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Subclinical Hypothyroidism and its Associated Disorders

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Abstract

Subclinical hypothyroidism is an early, mild form of hypothyroidism, a condition in which the body doesn't produce enough thyroid hormones. These hormones are required for normal heart, brain, and metabolic functions. Subclinical hypothyroidism is diagnosed with a blood test. Normal reference range for TSH is considered to be 4.5 mIU/L or 5.0 mIU/L slightly elevated TSH levels along with normal range T3 and T4 hormones are considered to be presentation of SCH. Whether to treat these patients with thyroxine is still a question of debate. SCH is associated with various signs and symptoms. It is highly recommended to use thyroxine in SCH pregnant patients as there are convincing reports of danger to mother and fetus. Infertile SCH females have also shown to benefit with thyroxine therapy. SCH has also been linked with effects on cardiovascular disorders, lipid abnormalities, DVT, weight changes, neuropsychiatric disorders and male infertility. The data, however, is not adequate and further large-scale studies are required.

Keywords: Thyroid stimulating hormone; Tri-iodothyronine; Tetra-iodothyronine; Subclinical hypothyroidism

Abbreviations: DVT: Deep venous thrombosis; CVS: Cardiovascular system

Subclinical Hypothyroidism

Subclinical hypothyroidism, SCH is a condition in which thyroid stimulating hormone (TSH) is mildly elevated, with serum T3 and T4 levels being in normal range. The range of TSH is for diagnosis of SCH is between 4.5 mIU/L-10 mIU/L [1]. This state denotes a mild failure of gland which could be due to many reasons, most common being autoimmune disease. There is increase tendency in women to develop SCH. Old aged and black coloured individuals are also more prone to develop SCH.

Although this is more common in females, after age of 60, males and females have equal tendency to develop it [2]. A study conducted in United States, SCH was evidenced in 14% of 16533 persons evaluated [2]. The prevalence of this disease is indicated to be from 3% to 14% [3,4]. Many factors can lead to hypothyroidism, such as exposure to radiation, removal of the thyroid gland, drug induced causes (lithium, amiodarone) or inadequate treatment for thyroxine replacement. Other than these factors, autoimmune thyroid disease is the main etiological cause [5]. While diagnosing a patient with SCH, it is essential to exclude temporary elevations in TSH due to certain conditions such as heterophil antibodies affecting the assay, adrenal insufficiency, resistance to thyroid hormones, inadequacy of adrenal gland and TSH producing adenoma [6]. SCH has been misdiagnosed in elderly patients as advancing age leads to an increase in TSH levels [7].

The thyroid profile is usually repeated in a month or two to confirm whether patient has SCH or not. It is recommended to treat patients with thyroxine who have TSH levels above 10 mIU/l [8,9]. The treatment for patients with TSH levels in SCH range is still not clear and a question of debate.

Progression of SCH to Overt Hypothyroidism

If the patients have positive antithyroid antibodies, and goiter, their chances to develop overt hypothyroidism increases, increased by 4.3% per year [10]. If TSH values increase above 2 mIU/l along with positive anti thyroid antibodies, there is a further increased risk of developing overt hypothyroidism [10]. A study including 107 SCH patients reported progression to full blown hypothyroidism in 26.8% with higher TSH levels being a significant indicator [11]. However, a study reported 52% of SCH patients with TSH below 10, spontaneously recovered [12].

SCH Effects on Lipid Profile and Cardiovascular Risk Factors

Thyroid hormones have effects on lipid profile, with evidence that increasing TSH levels have a direct linear increase in total cholesterol, triglycerides, LDL, and a decrease on HDL levels [13].

A meta-analysis of 16 observational studies linked SCH with increased levels of total cholesterol, low density lipoproteins (LDL-C) and triglycerides. However high density lipoproteins (HDL-C) levels had no significant changes [14]. SCH has also been associated with cardiovascular diseases including increase in blood pressure and, arteriosclerosis, this risk increases with higher levels of TSH [15]. In a meta-analysis of seven cohort studies including patients with SCH and without SCH, it was found that cardiovascular events were higher at TSH levels >10 mIU/l, and minimal at lower levels of elevations (4.5-6.9 mIU/l) [16]. In another analysis of six cohort studies, higher TSH levels (10-19.9 mIU/l) were associated with increased risk of heart failure, as compared to a negligible trend in patients with lower TSH levels (7.0-9.9 mIU/l) [17].

There is limited data suggesting the use of thyroxine in regards to lipid and CVS benefits. In a meta-analysis study carried out on 350 patients, it was found that therapy with levothyroxine had beneficial effects on lipid profile and echocardiographic parameters such as myocardial relaxation [18], however evidence pertaining to TSH levels below 10 is still. Some studies do indicate the benefit in cardiac contractility and systolic time interval but then again the range of TSH levels was not indicated clearly [19]. However, a clinical review suggested that treatment with thyroxine in mild thyroid failure lowered total cholesterol levels and LDL levels in patients [20].

Some studies have indicated a beneficial response to therapy with T4 in atherosclerosis causing lipids with TSH between 2.5-4.5 mIU/L [21,22]. A report indicated that patients with SCH (median 6.3 mIU/l) and pre-existing heart failure had a higher rate of mortality as compared with euthyroid candidates [23]. Recommendation is to treat patients with TSH over 10 mIU/l, as studies have shown benefit of treatment with thyroxine on serum cholesterol levels in patients with higher TSH levels (10 mIU/l) [24].

SCH and Neuropsychiatric Symptoms

Thyroid hormones are essential for neurodevelopment and functioning. Studies have shown a link between thyroxine and cognitive function augmented by cholinergic activity [25]. In another study higher thyroxine levels were associated with enhanced visual, psychomotor and verbal activity [26]. Further studies have linked cognitive impairment with increasing TSH levels [27]. In a RCT, after inducing SCH, it was found that treatment with T4 improved mental health and motor coordination [28]. In the contrary a 6-month study, thyroxine replacement in female patients with TSH levels between 5-10 mIU/l showed no benefits in symptoms such as anxiety, depression, weight, and lipid profiles [29]. A meta-analysis concluded that there was no evidence of association between SCH and cognitive impairment in healthy, social elderly persons [30]. In some studies, it was found that patients with SCH had poorer responses to antidepressant therapy [31] and that risk to develop depression during life was higher for SCH (56%) as compared to those who did not have this condition [32].

SCH and Effects on Weight

Weight gain is one of the reported symptoms of hypothyroidism. In a 5-year study carried out in Denmark, it was found that women with TSH levels above 3.6 mIU/l had a slightly increased risk of weight gain as compared to those who had a TSH in the range 0.4-0.99 mIU/l [33]. Older women with SCH (mean value 6.7 mIU/l) have been linked to weight changes [34]. A community based longitudinal study of 11 years has also reported an association of weight change and SCH [35]. Another 6-year longitudinal study observed a direct link with increasing T3, T4 and risk of obesity [36]. In the contrary, a large scale study done on middle aged and elderly subjects yielded no association between SCH and weight gain [37].

SCH and DVT

Hypercoagulable states have been reported in overt and SCH states a pilot study on 50 adults observed 14% of patients had an association between unprovoked DVT and SCH [38]. A prospective multicenter cohort study on elderly patients concluded that subclinical hyperthyroidism was associated with a decreased risk of recurrence venous thromboembolism whereas SCH patients showed a non-statistically significant pattern of an association with rVTE (recurrent venous thromboembolism) especially in the first year of follow-up [39]. Data is limited pertaining to this issue and larger studies are required to confirm these findings.

SCH and Pregnancy

Thyroid dysfunction during pregnancy can have deleterious effects, both to the mother and fetus. Hypothyroidism in pregnant women can lead to hypertension, preterm labor and eclampsia [40]. Fetal outcomes include still birth and premature delivery and low intellect [40]. Studies also indicate low intellect in children of mothers with SCH [41,42]. Euthyroid mothers with positive thyroid antibodies have also shown to have children with low intellect [43]. There is evidence that thyroxine therapy can reduce the risk of miscarriage in mother and lack of intellectual and psychomotor development in children [43]. Thyroxine levels are of utmost importance in a pregnant woman, as shown in a study of pregnant mothers that T4 levels near 10th percentile (even with normal TSH levels), had children with low intellectual and psychomotor development [44,45]. It is recommended for a pregnant woman that the TSH should be <2.5 mIU/l, with T4 in normal range. According to ATA guidelines, thyroxine should be initiated if she is diagnosed with hypothyroidism or has positive antithyroid antibodies and TSH>2.5 mIU/l. According to these guidelines, during pregnancy, the reference range for TSH in first trimester is <2.5mIU/l and in the second and third trimester between 3.0-3.5 mIU/l.

SCH and Infertility

Thyroid hormones are essential for normal sexual function in both males and females. They have a strong influence on the maturation and spermatogenesis in males. Both hyper functioning and hypo functioning thyroid gland has effects on sperm motility and function [46]. Studies on hypothyroid males have shown a decrease in the levels of progesterone and testosterone.

A study conducted on 1072 infertile men indicated a decrease in overall gonadal function in hypothyroid males with significant decrease in gonadal steroids [47]. Hypothyroidism adversely affects erectile function and semen quality in men. A study conducted on 24 patients with hypothyroidism and 66 normal individuals indicated erectile dysfunction along with oligospermia, low sperm motility and abnormal morphology [48]. A study indicated 30% of 394 infertile females had hypothyroidism (TSH>4.2 mIU/l). Out of these hypothyroid patients 77% conceived on treatment with thyroxine within 6 weeks to 12 months [49]. Thyroxine also decreased the high prolactin levels in these women [49]. Another study conducted on 69 SCH infertile females observed that treatment with thyroxine resulted in 58 patients conceiving successfully [50]. This study also indicated a shorter duration of infertility. A similar study including 96 SCH infertile females observed pregnancy in 33.7% of subjects after treatment with thyroxine within 6 months to 2 years [51].

Conclusion

Studies pertaining to SCH and its associated symptoms are still lacking. The data in regard to treating these patients with thyroxine is even more limited. Large scale studies are required to understand the effects and treatment options in these cases. There is strong consensus backed up by scientific data for treating pregnant SCH females with thyroxine. This replacement has prevented miscarriages, preterm labor

and low intellect in children. Thyroxine replacement has also been beneficial for infertile female patients with SCH. It has increased the conceiving rates in such cases. SCH and its association with CVS disorders, DVT lipid abnormalities, depression and weight changes still requires extensive studies. However, patients may be given a trial of low dose thyroxine in certain cases such as lipid abnormalities, refractory depression. SCH patients who have goitre and/or positive antithyroid antibodies usually develop overt hypothyroidism; therefore, thyroxine can be initiated in these cases.

Finally, the age of patient should be considered when giving a trial of thyroxine in SCH patients as there is increased risk of cardiac arrhythmias and angina in elderly [52]. Patient preference and decision is yet another key factor in determining the decision of initiating thyroxine therapy [53].

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