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SUB-CLINICAL HYPOTHYROIDISM: COMPLICATIONS AND EFFECTS OF THYROXINE THERAPY

S. P. JADKAR [*1], J. V. GANU [1] and K. N. PUJARI[1]

[1]Department of Biochemistry, Government Medical College, Miraj

*Corresponding Author Email: drsangitajadkar@gmail.com

ABSTRACT

Sub clinical hypothyroidism (SCH) is typically defined as elevated plasma TSH while free plasma T4 and T3 remain within normal range. SCH or mild thyroid failure is a common problem with a prevalence of 3% to 8% in the population. It increases with age and higher in women compared to men. There are various complications due to SCH such as, abnormal lipid metabolism, cardiac dysfunction, neurological, mental dysfunction, and neuromuscular dysfunction, psychiatric & cognitive dysfunction. The potential benefits and risks of therapy for SCH have been debated for two decades. The possible advantages of treating SCH generally fall in to 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 & therapy potentially decreases the risk of death from cardiovascular causes. Finally, treatment may reverse the symptoms of mild hypothyroidism, including psychiatric and cognitive abnormalities. This review includes a discussion on diagnosis of SCH, its complications and effects of therapy.

KEY WORDS

Sub-clinical hypothyroidism, Thyroxine therapy, Thyroid hormones.

INTRODUCTION

Sub clinical hypothyroidism (SCH) is typically defined as elevated plasma TSH while free plasma T4 and T3 remain within normal range [1]. With the advent of serum thyrotropin radioimmunoassay in the 1970s, the entity of mildly elevated TSH and normal thyroid hormones levels was recognized [2, 3]. Serum TSH has a log-linear relationship with circulating thyroid hormone levels. TSH is a sensitive and specific measure of thyroid function and serum TSH assay is the necessary test for diagnosis of mild thyroid failure when the peripheral thyroid hormone levels are within normal laboratory range [1]. The diagnosis of SCH is determined mainly by laboratory evaluations; because it has been observed that most patients exhibit few or no signs and symptoms of thyroid dysfunction .Some studies suggest that few patients do indeed have clinical, biochemical or functional manifestations of mild thyroid failure such as abnormal lipid metabolism, cardiac dysfunction and neurological and mental dysfunction [4].

Prevalence:

Sub clinical hypothyroidism or mild thyroid failure is a common problem with a prevalence of 3% to 8% in the population [5, 6], being higher in women (7-8%) as compared to men (2.8-4.4%). The age dependant increase in rates of SCH is higher in women than in men with near equal rates between genders around the mid 70s [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. Serum TSH of less than 10 mIU/L is observed in 80% of patients with SCH.

Diagnosis:

Other causes of raised TSH:

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].

Some drugs such as sulfonyureas, lithium, amiodarone, ethionamide, phenylbutazone, aminoglutethimide, and iodine can interfere with thyroid hormone production or release and secondarily result in a slight elevation of TSH. In addition, dopamine antagonist such as metaclopromide and domperidone may cause exaggerated TSH response to TRH stimulation by altering the inhibitory effect of dopamine on TSH secretion. Furosemide has also been shown to increase levels of TSH, especially in recovering critically ill patients. Other conditions that cause elevated TSH include thyroid hormone resistance, thyroid hormone secreting tumors (both should be associated with high free thyroxine level), psychiatric illness, adrenal insufficiency, renal failure, hyperprolactinemia and systemic illness [7].

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 [1, 8].

Reference Range of Serum TSH:

Lowering the upper limit of normal for the serum TSH level up to 3 to 2.5 mIU/L has been proposed. For this, the supporting argument was the higher level of antithyroid antibodies detected in persons with a serum TSH between 3.0 to 5.0 mIU/L and higher rate of progression to clinical thyroid disease [9]. But studies have shown that decreasing the reference range to 3.0 mIU/L will result in more than a 4 fold increase in diagnosis of hypothyroidism among patients without history of thyroid disease and no evidence supports a benefit for intervening at these levels of TSH [9].

Reference ranges for serum TSH was defined by an expert panel representing American Thyroid Asso, Am. Asso of Clin Endocrinologists as 0.45 to 4.5 mIU/L and SCH was defined as serum TSH more than 4.5 mIU/L with normal T3 and T4 values in the absence of symptoms [9]. The American thyroid association recommends screening for measurement of serum TSH beginning at the age of 35 yrs and every 5 yrs thereafter [10]. Because of potential implications of SCH for adverse outcome of pregnancy [11] and neuropsychiatric development of the fetus [12], aggressive case findings in pregnant women or in women anticipating pregnancy has been suggested [13].

Proposed Adverse Consequences of SCH:

Although studies have pointed to some adverse effects of SCH, no consensus exists as to the clinical importance of the adverse effects and the benefits of levothyroxine therapy, particularly for the 80% of patients with SCH who have a TSH of less than 10miu/l, because of the different levels of TSH and degrees of thyroid dysfunction in the studies [14, 15].

The potential benefits and risks of therapy for SCH 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 [16].

A discussion of some of the proposed adverse effects of SCH and effect of levothyroxine therapy follows:

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 [17]. 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 6miu/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 10 mIU/L [18].

Systemic Symptoms of Hypothyroidism:

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 [19]. 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 [20, 21]. In a previous scientific review in 2004 [13], 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 [22].

Lipid Abnormalities and Other Cardiac Risk Factors:

The Colorado Health Fair study showed that the mean total cholesterol level was 216 mg/dL (to convert to mmol/L, multiply by 0.0259) for euthyroid patient and 224 mg/dl for patients with SCH [23]. Several randomized studies have shown reduction of low-density lipoprotein cholesterol by levothyroxine therapy. However, most of the studies showing benefits are not categorized for serum TSH levels of 5.0 to 10.0 mIU/L. A meta-analysis of 13 studies concluded that lipid profile improved with therapy [24]. In a 2004 review, data were considered insufficient to show benefits of levothyroxine therapy on lipid levels [13]. In estimating, the possibility that lipid levels will improve with levothyroxine therapy is fair if the serum TSH level is greater than 10 mIU/L and questionable if the TSH level is less than 10 mIU/L.

In a large population based study, emerging risk factors such as elevated C-reactive protein, homocysteines and lipoprotein (a) levels were not found to have a role in SCH [25]. Improvement of endothelial dysfunction and insulin resistance after levothyroxine therapy has been suggested [26, 27]. In the absence of large scale randomized trials, evidence remains inconclusive.

The effects of sub clinical hypothyroidism on serum lipid levels remain controversial. Some [28], but not other [29], cross sectional studies have demonstrated that serum levels of total cholesterol and LDL cholesterol are higher in patients with SCH than in euthyroid controls. A recent meta-analysis of the effect of therapy for SCH on serum lipid levels demonstrated a mean reduction in the total cholesterol level of 7.9 mg/dl (0.2 mmol/L) & in the LDL cholesterol level of 10mg/dl (0.26 mmol/L) [30]. Changes in HDL cholesterol were heterogenous among the studies and were not statistically significant. Patients with higher cholesterol levels {≥ 240 mg/dl (6-21 mmol/L)} & patients with SCH as a result of inadequately treated overt hypothyroidism had greater reductions in

cholesterol levels. In patients with newly diagnosed SCH whose total cholesterol level was less than 240mg/dl, the mean reduction in total cholesterol was only 0.7 mg/dl (0.02mmol/L) which was not statistically significant. Small studies [31] have suggested that patients whose serum thyrotropin level is less than 10 mIU/L may have no reduction in cholesterol levels with thyroxine replacement, but the metaanalysis did not directly address this issue.

In a cross-sectional cohort study of middle-aged Dutch women, those with SCH were approximately twice as likely as euthyroid control women to have "atherosclerosis" 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 SCH, but published data are few and conflicting [32].

Adverse Cardiac End Points:

The cross-sectional Rotterdam Study showed an association of SCH with myocardial infarction and aortic calcification [33]. In contrast, the Wickham study [34] showed no increased cardiac mortality in a 20 year follow up. A more recent observational study did not show any association between unrecognized SCH and cardiovascular events or mortality [35]. However, several more recent meta-analyses of observational studies found an association between SCH and coronary artery disease [36-38]. The risk is lower when higher quality studies are pooled [37]. A recent analysis of 7 cohort studies concluded that the relative risk of all cause mortality was increased compared with euthyroid controls, particularly in patients with comorbid conditions [39]. Another metaanalysis of 15 studies showed an increased prevalence and incidence of cardiovascular mortality only in a relatively younger population [40]. Taken together, the findings of these recent metaanalysis suggest that a cardiovascular risk exists for persons younger than age 70 years with no effect for those aged 70 to 80 years and a possibly protective effect for those older than 80 years [41]. Thus, the cardiovascular risk issue remains controversial, and large scale, government sponsored, multicenter, randomized, placebo controlled studied are needed to assess the efficacy of levothyroxine therapy in risk reduction.

Cardiac Dysfunction:

Studies have shown slowed left ventricular relaxation time, increased vascular tone at rest, and left ventricular systolic dysfunction with exercise and impaired endothelial function [42]. Some studies have shown improvement of cardiac contractibility and systolic time interval with levothyroxine therapy [42]. No evidence exists to support an association between heart failure and a serum TSH level of less than 10.0 mIU/L. Again, most studies were not categorized for degrees of TSH elevation, and data remain insufficient for a TSH level less than 10miu/l but strongly suggestive for a TSH level greater than 10mIU/L.

In some studies (not all) resting pre-ejection period (PEP), left ventricular ejection time (LVET) was increased in SCH 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 SCH have subtle abnormalities in systolic time intervals, diastolic function and myocardial contractility that may improve during treatment [43].

Adverse fetal effects:

A seminal study by Haddaw et al [12] 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. Although this was a single study, it nevertheless points to the need for screening of pregnant women and therapy for mild thyroid failure in women who are pregnant or planning on becoming pregnant.

Neuromuscular Dysfunction:

It has been suggested that neuromuscular symptoms and dysfunctions are common in patients with SCH and can be reversed by levothyroxine treatment [44]. A definitive answer will require more studies with TSH levels stratified as less than or greater than 10 mIU/L.

Psychiatric and Cognitive Dysfunction:

Data related to aggravation of depression, bipolar disorder, and effects on cognitive function have been presented [45]. A recent study showed no association with anxiety, depression or cognitive dysfunction [20]. Nonetheless, it is still reasonable to have a low threshold for therapy for SCH in patients with depression, bipolar disorder and cognitive dysfunction.

Effects on Symptoms, Mood and Cognition:

The questions of whether persons with SCH have symptoms, and the extent to which the putative symptoms are reversible with thyroid hormone therapy, remain unanswered. Several studies have suggested that mild symptoms of hypothyroidism are more prevalent in patients with SCH than in age matched controls [29, 46, 47]. But not all studies have found this to be true [48].

Several studies have suggested that mild symptoms of hypothyroidism are more prevalent in patients with SCH than in age matched controls, but not all studies. There have been 3 published randomized, prospective, placebo-controlled trials of therapy for SCH. 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 (4.6m/L) 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 [49].

Patients with SCH 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 reported small but statistically significant improvements.

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

In women with SCH and ovulatory dysfunction, thyroxine therapy may restore fertility. Although difficulty losing weight to decrease with thyroxine therapy [49].

Recommendations for SCH:

Several randomized trials of thyroxine therapy for sub clinical hypothyroidism have been performed [50-53]. In one study, half the patients had fewer hypothyroid related symptoms with therapy [50]. In another study, thyroxine therapy improved psychometric test results. One study showed only improvement in memory scores. Some of these studies included patients with TSH levels as high as 39 mIU/L, and in some, fixed high doses of thyroxine were used [52]. Thus, the reported benefits are difficult to interpret. A recent randomized study in patients with serum TSH levels between 5 & 10 mIU/L

showed no clinical or metabolic benefit after 6 months of thyroxine therapy [53]. Thus, benefits of thyroxine therapy for patients with serum TSH levels between 5 & 10 mIU/L remain to be determined. The most convincing argument for therapy is the high rate of progression to overt hypothyroidism.

The American college of physicians stated that the available evidence is insufficient to make recommendations for or against the treatment of SCH [54]. However, the issue is still controversial. At present, some practical recommendations can be given. For patients with serum TSH levels higher than 10mIU/L, no controversy exists, and treatment is recommended. This strategy is justified because the rate of progression to overt hypothyroidism is high, and low density lipoprotein is reduced 8% with thyroxine therapy [55]. Thyroxine therapy for patients with SCH may improve quality of life, muscle function, mood, fertility, and cardiac function. For patients with TSH levels between 5& 10 mIU/L, observation or treatment is recommended on an individual basis. Younger patients with a relatively large goiter and thyroid peroxidase antibody positivity are usually treated. Symptomatic patients and patient with fertility problems should receive therapy.

Because of concern about possible aggravation of coronary disease symptoms, patients with SCH who have only mild elevation of serum TSH and normal serum thyroxine levels are usually followed up with a repeated TSH measurement & treated if there is progression of sub clinical thyroid disease. Children & aldolescents, pregnant women, & women contemplating pregnancy should receive treatment. Of note, in women with hypothyroidism who are receiving thyroxine therapy, the dose of thyroxine replacement may need to be increased 30% to 40% during pregnancy [56].

Observational data for possible adverse effects of SCH on the cardiovascular system are available [55]. A cohort study from Rotterdam showed that SCH in women older than 55 years with serum TSH levels between 4 & 10 mIU/L is strong risk factors, independent of cholesterol level, for atherosclerotic diseases & myocardial infarction [57].

In patients with SCH, a daily dose of 0.025 to 0.075 mg of levothyroxine is usually adequate to normalize serum sensitive TSH. The required dose varies with the level of serum TSH, serum thyroid hormones, & the age & weight of the patient. If the patients are already taking thyroxine, only a small increase is necessary. Serum sensitive TSH levels should be determined after 6 to 8 weeks of treatment to adjust the dose if necessary. Some thyroidologists aim for a serum sensitive TSH need to increase the replacement thyroxine dose for patients who have sensitive TSH levels between 3 & 5 mIU/L is anecdotal [58].

Screening:

Based on a computer model designed to assess cost effectiveness, Danse et al [59] recommended screening with serum sensitive TSH every 5 years in patients older than 35 years. Cost-effectiveness in women & patients older than 50 years is more substantial [59]. Recent recommendations from the American Thyroid Association are similar [60]. The American college of physicians recommends screening women who are older than 50 years but does not recommend screening younger women or asymptomatic men [54]. Consensus will be reached if more prospective randomized studies show benefits of therapy for SCH, the most common form of thyroid dysfunction. Recent evidence showed the adverse effects of SCH on neuropsychological development of the fetus, indicating the need for therapy for SCH in pregnant women [56]. These data point to

possible benefits of screening & therapy for subclinical thyroid disease in early stages of pregnancy, preferably before anticipated conception.

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***Corresponding Author:**
Sangita P. Jadkar
Department of Biochemistry,
Government medical College, Miraj-416410 (INDIA)
Email: drsangitajadkar@gmail.com