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Review Article

Subclinical Hypothyroidism: A Review on Clinical Consequences and Management Strategies

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Abstract

Subclinical hypothyroidism (SCH) is defined as an elevated serum thyroid-stimulating hormone (TSH) level with normal free thyroid hormone values. The prevalence of subclinical hypothyroidism is 3 to 8 percent in the general population, and up to 15 to 18 percent in women who are older than 60 years. It is more common in women than men, and its prevalence increases with age. Of patients with SCH, 80% have a serum TSH of less than 10 mIU/L. Management strategies including screening and treatment of subclinical hypothyroidism are still controversial. The strongest arguments for levothyroxine therapy are the high risk of progression to overt hypothyroidism. Initiating levothyroxine replacement therapy is recommended for all patients with a TSH greater than 10 mIU/L, even if the free thyroxine concentration is within normal laboratory range. However, treatment of patients with a serum TSH level between 5 and 10 mIU/L remains controversial. There was insufficient evidence for a clinically significant relationship between subclinical hypothyroidism and adverse cardiac events or cardiac dysfunction. Conflicting results have been found on the association between subclinical hypothyroidism and cognitive impairment, depression and the risk of fractures. This narrative review aims to assess current evidence on the clinical aspects, as well as screening and treatment recommendations in adults with subclinical hypothyroidism.

Search strategy:

We searched for reviews, guidelines for management and original articles related to subclinical hypothyroidism those published in different journal until 2015, e.g. Medline, Mayo clinic, Upto date, Journals of Hindawi publishing corporation, European Thyroid Journal and Pub Med. Keywords used included subclinical hypothyroidism and incidence, prevalence, cause, diagnosis, health consequences, screening, morbidity and mortality, indication of treatment, Management. After going through all, we only selected those which were more recent and evidence based guidelines. Clinical trials rather than from observational studies or reviews has been selected to prepare the manuscript.

Key Words: *Subclinical Hypothyroidism, Clinical Consequences of SCH, Management Strategies of SCH.*

Introduction

Subclinical hypothyroidism is defined as a serum thyroid stimulating hormone (TSH) above the defined upper limit of the reference range, with a serum free thyroxine (T4) within the reference range[1]. Patients with subclinical thyroid disease have few or no symptoms or signs of thyroid dysfunction and thus by its very nature subclinical thyroid disease is a laboratory diagnosis. Before diagnosis of SCH, other causes of an elevated TSH level, such as recovery from nonthyroidal illness, assay variability, presence of heterophile antibodies interfering with the TSH assay, and certain cases of central hypothyroidism with biologically inactive TSH and thyroid hormone resistance, should be excluded. However, the most common cause of elevated TSH is autoimmune thyroid disease.[1] Previous radioiodine therapy, thyroid surgery, and external radiation therapy can also result in mild thyroid failure. Transient SCH may occur after episodes of postpartum, silent, and granulomatous thyroiditis. Serum TSH has a log-linear relationship with circulating thyroid hormone levels (a 2-fold change in free thyroxine will produce a 100-fold change in TSH). Thus, serum TSH measurement is the necessary test for diagnosis of mild thyroid failure when the peripheral thyroid hormone levels are within normal laboratory range.[1, 2] It is therefore critically

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important that the reference limits for TSH be standardized. Perhaps the most ambitious attempt to address the contentious issues of subclinical thyroid disease in a non-biased and systematic way was undertaken recently by The (American) Endocrine Society, the American Thyroid Association (ATA) and the American Association of Clinical Endocrinologists (AACE). These societies co-sponsored a Consensus Development Conference in 2002 and contracted an independent consulting firm to review and summarize existing published evidence (195 articles in total). Principal conclusions of the panel were published earlier this year.[3] The panel concluded that the reference range for TSH should be based on the third National Health and Nutrition Examination Survey (NHANES III). The upper limit of the range should not be reduced as suggested by some associations[4] and a range of 0.45–4.5 mU/L should ultimately be adopted.[5] When the TSH level is above 10 mIU/L, levothyroxine therapy is generally agreed to be appropriate.[3,6] However, management of patients with a serum TSH level of less than 10 mIU/L is controversial.[7] Some authors argue for routine[6] and some for selective[3] therapy. Data on health-related quality of life and symptoms did not show significant differences between intervention groups. Some evidence indicates that levothyroxine replacement improves some parameters of lipid profiles and left ventricular function.[8]In the past decade a number of review articles addressing subclinical thyroid disease have been published. They have in turn focused on evolving issues regarding definition, diagnosis and management of this common condition. It is important to note that the literature in this area is still inadequate and consensus statements may often be an expert panel opinion rather than strictly evidence based.

Epidemiology of Subclinical Hypothyroidism

Subclinical hypothyroidism or mild thyroid failure is a common problem, with a prevalence of 3% to 8% in the population without known thyroid disease.[5,9]The prevalence increases with age and is higher in women.[5] After the sixth decade of life, the prevalence in men approaches that of women, with a combined prevalence of 10%.[5]Antithyroid antibodies can be detected in 80% of patients with SCH, and 80% of patients with SCH have a serum TSH of less than 10 mIU/L.[1] The progression to overt hypothyroidism is approximately 2–5% per year.[10] The rate of progression is proportional to baseline TSH concentration and is higher in individuals with antithyroid antibodies.

Consequences of Untreated Subclinical Hypothyroidism

In addition to progression to overt hypothyroidism a number of possible consequences of subclinical hypothyroidism exist. The panel attempted to define the nature of association of adverse cardiac events/cardiac dysfunction, effects on lipids, neuropsychiatric symptoms and systemic hypothyroid symptoms. An attempt was made to stratify for TSH (i.e. TSH less than or greater than 10 mU/L), although available data did not always distinguish between serum TSH concentrations. In general there was insufficient or no evidence to support an association between subclinical hypothyroidism and these clinical conditions.[11-13] A discussion of some of the proposed adverse effects of SCH follows.

a. Progression to Overt Hypothyroidism

Patients with SCH have a high rate of progression to clinically overt hypothyroidism, 2.6% each year if thyroperoxidase (TPO) antibodies are absent and 4.3% if they are present.[10] However, some persons do not show progression and some experience normalization. A TSH level greater than 10 mIU/L predicts a higher rate of progression, and a level of less than 6 mIU/L predicts a lower likelihood of progression. In a study in men and women older than 55 years with a mean follow-up of 32 months, the TSH level normalized in 52% of those with a serum TSH of less than 10mIU/L.[14]

b. Lipid Abnormalities and Other Cardiac Risk Factors

Interestingly although some studies assessing T4 replacement suggest that dyslipidaemia can be improved with treatment,[15] others have failed to confirm these findings.[16,17] The panel concluded that there was insufficient evidence for a clinically significant relationship between subclinical hypothyroidism and adverse cardiac events or cardiac dysfunction. Numerous small studies have demonstrated subtle echocardiographic changes,[18]however these studies all had significant limitations. It is of note that a single large cross-sectional study concluded that subclinical hypothyroidism was a risk factor for atherosclerosis and myocardial infarction. However, a longitudinal component of the same study failed to confirm any association, although event rates were low in both the euthyroid and subclinical hypothyroid groups.[19]Though some studies have shown improvement of cardiac contractibility and systolic time interval with levothyroxine therapy. But no evidence exists to support an association between heart failure and a serum TSH level of less than 10.0 mIU/L.[20] Whilst small interventional treatment trials have shown improvement in cardiac function, these are of uncertain significance, and there have been no randomized studies assessing T4 replacement therapy on important clinical endpoints. [21]

c. Adverse Fetal Effects

A seminal study by Haddow et al[21] showed a 7-point reduction in intelligence quotient in children aged 7 to 9

years whose mothers had SCH at pregnancy compared with the children of euthyroid mothers. If the T4 is low then treatment was advocated irrespective of the TSH result. If the TSH was greater than 10 mU/L then a trial of treatment was thought reasonable even if the T4 was normal, especially in women contemplating pregnancy. Where the TSH was less than 10 mU/L a trial of treatment could be considered if there were signs or symptoms consistent with hypothyroidism. The algorithm did not include the evaluation of antibody status. Monitoring of untreated patients at 6–12 monthly intervals was advocated.[22]

d. Musculoskeletal system and functional capacity

Persons with subclinical hypothyroidism more often suffer from weakness and myalgia,[23] and reduced muscle strength has been shown in these individuals.[24] Confirming this hypothesis, beneficial effects of levothyroxine replacement on strength measurements[24]and cardiopulmonary exercise performance[25] have been demonstrated. A possible mechanism for the lower exercise capacity could be higher oxygen requirements during exercise in people with subclinical hypothyroidism[25] as well as a possible association with anaemia.[26] On the other hand, large cohort studies did not find a reduction in functional mobility or functional capacity assessed in elderly individuals with subclinical hypothyroidism[27, 28] and persons with only mild elevations of TSH even revealed a slightly better mobility than euthyroid controls.[27]

High TSH levels as seen in hypothyroidism have been shown to directly affect bone metabolism through inhibition of osteoclast formation and survival, osteoblast differentiation and expression of collagen type 1.[29] A prospective study of 25,205 individuals from Norway did not show a significant association with hip or forearm fractures when the results were adjusted for age, BMI and smoking status.[30]A definitive answer will require more studies with TSH levels stratified as less than or greater than 10 mIU/L.

e. Psychiatric and Cognitive Dysfunction

An association between subclinical hypothyroidism and mood disorders including depression and increased anxiety,[31] as well as a reduced quality of life[32] have been suggested, whereas other studies did not confirm these findings.[33] Treatment failure for depression has been more commonly observed in patients with subclinical hypothyroidism.[34] Evidence of the association between cognitive dysfunction and subclinical hypothyroidism is conflicting,[35,36]and the most recent population-based cross-sectional study examining 2,050 participants including 141 individuals with subclinical hypothyroidism did not show an association with mild cognitive impairment, which represents the earliest detectable clinical stage of cognitive impairment.[37] In the currently largest RCT evaluating the impact of thyroxine replacement on cognitive function with inclusion of 94 elderly participants with subclinical hypothyroidism, treatment did not lead to an improvement of cognitive function after a follow-up of 12 months.[38] Nonetheless, it is still reasonable to have a low threshold for therapy for SCH in patients with depression, bipolar disorder, and cognitive dysfunction.

Screening for Subclinical Hypothyroidism

Screening remains a controversial area with lack of consensus amongst physician groups. For example whilst the ATA recommends screening all adults over the age of 35 yrs every 5 years,[39] the Royal College of Physicians (RCP) believe it unjustified in the general population but acknowledges that exceptions need to be made for various high risk groups.[40] Overall the panel recommended against population screening, but argued for case ascertainment in certain high risk groups, similar to recent recommendations by the US Preventive Service Task Force.[41] The panel believed that special consideration could be given to pregnant women, but only if they were at increased risk of thyroid disease (personal or family history of thyroid or autoimmune disease). Routine screening of pregnant women after consultation between physician and patient has however been recommended by the AACE.[42] It is noteworthy that controversy remains over what is the best screening test in this situation (TSH or T4).[43] Despite the impact of thyroid antibody positivity on the epidemiology of subclinical hypothyroidism, the panel did not advise the use of anti-thyroid peroxidase (TPO) antibodies. This differs from recommendations by the Royal College of Physicians (RCP),[40] the AACE,[44] the ATA[45] and Australian thyroidologists.[46]

Management of SCH

Several randomized studies of the effect of levothyroxine therapy in patients with SCH are available. One study limited to patients with serum TSH levels from 5 to 10 mIU/L did not show any benefit.[47] Some studies (range in TSH level, 3-32 mIU/L) showed improved symptom scores or improved memory in a quarter of patients. Many recent studies have not shown improvement in mood, anxiety, and cognition in older persons.[48-50] In a previous scientific review in 2004,[3]available data were considered insufficient to support a benefit for levothyroxine therapy in patients with SCH, in particular for the group with TSH less than 10 mIU/L, and a similar conclusion can again be drawn in 2008. Management of SCH differs depending on whether the serum TSH concentration is 3 to 5 mIU/L, 5.1 to 10 mIU/L, or higher than 10 mIU/L.[10]

a. Serum TSH Concentration of 3 to 5 mIU/L

Although persons with a serum TSH level of 3 to 5 mIU/L may be at higher risk of progression to hypothyroidism,[10]no firm evidence of health consequences exists. Lowering the upper limit of normal for the serum TSH level from 5.0 to 3.0 mIU/L is still controversial. In fact, in a randomized, crossover, 12-week study of patients with symptoms suggestive of hypothyroidism with serum TSH in the upper normal range, no difference in cognitive and psychological function was observed between levothyroxine-treated and control groups.[51] Given these findings, intervention cannot be recommended for this group, but follow-up by serum TSH measurement in 1 year would be a reasonable approach, particularly if antithyroid antibodies are detected.

b. Serum TSH Concentration of 5.1 to 10 mIU/L

Most studies are not stratified for different categories of serum TSH levels, and although benefits for symptoms and lipid levels have been shown for mild thyroid failure as a group, results cannot be extended to most patients with SCH who are in this subgroup. Large-scale randomized studies to conclusively show reduction of cholesterol with levothyroxine therapy in this subgroup are lacking.[1,52] One study of TSH levels of 5.0 to 10.0 mIU/L did not show any benefit.[47]Also, cognitive, neuropsychiatric, cardiac, and muscle abnormalities described in studies including a wide spectrum of TSH levels in SCH should be confirmed by larger randomized studies. The possibility that an elevated serum TSH level is a cardiovascular risk factor is still highly controversial. Hence, decision for levothyroxine therapy for this group should be individualized and should depend on the age of the patient (favoring therapy for younger persons), associated medical conditions, degree of TSH elevation, persistence and gradual increase of TSH, presence of antithyroid antibodies, presence of goiter, and hypothyroid symptoms. Given both the findings of reduced intelligence quotient in the children of women who had SCH while pregnant[21] and the adverse effects of mild thyroid failure on pregnancy outcome, levothyroxine therapy should be advised for pregnant women and women who anticipate becoming pregnant. Because of the effect of thyroxine on growth and development, levothyroxine therapy for children and adolescents is also reasonable.

c. Serum TSH Concentration Greater Than 10 mIU/L

Most thyroidologists agree that all patients with SCH and a serum TSH level above 10 mIU/L should be treated with levothyroxine.[53,54]Evidence is more compelling for the adverse effects of mild thyroid failure in this group. Studies have shown that levothyroxine therapy results in an 8-mg reduction in low-density lipoprotein levels.[54, 55] Among the factors that predict response of lipid levels to levothyroxine therapy are higher levels of TSH, insulin resistance, higher levels of pre therapy cholesterol, and type III hyperlipidemia.[56] Some evidence suggests that mild thyroid failure can aggravate bipolar disorder and depression[56] and that it is associated with abnormalities of muscle function, nerve conduction, cardiac function,[19] and cognitive and psychological function, with improvement after levothyroxine therapy.[52, 18,57-59]

Levothyroxine Therapy for SCH

For all patients with SCH and a serum TSH concentration above 10 mIU/L and for patients with serum TSH concentrations of 5.1 to 10.0 mIU/L in whom individualized decision for therapy is made, therapy should be started with levothyroxine. The usual required daily levothyroxine dose is 50 to 75μg.[60] Preferable starting daily dose is 25 to 75 μg, depending on the age of the patient, the level of free thyroxine, and the serum TSH level. Serum TSH should be checked after 8 weeks, and the dose should be adjusted. Once a normal serum TSH level has been achieved, TSH should be measured again after 6 months and then annually. [60] Some evidence indicates that levothyroxine replacement improves some parameters of lipid profiles and left ventricular function. Therefore, once commenced on treatment, then thyroid function should be monitored 2-3 months later to ensure serum TSH is controlled and then at least annually thereafter. In younger patients with symptoms, the goal of treatment should be to alleviate their symptoms, aiming for a serum TSH in the lower half of the reference range (0.3-2.5 mU/l).[61] However, for older individuals, if treatment is decided upon, then more relaxed targets are acceptable, aiming for a serum TSH between 1.0 and 5.0 mU/l in patients >70 years. Once patients with SCH are commenced on L-thyroxine treatment, then serum TSH should be monitored at least annually thereafter.[62]

Risks over Benefits of Treatment

There is also a danger of over-treatment, which could cause iatrogenic hyperthyroidism. Subclinical hyperthyroidism has been associated with negative outcomes including osteopaenia and atrial fibrillation.[63]One study found that 21% of participants on T4 therapy had a suppressed TSH suggestive of overtreatment.[64] It is worth noting that once on T4 therapy the optimal TSH level has yet to be defined. The panel and the ATA advocate treating to a TSH of 0.5–2.0 mU/L on the basis that this is the mean normal TSH level.[65]

Follow-Up of Untreated Patients

A proportion of patients with SCH will progress to overt hypothyroidism, 5-8% per year depending on the degree of

serum TSH elevation.[10, 66-68] On the other hand, thyroid function may normalize in 6-35% of SCH patients depending on initial TSH levels, thyroid autoantibody status and length and frequency of follow-up.[66, 69, 70] Hence, in the majority, SCH remains stable. Once SCH has been diagnosed then a repeat thyroid function test should be re-checked within 8-12 weeks along with thyroid auto antibodies. If thyroid function has normalized, then no further testing is required in those who are asymptomatic, have negative thyroid auto antibodies or do not have goiter. In those who have persistent SCH, thyroid function should be tested 6 monthly at least for the first 2 years and then yearly thereafter.[71,72] This is to gauge the tempo of any tendency to progression and to detect consequent overt hypothyroidism.

Conclusion

Subclinical hypothyroidism is a laboratory rather than a clinical diagnosis. Initiating levothyroxine replacement therapy is recommended for all patients with a TSH greater than 10 mIU/L, even if the free thyroxine concentration is within normal laboratory range. However, treatment of patients with a serum TSH level between 5 and 10 mIU/L remains controversial. The strongest arguments for levothyroxine therapy are the high risk of progression to overt hypothyroidism, the possible improvement of quality of life, and the possibility that SCH is a cardiovascular risk factor. Until there is widespread consensus, and appropriate large, well executed trials upon which to base recommendations, therapy of this subgroup should be individualized by taking into account patient preference, presence of symptoms, age, and associated medical conditions.

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