values are > 10 mU/L. The observation that subclinical hypothyroidism might have some survival value in the elderly age group has led both guidelines to the recommendation not to treat elderly individuals with TSH values of 4-10 mU/L. In younger subjects with mild to moderate subclinical hypothyroidism (TSH values between 4 and 10 mU/L) one may opt to institute levothyroxine treatment in the presence of symptoms (in

view of the chance that symptoms will improve), TPO-Ab (especially in case TPO-Ab concentration is high with the risk of imminent progression to overt hypothyroidism, or cardiovascular risk factors (in the hope based on circumstantial evidence obtained from population-based association studies and some observational intervention studies to diminish the risk of developing cardiovascular events). If these three conditions are absent, most will agree it is better not to treat. In case no treatment is given, follow-up with regular repeat TSH measurements is indicated. However there is certainly a role for clinical judgement in thes patients. Many practitioners will elect to try replacement therapy in patients with SCH who are symptomatic, especizally in patients under age 70, with careful attention to maintaining TSH in the normal range.

SUBCLINCAL HYPERTHYROIDISM

The prevalence of SH in an adult population depends on age, sex, and iodine intake. In a representative sample of U.S. subjects without known thyroid disease, 0.7% had suppressed TSH levels (< 0.1 mU/L), and 1.8% had low TSH levels (< 0.4 mU/L). Similar rates have been reported in studies from Europe, with higher levels in women and older subjects. The differential diagnosis of an isolated low or suppressed TSH level includes exogenous thyroid hormone use, nonthyroidal illness, drug effects, and pituitary/hypothalamic disease, all of which need to be ruled out before the diagnosis of SH can be established in a patient with an isolated low or suppressed TSH level. In addition, mean serum TSH levels are lower in black non-Hispanic Americans, some of whom may have slightly low TSH levels without thyroid disease. Finally, some otherwise healthy older persons may have low serum TSH levels, low normal serum levels of free T4 and total T3, and no evidence of thyroid or pituitary disease, suggesting an altered set point of the pituitary-thyroid axis.

The natural history of SH is variable, with annualized rates of 0.5 – 7% progression to overt hyperthyroidism and 5 – 12% reversion to normal TSH levels. In one study, 51.2% of patients had spontaneously developed a normal TSH when first checked at some time within 5 years (mean time to repeat TSH 13 months). Progression from SH to overt hyperthyroidism appears more likely if the TSH is suppressed (< 0.01 mU/L), rather than low but detectable (0.01 – 0.4 mU/L). Patients with GD rather than a TMNG as the cause of SH may be more likely to spontaneously remit. In patients at high risk of complications from SH, TSH and free T4 should be repeated within 2-6 weeks. For all other patients, it is important to document that SH is a persistent problem by repeating the serum TSH at 3-6 months, prior to initiating therapy. In clinical series, TMNG is the most common cause of SH, especially in older persons.

The second most common cause of SH is GD, which is more prevalent in younger persons, and is also common in patients who previously received ATD therapy. Other unusual causes include solitary autonomously functioning nodules, and various forms of thyroiditis, the latter of which would be more strictly termed ''subclinical thyrotoxicosis.

Since SH is a mild form of hyperthyroidism, it is not surprising that deleterious effects seen in overt hyperthyroidism might also occur in SH. There have been a large number of recent studies elucidating these effects:

1. Overall mortality. A number of longitudinal studies have examined correlations between SH and overall mortality, with variable results. Some studies report increased overall mortality rates in SH subjects , especially older subjects, while others indicate no relation. Limitations of some of these studies include sample sizes, age ranges, length of follow-up, and diagnosis of SH by a single TSH measurement. A recent meta-analysis of individual-level data from 52,674 participants, pooled from 10 cohorts and providing greater power, concluded that SH confers a 24% increased risk of overall mortality

2. Cardiovascular disease. A recent large study of 26,707 people followed for 12 years reported increased cardiovascular mortality with SH. Some other, smaller studies have reached similar conclusions , although other smaller studies have failed to find a correlation. , the highest relative risk for atrial fibrillation occurred in younger subjects, possibly because other causes predominate with age, and in subjects with lower TSH levelsyroid A further population-based study found that SH increased the risk for stroke in subjects over age 50 years with a hazard ratio of 3.39 , although a recent meta-analysis of stroke risk in SH found insufficient number of events to draw definitive conclusions. Complementing these epidemiologic studies, investigations of smaller numbers of subjects with SH have revealed increased heart rate at rest and during exercise, decreased heart rate variability, and increased frequency of atrial and ventricular premature beats, which improve with treatment of SH. Taken together, these data provide a strong argument for the treatment of SH in older subjects to avoid dysrhythmias and possible subsequent stroke. Whether younger patients should be treated for the same preventive indications is less clear. The most recent data provide evidence that relative risks of cardiovascular mortality and atrial fibrillation are elevated in younger, as well as older, patients with SH. However, the absolute risks of these events are very low in younger patients, so the risk/benefit ratio of treating younger SH patients is not clear. Clinical judgement should be used in these cases, and treatment decisions individualized.

3. Osteoporosis and fractures. Most studies of endogenous SH show decreased bone mineral density in post-menopausal women, but not in men or pre-menopausal women. However, it is not clear that this translates to increased fracture risk.. The most recent and by far the largest individual

Table 3: When to treat SH?

Factor	TSH (<0.1 mU/L)	TSH (0.1-0.4 mU/L)[a]
Age > 65	Yes	Consider treating
Age <65 with comorbidities		
Heart disease	Yes	Consider treating
Osteoporosis	Yes	Consider treating
Menopausal, not on estrogens Or bisphosphonates	Yes	Consider treating
Hyperthyroid symptoms	Yes	Consider treating
Age < 65, asymptomatic	Consider treating	Observe

[a]Where 0.4 mUL is the lower limit of the normal range.

study to date (231,355 subjects) reported a hazard rate for all major osteoporotic fractures combined (hip, humerus, forearm, spine) of 1.13 (confidence intervals 1.014-1.26). Risk increased with duration of SH, such that after a median follow-up of 7.5 years, 13.5% of subjects with a low TSH level had experienced at least one major osteoporotic fracture, compared to 6.9% of subjects with a normal TSH level. Other studies have not found increased fracture rates in SH subjects.

4. Mood and cognition. A large body of literature has investigated possible correlations between SH and cognitive decline. Approximately equal numbers of studies report significant associations between SH and measures of cognitive decline and the development of dementia, vs. no associations. Therefore, at this time, no conclusions regarding this issue can be reached. There appears to be no correlation between SH and depression.

5. Physical functioning. Four studies have investigated whether SH is associated with selfreported functional capacity or objective measures of physical functioning. Three could find no correlation, while the fourth found a correlation between SH and lower physical performance in men only.

When to treat SH (Table 3)

When TSH is persistently < 0.1 mU/L, treatment of SH should be considered in asymptomatic individuals < 65 years of age. Treatment of SH is controversial, since few intervention studies to show benefit have been performed, especially for clinically important endpoints such as cardiovascular events, atrial fibrillation, and fractures. Additionally, none of these studies included a control arm. Thus the evidence rests only with small uncontrolled studies that have shown improvements in cardiac structure and function, heart rate and the frequency of premature atrial and ventricular beats, bone mineral density, and muscle strength. In 2004, a panel of experts determined that the evidence for benefit was sufficient to warrant therapy of SH in older individuals whose serum TSH level was < 65 years of age. However, younger subjects should be monitored at regular 6-12 month intervals, and treatment should be considered if the TSH persistently decreases to < 0.1 mU/L. In patients with symptoms of hyperthyroidism, a trial of betaadrenergic blockers may be useful to determine whether symptomatic therapy might suffice. A TSH level between 0.1 and 0.4 mU/L on repeated measurement over a 3– 6-month period is considered persistent, effectively ruling out transient thyroiditis as a cause. The thyroid disorder underlying SH with TSH persistently within this range should be diagnosed before considering treatment to avoid treating patients with transient, functional disorders related to acute illness, drugs, and other causes of low TSH.

How to treat SH

If SH is to be treated, the treatment should be based on the etiology of the thyroid dysfunction and follow the same principles as outlined for the treatment of overt hyperthyroidism. The treatment of SH is similar to the treatment of overt hyperthyroidism. RAI is appropriate for most patients, especially in older patients when toxic multi nodular goiter is a frequent cause of SH. There are no data to inform whether elderly patients with SH would benefit from pretreatment with Anti thyroid drugs to normalize thyroid function before Radio active iodine therapy. Given the low risk of exacerbation , the risks of ATD therapy may outweigh any potential small benefit. A course of ATD therapy is a reasonable alternative to RAI in patients with GD and SH, especially in younger patients, since remission rates are highest in persons with mild disease

Some patients with SH due to GD may remit spontaneously without therapy, so that continued observation without therapy is reasonable for younger patients with SH due to GD. A small subset of elderly patients with persistently low TSH and no evidence of true thyroid dysfunction can be followed without intervention, especially when the serum free T4 and total T3 levels are in the lower half of the normal range. Treatment with beta-adrenergic blockade may be sufficient to control the cardiovascular-related morbidity from SH, especially that of atrial fibrillation. Some patients with SH due to mild GD may remit spontaneously and may be followed without therapy with frequent (every 3-6 months) monitoring of thyroid function. In select patients with SH due to Toxic multi nodular goiter who have compressive symptoms, or in whom there is concern for malignancy, surgery is also an option.

The goal of therapy for SH is to render the patient euthyroid with a normal TSH. Since the rationale for therapy of SH is to a large degree preventive, there are few end points that can be used to document that therapy has been successful. Based on the original indication for treatment, it is reasonable to follow hyperthyroid symptoms or bone density.otherwise, the major end point is a TSH level within the age-adjusted reference range.