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A Review on Subclinical Hypothyroidism: Decision Whether to Treat or Not?

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Abstract

Subclinical hypothyroidism (SCH) is a condition of mild thyroid failure in which there is slightly raised concentration of thyroid stimulating hormone (TSH) (> 5mIU/L) is seen but with normal concentration of free tetra-iodothyronine (FT4) hormone in blood serum. This underactive thyroid condition among peoples worldwide varies from 4-10 % and this SCH condition is more common in females than males. But there is high chance of SCH cases for progression to overt or clinical hypothyroidism with time. The general symptoms of SCH are tiredness, decreased cognition, sleep disturbances, tingling, cold feeling etc and cardiovascular risk factors are associated if left untreated. For screening purpose and initiating levothyroxine treatment large randomized clinical investigation is necessary. At present, levothyroxine therapy is recommended for SCH patients of TSH level > 10 mIU/L and individualized therapy based on symptoms is made for all SCH cases in which TSH level < 10 mIU/L. In this review, we discuss when we should start levothyroxine treatment for SCH patients and what are the outcomes after the levothyroxine treatment in detail.

Keywords: Subclinical hypothyroidism; Levothyroxine therapy; Tetraiodothyronine

Introduction

Subclinical hypothyroidism (SCH) is a mild failure condition of thyroid in which there is slightly raised levels of thyroid-stimulating hormone (TSH) in blood serum but with normal free tetra-iodothyronine (FT4) hormone level. The normal range for TSH is 0.3-5mIU/L for healthy euthyroid patients and for subclinical hypothyroid patients the TSH value is < 10 mIU/L but more than 5 mIU/L with normal FT4 value and hypothyroid patient is having TSH > 10 mIU/L but lower FT4 level in blood serum (1-3). In hypothyroidism the thyroid gland is hypoactive and unable to synthesize the required tetra-iodothyronine (T4) hormone and so the TSH level increases so as to enhance the FT4 hormone and hence TSH is >10 mIU/L. In study carried in whickham, england by Tunbridge et al, it was found that 7.5% women and 2.5% of men irrespective of their age suffered from slightly raised TSH level >6 mIU/L. Worldwide the SCH is varying from 4 to 10 % [1-3].

The symptoms may vary from patient to patient and the different symptoms commonly observed are tiredness, cold feeling, tingling sensation, weight gain, decreased cognition, depression, sleep disturbances etc. If left untreated, then there is possibility of arising different complications like hyperlipidemia, cardiovascular disease etc [4-6]. The treatment strategy also depends upon the conditions or severity of the patients whether the patient is younger or older in age, pregnancy, existing heart disease, and risk of progression to clinical or overt hypothyroidism etc. Generally, Levothyroxine treatment normalizes the symptoms in hypothyroid patient. But as from the name itself it is clear that SCH is under treatment condition. In most of the SCH cases, the patients are kept under observation and ''wait and see" strategy is followed for auto normalization of elevated TSH levels to normal range values. In a study, it was observed that 37% of female SCH patients got normalized within a follow up period of 32 months [7].

This normalization process is mostly found in patients having negative anti-thyroid antibodies i.e., thyroid peroxidase antibodies (TPO). But based on severity of symptoms in SCH patient, possibility to changes to overt hypothyroidism, age of the patients, cardiovascular diseases, levothyroxine treatment is initiated by physician. Levothyroxine therapy is routinely done for Patients with TSH >10 mIU/L and selective individualized treatment is provided to SCH patients having TSH <10 mIU/L [8-10]. Each year 2.6 % SCH patients not having thyroid peroxidase antibodies and 4.3 % SCH patients having the thyroid peroxidase antibodies progress into overt or clinical hypothyroidism [11]. It is advised to lower the upper limit of normal range to lower half for

better patient quality of life if patients suffering from symptoms of hypothyroidism even the TSH is 3- 5 mIU/L. Hence, lowering the upper limit of TSH to 2.5mIU/L is recommended as worldwide most of the euthyroid people are having TSH value upto 2.5 mIU/L [12,13].

The levothyroxine therapy for SCH patients having TSH <10 mIU/L showed no significant improvement except tiredness in general symptoms although some studies suggests that in very few younger patients of age less than 55 years showed improvement in cognitive function also [14,15]. In this review, there would be discussion of whether LT4 treatment should be initiated or not for SCH patients and if started then what are the outcomes observed after levothyroxine therapy on the patients' symptoms.

Thyroid Definitions: The different definitions related to thyroid functionality are as follows given in the table 1.

Table 1: The different hormone levels in in normal and in different types of hypothyroid conditions.

	Clinical Hypothyroid	Subclinical Hypothyroid	Euthyroid	Normal Range
TSH	>10 mIU/L.	5-10 mIU/L	0.3-2.5 mIU/L	0.3-5mIU/L
FT4	< 0.9 ng/dL	0.9-1.9 ng/dL	0.9-1.9 ng/dL	0.9-1.9 ng/dL

What should be the Upper Limit of Normal TSH value?

Although upper limit of serum TSH value is advised to reduce to 3 or even 2.5 mIU/L from 5 mIU/L by experts but this recommendation is still controversial among physician [16-19]. This is proposed because of higher risk for progression to overt hypothyroidism due to presence of positive thyroid peroxidase antibodies in most of the patients with TSH value 3-5 mIU/L. It was found that if we exclude individuals with goitre, anti-thyroid antibodies, and patients with hereditary thyroid disease, the serum TSH level is 2.5mIU/L. But logic against this proposal is that if the upper limit of TSH is decreased to 3 mIU/L then 22-28 million of american population would fall into hypothyroidism without any kinds of hypothyroidism symptoms and there is not any clear evidence stating the benefits of levothyroxine treatment at this stage [13,19]. Though there is risk for progression to overt hypothyroidism due to positive anti-thyroid antibodies in TSH level 3-5 mIU/L but due to no clear benefitted result of levothyroxine treatment on such patients they are normally kept for follow up period for auto normalization of TSH value. For pregnancy, in 1st trimester the TSH value of 0.3-2.3 mIU/L and upper limit of 3.5 mIU/L for 2nd and 3rd trimester is proposed [16].

Screening for Subclinical hypothyroidism (SCH)

Uniform public rules for evaluating for thyroid abnormality with serum TSH levels have not been set up. Nonetheless, on account of the higher incidence of SCH worldwide and related metabolic danger factors like hyperlipidemia, the American Thyroid Association suggests screening by estimation of serum TSH starting at age 35 years and after every 5 years onwards [20]. The proof for screening is especially convincing in ladies but in adults also it can be justified as the screening is cost effective based on time period for retest. Prior to suggesting routine screening of everyone, huge scale randomized clinical trials are required to demonstrate that treatment will improve the life quality of those healthy patients who have the somewhat raised TSH level (5-10 mIU/L) who are kept under SCH c Most of the thyroidologist are in favor of routine screening for ladies before planning pregnancy and also during pregnancy [21]. Examination of thyroid functionality and autoantibodies are not suggested for each lady; however, it needs to be checked in first trimester, in those with an individual or family background of thyroid illness, goitre, other immune system sickness including type I diabetes or when there is clinical doubt of thyroid dysfunction [22].

Suspected Adverse Consequences of SCH

Progression to Clinical Overt Hypothyroidism

Patients with SCH have a high pace of progression to clinically clear hypothyroidism, 2.6% every year if thyroid peroxidase (TPO) antibodies are missing and 4.3% progresses if antibodies are available. A TSH level more prominent than 10 mIU/L have a higher tendency of movement, and a TSH of under 6 mIU/L predicts a lower probability of movement to overt hypothyroidism. In a clinical observation, consisting of male and female of age more than 55 years and having TSH value < 10 mIU/L, it was found that 52% of participants were normalized within follow up period of 32 months [23,24].

Lipid Abnormalities and Other Cardiac Risk Factors

The Colorado health fair investigation showed that the mean absolute cholesterol level was 216 mg/dL for euthyroid patients and 224 mg/dL for patients with SCH [19]. A meta-investigation of 13 examinations witnesses that the lipid profile improved with therapy [25,26]. A few randomized examinations have shown decrease of low-density lipoprotein (LDL) cholesterol by levothyroxine treatment. However, a large portion of the investigations did not show improvement for serum TSH levels of 5.0 to 10.0 mIU/L. But in a 2004 survey, information obtained were treated as deficient to show any advantages of levothyroxine treatment on lipid profiles [27]. As per my own assessment, the probability that lipid levels will improve with levothyroxine treatment is reasonable if the serum TSH is greater than 10 mIU/L and uncertainty may exist if the TSH level is under 10 mIU/L.

Cardiac Dysfunction

In SCH patients, some studies conclude that there is increased vascular tone, enhanced relaxation times for ventricles, dysfunction of left ventricles during exercise and decreased

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endothelial functionality. A few investigations have shown improvement of cardiovascular contractibility and systolic time span with levothyroxine therapy [28]. No evidence is there which helps in a relationship between cardiovascular dysfunction and a serum TSH level of under 10.0 mIU/L. most of the investigations were not classified for levels of TSH rise, and information are still inadequate for a TSH level under 10 mIU/L but recommended strongly for a TSH level more than 10 mIU/L [28].

Adverse Effects on Foetus

A fundamental report by Haddow et al. [29] showed a 7-point decrease in IQ in children of ages 7 to 9 years whose mothers were suffering from SCH in comparison to the offspring of euthyroid ladies. Although, it was a single report, focuses were made to the requirement for screening of pregnant ladies and treatment for gentle thyroid failure in ladies who are pregnant or preparing for getting pregnant.

Neuromuscular Dysfunction

It has been seen that neuromuscular side effects and functional abnormality are basic in patients with SCH and can be resolved by levothyroxine treatment [30]. A complete answer will require more investigations to know whether TSH levels here under discussion is more than or less than 10 mIU/L not clear.

Impaired Cognitive Function

We noticed an evident particular memory deficiency in hypothyroid and SCH patients. Proof from animal models recommends that thyroid hormones take part important role in the regulation of neuron formation. Thyroid hormone receptors are known to be very abundant in the hippocampal region, and the hormone helps in neurogenesis in the growing up of human brain. when there is a lack in Thyroid hormone, then it brings about a prevention in neuronal maturation, bringing about a decrease in size and number of granule cells in the hippocampus. We noticed lack or shortages in visuospatial, verbal, and associative memory before LT4 therapy. After 6 months of LT4 replacement therapy, patients with SCH not showed any differences at this point from ordinary control subjects. SCH patients showed a very good improvement after 3 months of LT4 replacement on measures of visual spatial and verbal memory [31,32] (Table 2).

Table 2: Evidence on Strength of associations and risk-benefit of levothyroxine therapy in SCH patients. LDL-C: low density lipoprotein cholesterol. Obtained from JAMA (30) with prior permission.

Clinical Conditions	Possibility of Association	Benefits of Treatment
Progression to Clinical hypothyroidism	Good	Variable
Heart or cardiac dysfunction	Insufficient	Insufficient
Adverse cardiac end points	Insufficient	No evidence
Systemic symptoms of hypothyroidism	No clear evidence	Insufficient
Increasing serum total Cholesterol and LDL-C level	Insufficient	Insufficient
Psychiatric symptoms	No clear evidence	Insufficient

Treatment Approach for SCH

The management strategy for SCH patients is based on serum TSH level whether TSH is 3-5 mIU/L, 5-10 mIU/L or more than 10 mIU/L.

Serum TSH level 3 to 5 mIU/L

Bringing down the upper serum TSH level from 5.0 to 3.0 mIU/L is yet in disagreed. Levels somewhere in the range of 3 and 5 mIU/L are probably not going to show a clinically significant anomaly and levothyroxine treatment at these levels may or may not show any positive results. In spite of the fact that people with a serum TSH level of 3 to 5 mIU/L might be at greater risk of hypothyroidism, no firm proof of wellbeing outcomes exists [23]. Indeed, in a randomized, hybrid, 12-week investigation of patients with manifestations of hypothyroidism with serum TSH in the upper normal range, no improvement in memory and psychological functioning was seen between levothyroxine-treated and control groups [33]. After these discoveries, treatment can't be suggested for this groups, however follow-up by serum TSH estimation in 1 year would be a sensible methodology, especially if anti-thyroid antibodies are identified.

Serum TSH level 5 to 10

If the patient is having symptoms of hypothyroidism, then 6 month of levothyroxine trial therapy is recommended and if patient symptoms decreases then then the therapy is continued. When the patient is having both TSH level of 5 to 10 and presence of thyroid peroxidase antibodies then yearly monitoring of TSH concentration is advised. If patient is without anti-thyroid antibodies, then checking up of blood TSH after every three years is sufficient [34].

Serum TSH Level More Than 10 mIU/L

Most of the physicians recommend beginning levothyroxine therapy in this condition. There is evidence that after levothyroxine therapy the hyperlipidemia is resolved to a significant extent as there is 4-fold reduction in low density lipoprotein in patients

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observed. The other general symptoms like nerve conduction abnormalities, memory, other psychological functioning, and heart problems improved after levothyroxine treatment in these patients as confirmed from evidence [11,35].

SCH Management in Pregnancy

One circumstance where assessment is reliable as to treatment of SCH with thyroxine is with regards to pregnancy or desire for upcoming conception or pregnancy. There is proof that spontaneous abortion rates and paces of unexpected premature labour are less if SCH is treated with thyroxine. Some proofs say that thyroxine treatment of biochemically euthyroid ladies with thyroid autoimmunity improves pregnancy result, which combined with proof that even gentle thyroid chemical inadequacy is related with an unfriendly impact on youth neurodevelopment, has driven expert affiliations and master gatherings to support the thyroxine treatment [27,29,36,37]. Recent research recommends that insufficient maternal T4 treatment is related with weakened memory development in their child. Although, Proof of clinical advantages are however insufficient, but it is smarter to treat subclinical hypothyroidism (SCH) before clinical overt hypothyroidism develops. The American thyroid association has recommended this following TSH ranges during pregnancy for better outcomes (Figure 1).

1st trimester: 0.1 to 2.5 mIU/L.

2nd trimester: 0.2 to 3.0 mIU/L.

3rd trimester: 0.3 to 3.0 mIU/L.

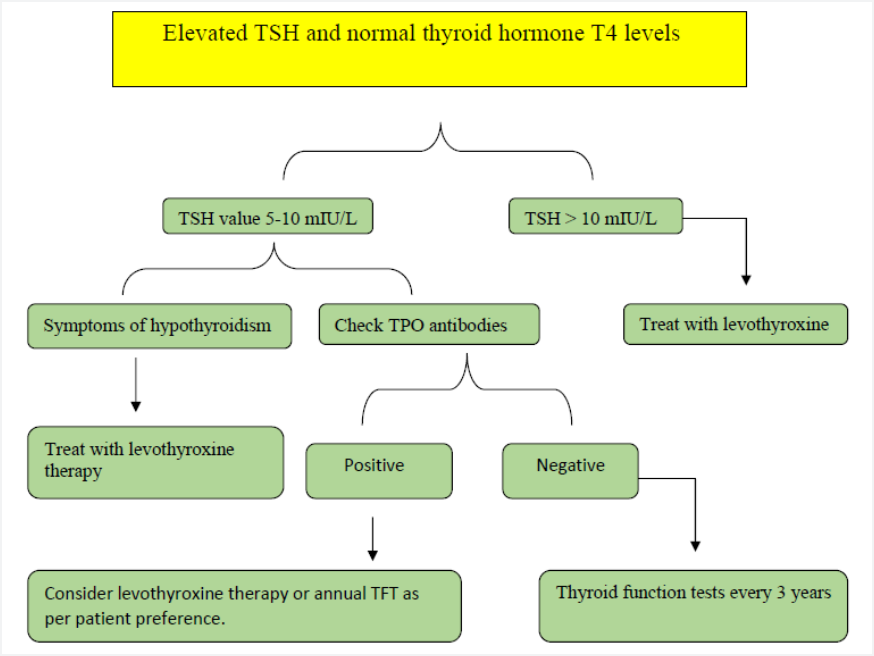

Figure: 1: Algorithm for SCH management in non-pregnant adult patients (42) Reprinted.

TFT: Thyroid function test; TPO: Thyroid peroxidase

Factors Satisfying the Levothyroxine Treatment in SCH Patients with Serum TSH level 5-10 mIU/L (14)**.**

- Goitre
- Pregnancy or planning for pregnancy.
- Presence of TPO anti-thyroid antibodies.
- Young age of patients like childhood or adolescence.
- Occurrence of ovulatory dysfunction, infertility etc.
- Hyperlipidemia
- If continuous increase in TSH value observed and
- Having mood disorders, depression, memory impairing etc. Primary.

Levothyroxine Therapy in SCH Patients

For all patients with SCH and a serum TSH value over 10 mIU/L and for patients with serum TSH level of 5.1 to 10.0 mIU/L in whom individualized choice for treatment is made, treatment should be begun with levothyroxine. After analysis, i would say that daily levothyroxine dose requirement is 50 to 75 µg (13). Expecting future progression of thyroid failure, some endocrinologists suggest a full substitution dose. The treatment should begin with daily dose of 25 to 75 µg of levothyroxine based upon the age of the patient, the degree of free thyroxine available

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and the serum TSH level. It is very necessary to monitor the Serum TSH after two months, and the dose need to be changed as per TSH level. When a normal serum TSH level has been accomplished, TSH should be estimated again following a half year and afterward yearly. In younger SCH people, the target for serum TSH should be 0.3 to 3.0 mIU/L. For older age patient the target can be even [11,37].

Conclusion

Starting levothyroxine treatment is suggested for all patients of SCH with a TSH level more than 10 mIU/L. But treatment of patients with a serum TSH level somewhere in the range of 5 and 10 mIU/L still remains under doubt. The strong logic for levothyroxine treatment is presence of TPO antibodies, goiter, high danger of changing to clinical hypothyroidism, enhancement of patient's life quality and seeing the probability that SCH can lead to cardiovascular diseases. When serum TSH level of 3 to 5 mIU/L is there then it suggests for keeping under observation for auto normalization of TSH mainly if TPO antibodies are present. The regulation of SCH during pregnancy with TSH concentration of 3-5 mIU/L requires levothyroxine treatment with or without positive TPO anti-thyroid antibodies, as the objective of treatment is to maintain TSH under 3 mIU/L to avoid any harm to foetus in positive TPO antibodies cases. Current research reveals that SCH patients younger than 70 years are more prone to cardiovascular disease, but patients of age more than 80 years need no treatment. treatment of SCH patients should be individualized by considering patient preference, based on manifestations, age, and related ailments.

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