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Should Subclinical Hypothyroidism Be Treated?

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Abstract

Subclinical Hypothyroidism, SCH, has been detected with increasing frequency in recent years and has brought about major controversies regarding management and treatment [Meier et al., 2001]. The condition is characterized as having a high concentration of thyroid stimulating hormone, yet normal thyroid hormone levels and is often asymptomatic. Scientific articles retrieved from various databases helped determine some of the long term risk factors associated with SCH, including progression to overt hypothyroidism, fatty liver disease, cardiovascular disease, neuropsychiatric complications and reproductive malfunctions. Studies determining the clinical and metabolic effects of L-thyroxine hormone replacement therapy on symptoms and potential risks of SCH on various patient populations were investigated and compared to controls that were not treated or were given a placebo drug. After considering both the arguments promoting treatment and others opposing it, conclusions were drawn regarding the promotion or discouragement of hormonal treatment for patients in different age brackets and stages of life. In general, the greatest benefits of treatment are observed in patients with thyroid-stimulating hormone levels ranging over 10mIU/L, younger patients with slightly elevated thyroid-stimulating hormones who are at risk for cardiovascular disease and for pregnant women with gestational SCH. On the contrary, L-thyroxine treatment therapy is not as crucial for the elderly population or patients with slightly elevated thyroid-stimulating hormone values when there are no apparent symptoms of hypothyroidism being experienced.

Introduction

Describing a condition as 'subclinical' implies that it is asymptomatic, thereby suggesting that a less aggressive treatment plan is needed and possibly rendering the condition unworthy of treatment altogether. However, there is controversy regarding whether the condition is indeed 'subclinical' and if it is necessary or beneficial to treat. Hypothyroidism is an endocrinological disorder in which there is inadequate production of thyroid hormones, triiodothyronine (T3) and thyroxine (T4) by the thyroid gland. These hormones strongly influence energy metabolism, digestion and body heat production. Additionally, they play a key role in cardiac contraction rate, memory, psychological health and sleep. In the case where the gland itself fails to secrete sufficient hormone concentrations, the disease is considered primary. However, if the root of the problem is traced back to insufficient stimulation of a structurally healthy gland due to decreased thyroid-stimulating hormone (TSH) released from the adenohypophysis, then the condition is regarded as secondary or central. Diminished secretion of thyrotropin-releasing hormone (TRH) from the hypothalamus would cause the condition to be considered tertiary hypothyroidism [Hadley & Levine, 2007; Wiersinga, 2010]. Subclinical hypothyroidism (SCH) ranks as a grade of primary hypothyroidism and is characterized biochemically as an elevated serum TSH concentration, with a normal serum-free T4 level, as well as T3 level [Meier et al., 2001]. When a patient's thyroid function is normal and hormone secretion is balanced according to homeostasis, he/she is considered euthyroid. Euthyroid adults should exhibit TSH levels within a range of 0.2-7.6 mIU/L, a T3 concentration of 4.3-12.5 mcg/dL and a free T4 concentration of 0.7-1.7 ng/dL [Robertson, Shilkofsky 2005]. Some experts have suggested that the TSH upper limit should be only 2.5 or 3 mIU/L, while others argue that the serum TSH distribution gradually shifts towards higher values with age and must be adjusted accordingly. Others have proven through their studies that the accepted reference range for serum TSH should be altered as patients age and that maintaining a 4.5 mIU/L upper limit for TSH concentration results in the prevalence of SCH to be significantly overestimated in the

elderly population. Nonetheless, while there is controversy over the appropriate upper limit of normal serum TSH, most laboratories agree that it is 4 to 5 mIU/L [Surks et al., 2007]. Biochemical testing and laboratory test results alone are required in order to diagnose SCH since patients often present with vague symptoms elevated TSH levels. Much research has been done regarding whether to treat SCH in populations of various age brackets and stages. A general consensus has been reached based on the existing and potential risk factors involved and the success rates of levothyroxine thyroid hormone replacement.

Methods

Relevant information was accumulated via original research literature obtained from databases such as Google Scholar, Proquest, Pubmed and Touro College's Online Library. Medical journals, JCEM and JAMA, served as a source of information as well. Books, including a medical book and science textbook, were used to provide background information. All content was critically analyzed and compared to assure validity.

Epidemiology

Based on the results of population-based studies, the prevalence of SCH in adults ranges from 4 to 15 percent [Turnbridge et al., 1977] and affects approximately 10 million people in the United States [Huber et al., 2002]. In one of the best longitudinal studies conducted, Turnbridge et al. (1977) found that 7.5% of women and 2.8% of men of all ages in Whickham, England have TSH levels exceeding 6 mIU/L. Twelve such studies done within different cultures, similar to theirs, were reviewed, and they concluded that primary thyroid-gland malfunction occurs in approximately 5% of any population. Of the 16,533 participants in the United States Third National Health and Examination Survey (NHANES III), 4.3% had SCH [Hollowell et al., 2002]. Of the 25,862 participants included in the Colorado Thyroid Disease Prevalence Study, an elevated TSH level was found in 9.5% of the population [Canaris et al., 2000]. Furthermore, the frequency of SCH is found to be higher in females than males,

risks with age and is less in blacks than in whites [Kanaya et al., 2002]. It is important to note that since thyroid hormones contain iodine, the inhabitants' thyroid functioning is highly dependent on the iodine reserve of their specific region. When analyzing population-based studies, it's crucial to consider how the degree of iodine repletion or depletion in that geographical environment affects its populations intake and in turn, thyroidal health [Laurberg et al., 1998]. For example, in Africa, lack of dietary iodine is the chief determinant of thyroid pathology, instigating a spectrum of iodine deficiency disorders, including hypothyroidism [Okosieme, 2006].

Clinical Findings

While the clinical manifestations of SCH vary, patients sometimes report mild signs and symptoms similar to those experienced due to overt hypothyroidism. However, these symptoms are characterized as neither sensitive nor specific [Meier et al., 2001]. Based on the Colorado Thyroid Disease Prevalence Study involving 2,336 participants with SCH, symptoms reported by patients with SCH included dry skin (28%), poor memory (24%), slow thinking (22%), muscle weakness (22%), fatigue (18%), muscle cramps (17%), cold intolerance (15%), puffy eyes (12%), constipations (8%) and a hoarser voice (7%) [Canaris et al., 2000]. Conflicting data is seen from a community-based cross-sectional study where 1,423 participants, ranging from ages 18-75 years old, had TSH screenings and their symptoms were evaluated. The data collected indicated that subclinical thyroid disease is not associated with lower well-being or impaired health-related quality of life. Therefore, attempts to clinically identify SCH based on reported symptoms are unsuccessful [Bell et al., 2007]. However, significant evidence highlights numerous long-term consequences of SCH, though they do not appear obvious from patients' reports.

Progression to Overt Hypothyroidism

A significant number of patients with SCH eventually develop overt hypothyroidism. In a study done by Huber et al., after a mean observation period of 9.2 years, 23 out of 82 patients (28%) who entered the study with subclinical hypothyroidism developed overt hypothyroidism, as defined by low T4 concentration and elevated TSH (>20 mIU/L). The risk of progression to overt hypothyroidism was seen to correlate to the initial serum TSH level of the patient; the higher the concentration, the greater the risk. Of the 82 women with TSH concentration values ranging from 4-6 mIU/L, the frequency of progression to overt hypothyroidism was 0% after 9.2 years. When only the patients with a serum TSH concentration above 6 mIU/L were evaluated ($n = 61$), after 10 years, the cumulative incidence of overt hypothyroidism was 55.3% [Huber et al., 2002]. Overt hypothyroidism is particularly common in older patients whose TSH levels exceed 10 mIU/L or those who have circulating thyroid

antibodies [Ayala et al., 2000]. Obviously, overt hypothyroidism poses a greater threat to one's overall health related quality of life as it presents with classical symptoms of fatigue, depression, weight gain, cold intolerance, bradycardia, constipation, dry skin, facial edema and loss of hair [Carle et al., 2014]. More severe dysfunction of the thyroid gland also stimulates a negative feedback mechanism in which more and more TSH is secreted, ultimately causing the gland to swell, referred to as goiter.

Fatty-liver Disease

Since thyroid hormones play a fundamental role in lipid metabolism, mild hypothyroidism may cause hypercholesterolemia and play an essential role in the pathogenesis of non-alcoholic fatty liver disease (NAFLD). Non-alcoholic fatty liver disease is defined as "extrahepatic accumulation of fat in the absence of excess alcohol consumption" [Liu et al., 2017]. A cross-sectional study reported the prevalence of fatty-liver disease and abnormal liver enzyme levels to increase progressively with rising TSH levels compared to patients with euthyroidism, suggesting associations between the spectrum of SCH and liver malfunction. In one study population, the incidence of fatty-liver disease and abnormal liver enzyme level was 29.9% and 20.1%, respectively, for patients with SCH [Chung et al., 2012]. SCH patients experience higher amounts of liver aspartate aminotransferase (AST) and alanine aminotransferase (ALT), an enzyme released into the bloodstream when the liver is damaged [Liu et al., 2017].

Cardiovascular Disease

Thyroid hormones are known to affect the heart and vasculature. As a result, the impact of SCH on the cardiovascular system has become an important subject of research [Liu et al., 2010]. While it is undisputed that overt hypothyroidism is linked to increased risk for cardiovascular diseases (CVD), conflicting data raises controversy whether SCH is also associated with heart disease. Heterogeneity among individual studies can be explained by the different TSH cutoffs used, varying cardiovascular disease definitions or differences in participants' age, gender, or severity of SCH (as measured by TSH level) [Rodondi et al., 2010]. Clinical hypothyroidism has been known to cause an increase in blood pressure. Since thyroid hormone directly acts on arterial smooth muscle cells of blood vessels, causing vasodilation, when hypothyroidism occurs, a lower hormone level increases the vascular resistance and in turn the level of blood pressure. In a cross-sectional survey the incidence of high blood pressure, hypertension, in the SCH group was significantly higher than the control, the euthyroid group. The conclusions drawn from this study coincide with previous data collected by Luboschitzky et al. in 2002 [cited in Liu et al., 2010].

Furthermore, since SCH has been linked with abnormal lipid metabolism, it is consequently related to increased risk for coronary heart disease. An increased serum total cholesterol

and low density lipoprotein cholesterol (LDL-C) was detected as a feature of SCH in some of the literature, while contrasting research found cholesterol levels to be in normal range. Nonetheless, several studies suggested a connection between SCH and development of atherosclerosis, and more recently published research established SCH as a risk factor for myocardial infarction [Meier et al., 2001; Anderson et al. 2015]. A meta-analysis from 7 studies, including 2,020 patients with SCH, confirmed a substantial trend of increased risk of coronary heart disease by highlighting events like nonfatal myocardial infarction, angina and necessary coronary revascularizations common to patients with elevated serum TSH concentrations, especially of those that were 10 mIU/L or greater. Results from a meta-analysis of patient-level data from 11 prospective cohort studies showed greater risk for coronary heart disease mortality for patients suffering from SCH with serum TSH concentrations above 10mIU/L. Rodoni et al. reported increased systemic vascular resistance, arterial stiffness, altered endothelial function, increased atherosclerosis and altered coagulability to be associated with SCH and the acceleration of development of coronary heart disorder. On the contrary, minimal TSH elevation (4.5-6.9 mIU/L) was not linked to cardiovascular disease or mortality [Rodoni et al., 2010].

Neuropsychiatric Symptoms

While there is evidence that SCH is linked to neuropsychiatric complications, there has been conflicting research as well. One study assessed the history of major depression in subjects with SCH compared to euthyroid subjects. The frequency of depression was substantially higher in those who met the criteria for SCH (56%) than in those who did not (20%), suggesting that SCH may lower the threshold for the occurrence of depression [Haggerty et al., 1993]. Similar results were found in a later study where signs of neuropsychiatric dysfunction like somatization, cognitive impairment disturbances, psychomotor retardation and sleep disorders were seen in 63.5% of a population with mild thyroid failure [Demartini et al., 2010]. However, another study revealed opposite research as patients with SCH scored equally as well as the euthyroid control group on 14 cognitive function tests [Jorder et al., 2006].

Reproductive Malfunctions

Alteration of the thyroid's physiology under the impact of placental human chorionic gonadotropin (hCG) during the first trimester, results in adjustments to TSH levels. During the first trimester, a white woman maintains an upper limit TSH concentration of 2.5 mIU/L and 3.0 mIU/L during her second and third trimester periods [Stagnaro-Green et al., 2011]. SCH during gestation poses fewer risks than overt hypothyroidism would, but still puts women at increased risk for preterm delivery at or before 34 weeks of gestation, placental abruption (3 times more

likely to occur in women with SCH) and/or pregnancy loss compared to euthyroid women. Severe preeclampsia, defined as gestational hypertension is noted as a risk factor for pregnant women with SCH [Casey et al. 2005; Novakovic et al., 2018]. A meta-analysis of 15 cohort studies involving 1,896 pregnant women with SCH arrived at conclusions similar to Novakovic et al. and showed that SCH during gestation causes significant impairment to the intelligence and neurological development of the offspring [Liu et al., 2018].

It's possible to acquire SCH as a result of pregnancy; an estimated 15% of pregnancies in the U.S are affected by gestational SCH [Blatt et.al., 2012]. Over the gestational period, increased metabolic needs result in increased production of thyroid hormones by approximately 50% compared to euthyroid, non-pregnant women. Consequently, necessary daily iodine intake levels rise by 50%. More renal blood flow and glomerular filtration results in an increase in iodide clearance from blood plasma. Thus, more iodine is necessary in the diet of a pregnant woman. The stress imposed on the thyroid gland during gestation results in SCH for many women with compromised dietary iodine levels. Clinical studies have proven that iodine deficiency during gestation causes impaired development of the brain and impedes mental function development of the fetus [Farebrother et al., 2015]. Measuring the IQ of children whose mothers had not been treated for SCH during pregnancy revealed mean IQ scores of 7 points lower than controls [Haddow et al., 1999]. Casey et al. (2005) proposed that preterm parturition results in prematurity which contributes to neurodevelopment delay and reduces intelligence quotient.

Effects of Levothyroxine Hormone Replacement

In general, the research showing correlation between T4 replacement and improvement of hypothyroid symptoms is conflicting and is probably due to differences in the populations studied, various TSH cut-off concentrations and age range. Levothyroxine, which is a synthetic form of T4, is usually administered to patients suffering from overt hypothyroidism. Nevertheless, there is much controversy whether patients exhibiting mild thyroid failure with similar symptoms should be prescribed levothyroxine as well [Meier et al., 2001]. Some, but not all, research conducted show how treatment facilitates improvement of hypothyroid symptoms experienced by patients with SCH. Subjects with mild thyroid failure who were treated with L-thyroxine showed significantly greater improvement in overall hypothyroid symptoms than did subjects who were given placebo [Cooper et al., 1984]. Nonetheless, in all the clinical trials reviewed, with ongoing dosage monitoring, L-thyroxine succeeded in lowering previously elevated TSH concentrations to healthy levels.

By decreasing TSH concentration to euthyroid levels, L-Thyroxine prevents the progression to overt hypothyroidism

[Ayala et al., 2000]. Following T4 treatment, ultrasound verified 80% thyroid volume reduction in patients with goiter [Romaldini et al., 1996]. In one study, L- thyroxine and a placebo drug were randomly administered to 63 female patients over a span of 48 weeks in order to achieve euthyroid TSH levels. In the thyroxine treated group, the mean serum TSH concentration was 12.8 ± 1.4 mIU/liter before and 3.1 ± 0.3 mIU/liter after treatment, whereas TSH levels remained unchanged in the control group.

When lipid concentrations were measured after thyroxine treatment, it was observed that the total cholesterol and low density lipoprotein cholesterol decreased substantially, especially in those with TSH concentrations of 12 mIU/L and above. From the observed improvement, it is approximated that treatment reduces the risk of cardiovascular disease and mortality by 9-31%. In contrast, no change in any variable of thyroid function occurred in the placebo group (Meier et al., 2001). Substantial improvement of cardiac function in treated patients was reflected by a sensitive measure of myocardial contractility [Cooper et al., 1984]. In a study done in Copenhagen, Denmark, the participating cohort included patients over 18 years old with the mean age being 55.2 years. The total of 12,212 subjects were subdivided into 2 groups, one with TSH levels of 5-10 mIU/L and another with TSH levels above 10 mIU/L; some were treated from both groups. In this large cohort study no association between treatment and risk of myocardial infarction or mortality was revealed, besides in younger patients where it may seem that treatment had marginal protective advantage. However, limitations of the study such as no access to patients' blood pressure or serum lipid levels and a relatively short follow-up period of 5 years cause it to have less credence since patients could have suffered from cardiac complication later on in time [Andersen et al., 2015].

A study involving 415 patients with SCH (defined as TSH ≥ 4.2 mIU/L) administered levothyroxine to measure its effect on non-alcoholic fatty liver disease and abnormal liver enzyme levels. After treatment with LT4, the incidence of fatty liver disease in patients with more pronounced SCH (TSH concentration ≥ 10 mIU/L) reduced from 48.5% to 24.2%, while in patients with milder SCH (TSH concentration 4.2-10 mIU/L), frequency of fatty liver disease and alanine aminotransferase was not significantly altered by LT4 supplementation. However, mild SCH patients with elevation of total cholesterol who received LT4 treatment showed decreases in the incidence of fatty liver disease and serum alanine aminotransferase levels. Those with higher TSH values experienced a decrease of 5.61 IU/L in serum aspartate aminotransferase and a small decrease in serum alanine aminotransferase. Patients with milder SCH showed a reduction in serum alanine aminotransferase from 19.09 IU/L to 17.95 IU/L, yet serum aspartate aminotransferase remained stable throughout the study in the untreated, mild SCH control

group. Observing how these parameters became less prevalent in patients who received treatment, but remained comparably stable in patients who weren't treated, provides concrete evidence of the success LT4 therapy has with prevention of non-alcoholic fatty liver disease [Liu et al., 2017].

In another randomized double-blind, placebo-controlled trial, TSH values decreased by 8.6 mIU/L. Patients treated with LT4 showed improved psychometric memory score involving their thinking, memory and attention versus untreated control patients [Jaeschke et al., 1996]. Unfortunately, in another study, LT4 treatment was not enough to generate complete remission of depressive symptoms, suggesting psychiatric evaluation in patients affected in this way by SCH is needed [Demartini et al., 2010].

Regarding SCH during gestation, miscarriage was significantly less frequent among treated women compared to untreated women in a national U.S. cohort of 5,405 pregnant women. However, the treated group also had increased odds for preterm delivery, gestational diabetes and preeclampsia [Maraka et al., 2017]. Conflicting data claims LT4 decreased the rate of preterm delivery considerably in pregnant women who received treatment compared to their control who did not (SCH defined as TSH ≥ 4 mIU/L; 5.3% incidence for treated women versus 29.4% in control group) [Nazarpour et al., 2017]. Further complicating the matter, another study revealed no difference in the prevalence of preterm delivery, gestational hypertension, miscarriage rates or adverse fetal outcomes between women who received LT4 treatment and those who got the placebo [Casey et al., 2017]. During pregnancy, beginning treatment for compensated maternal iodine status to ensure proper brain development in the fetus is extremely time-sensitive; until the end of the second trimester, iodine treatment protects the neurological system from consequences of iodine deficiency. Since head circumference reflects brain mass, the head circumference of an underdeveloped child will be significantly diminished. Microcephaly, where head circumference is more than 3 standard deviations below the norm, was diagnosed in 27% of children of untreated mothers as opposed to 11% frequency in their treated control [Cao et al., 1994]. Yet, opposing data says that no significant discrepancies are noted when comparing IQ scores and neurodevelopment of 5 year old children of mothers who received LT4 to those who took the placebo drug [Casey et al., 2017]. Additional research trials are needed to determine whether LT4 therapy during gestation prevents adverse outcomes, possibly induces some issues or simply doesn't have any effect at all.

In opposition to treating SCH, various studies, such as the meta-analysis of 12 clinical trials (9 of them with TSH concentration cut-offs of less than 10, 12 and 15 mIU/L), show no changes in hypothyroid symptoms or quality of life in the treated group versus the control, the group who received the placebo

drug [Villar et al., 2007]. While SCH and cognitive dysfunction have been linked, T4 treatment in a population over 65 years of age proved it to be ineffective for aiding cognitive function [Parle et al., 2010]. Similarly, a double-blind, randomized, placebo-controlled, parallel-group trial involving 737 adults (65 years of age+, TSH levels ranging from 4.60-19.99 mIU/L with a mean TSH of 6.40 ± 2.01 mIU/L) concluded that there are no apparent benefits to L-thyroxine treatment in the quality of life in older adults. There was no benefit observed in regard to hypothyroid symptoms, executive cognitive function as measured by the letter-digit coding test or degree of lethargy experienced by the group whom received treatment. However, after 12 months, the mean TSH level was 5.48 ± 2.48 mIU/L in the placebo group, as compared with 3.63 ± 2.11 mIU/L in the levothyroxine group; clearly, in terms of reaching healthy TSH levels, the treatment was successful [Stott et al., 2017].

While research supports that untreated SCH during pregnancy is linked to many adverse obstetric outcomes, many claim that insufficient evidence exists supporting the benefit of LT4 therapy on clinical improvement for women with SCH. Implementing guidelines to treat all pregnant women with SCH would lead to prescription of LT4 for up to 600,000 pregnant women in the U.S every year which would obviously have enormous impact on the cost of healthcare [Maraka et al., 2017]

Strengthening the argument that SCH should not be treated, there is potential danger for a patient to overdose on levothyroxine, causing TSH values to decrease abnormally. Statistical analysis claims that the incidence of this is as frequent as 10-33% as treated SCH patients exhibit unusually low TSH levels. Overtreatment would completely reverse the original condition inducing symptoms of excess thyroid hormone. Many times, this is due to polypharmacy and drug interaction; research done reiterates the importance in monitoring TSH therapy in the older population, because of risk of over-replacement. In their trial with 339 thyroid hormone users, 41% had a low TSH, 16% had a high TSH, and 43% were in the euthyroid range after treatment [Parle et al., 1993; Somwaru et al., 2009]. Additionally, those against treatment resent the lifelong commitment to daily medication in asymptomatic patients, and the cost for both the hormone and for consistent monitoring of its efficacy.

Conclusion

Based on the results of T4 replacement successfully reducing hypothyroid symptoms and potential risks associated with SCH in certain populations, it is recommended that LT4 replacement be given to those patients who present with abnormal thyroid function tests. The most obvious benefit appears to be limited to patients with baseline TSH levels of ≥ 10 mIU/L as they are most likely to experience progression to overt hypothyroidism, atherosclerosis, myocardial infarction and non-alcoholic fatty liver disease. The research regarding pregnant women with SCH

poses no doubt to experts and healthcare providers in their unanimous decision to err on the side of caution and prescribe levothyroxine substitution for both the mother's and fetus's advantage. Adverse obstetric effects and risk factors far outweigh any arguments against treatment. However, treatment of patients with minimally elevated TSH values (between 4.5 and 10 mIU/L; differing depending on individual study TSH cut-off) demonstrated minimal change in health related quality of life and only burdened patients with responsibilities to monitor treatment and cover its cost, suggesting that these patients not be treated. However, based on the increased protection against cardiovascular disease and mortality in treated younger patients (<65 years) with TSH ranging from 7 to 9.9 mIU/L, some recommend treatment. But in the elderly population where LT4 treatment exacerbates the issue of polypharmacy and may instigate harmful drug-interactions, coupled with the fact that there is a lack of treatment trials showing benefit of treatment in this population, only those who present with symptoms suggestive of hypothyroidism should be treated. Of course, long-term monitoring and annual clinical evaluation of TSH concentration should be implemented to help ensure optimal dosage. Whether reference ranges should be adjusted for age, implementing a higher cutoff for starting treatment in older patients, awaits further research. Future research clarifying the reference ranges for thyroid function tests, specifically the upper limit for TSH, will help resolve conflicting data and enable researchers to easily compare data from different clinical trials in order to determine whether or not the condition requires levothyroxine treatment.

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