Review Article

Subclinical hypothyroidism in adults: Consensus statement of Indian thyroid society

ABSTRACT

Subclinical hypothyroidism (SCH) is the most prevalent thyroid disorder in the Indian population. Since the last publication of the 2015 Indian Thyroid Society guideline on SCH, many significant clinical and scientific advances have occurred in the field. The aim of this guideline is to inform clinicians, researchers, and health policymakers about published evidence related to the diagnosis and management of SCH in adults. The specific clinical questions addressed in this consensus are based on the inputs from the task force of experts in the field of endocrinology and thyroid disease. The consensus statements are derived based on the latest published articles and evidence in SCH. A well-defined grading system has been followed for the critical appraisal of evidence and grading strength of recommendations. The guideline includes recommendations on the prevalence, causes, consequences, screening, diagnosis, and treatment of SCH. Other aspects detailed are the role of levothyroxine, its impact on the timing of treatment, and its benefits on various SCH consequences and populations. Therefore, these evidence-based recommendations are developed to inform clinical decision-making in the management of SCH in adults. While in some cases individualization of treatment is a necessity, these recommendations can provide standards of optimal care for patients with SCH.

Keywords: Consensus, evidence-based recommendations, Indian Thyroid Society, levothyroxine, subclinical hypothyroidism, thyroid disorder, timing

INTRODUCTION

Subclinical hypothyroidism (SCH) is the most prevalent thyroid disorder, biochemically defined as a persistent elevation in serum thyroid stimulating hormone (TSH) concentration (12 weeks or longer) with the serum free thyroxine (FT4) concentration within the reference interval. Moreover, patients with SCH can be categorized into those with mildly elevated TSH (4.5–10 mIU/L), and those with markedly increased serum TSH levels (>10 mIU/L).[1,2]

SCH presents with no or nonspecific signs of hypothyroidism.[3] The condition often goes undiagnosed and inappropriately treated due to subtle and nonspecific clinical symptoms and signs. Moreover, it is significant to tailor the diagnosis and management of SCH in specific populations such as children, geriatric patients, and those with comorbid conditions due to the physiological changes in thyroid hormones with age and illness.[4]

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Objective

The aim was to update the recommendations for the management of SCH in adults.

Expert panel and consensus process

The task force consisted of experts in the field of endocrinology and thyroid disease. Various published data and guidelines were explored to address screening, diagnosis, and management of SCH and its related complications. This document provides much-required insights and useful, practical, and accurate guidance that aids a practicing clinician. The guideline was developed through a series of E-mails, conference calls, and face-to-face meetings. The task force prepared the initial draft with the help of a medical writer, and it was reviewed and commented on by members of the Indian Thyroid Society.

METHODS

The sections and recommendations addressed in the guideline were based on feedback from task force members and previous trials and guidelines. The task force members followed a well-defined grading system (Table mentioned below) for the critical appraisal of evidence and grading strength of recommendations.

Level of evidence	Description
Level A	Data derived from multiple randomized trials or meta-analyses
Level B	Data derived from a single randomized trial or large nonrandomized trial
Level C	Consensus of opinion of experts or small studies, retrospective studies, or registries
Level D	Data derived from clinical experience
Class of recommendations	
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, or effective. It is recommended
Class IIa	Evidence is in favor of efficacy/usefulness and should be considered
Class IIb	Efficacy/usefulness is less well established and recommendations may be considered
Class III	Evidence and or general agreement that a given treatment or procedure is not beneficial, useful, or effective and in some cases may cause harm. Not recommended

Clinical question

Is the prevalence of SCH increasingly observed in clinical practice?

SCH presents a large epidemiological burden in India.[4] It is the most common thyroid disorder affecting 3%–15% of the adult population.[2] Various clinical and epidemiological studies conducted across India have shown a prevalence rate varying between 6% and 15%. Moreover, its incidence increases with advanced age, female gender, and greater dietary iodine intake.[3]

In addition, SCH is more prevalent in females than males and in the elderly. According to a recent Indian study, SCH prevalence was 24.7% and showed a higher prevalence in the older population aged between 61 and 70 years (38.5%).[5]

The prevalence of SCH increases with age in both men and women but is more common in elderly females (7%–18%) than males (2%–15%).[6]

Various studies showed the association of its increased incidence with increasing age. In India, a population-based study found a high occurrence of SCH in women (11.4%) versus in men (6.2%). Also, the study showed that increasing age has a significant association with SCH.[7,8]

According to a 2020 study, the prevalence of SCH was 4.90% (113/2306) in female and 2.26% (68/3013) in male participants, and the difference by gender was significant ($P < 0.001$). The age-specific prevalence curve was different between male and female participants. The prevalence in each age category was higher in female participants than that in male participants. Researchers found that when compared with males, the prevalence in female participants increased with age; 1.68% in the 20–29 years, 1.75% in 30–39 years, 3.59% in 40–49 years, and 3.89% in 50–59 years.[9]

In addition, the prevalence was 2.08% in male subjects <60 years and 3.64% in males aged 60 or older ($P = 0.104$). However, in female participants, the prevalence of SCH was 3.86% and 5.91% in the participants younger than 40 and aged 40 or older, respectively; the difference was significant ($P = 0.023$).[9]

Thus, the prevalence of SCH rises with age and the prevalence is higher in females than males.

Clinical question

What causes are identified for SCH?

The most common cause of SCH is chronic autoimmune thyroiditis (Hashimoto's disease or autoimmune atrophic thyroiditis). Both exogenous and endogenous factors cause SCH. The endogenous factors include sub-acute thyroiditis, and chronic autoimmune thyroiditis, whereas, the exogenous include inadequate therapy with the thyroid replacement, the effect of antithyroid drugs, thyroidectomy, thyroid infiltration, occupational exposure to pesticides, chronic excessive iodine intake, external radiation, and radioiodine therapy.[5,10]

Several non-thyroid factors transiently elevate TSH, resulting in misdiagnosis as SCH. It is necessary to distinguish between these non-thyroid causes of elevation in TSH from true SCH [Table 1].

Clinical question

What should be the clinical lookout for suspicion of a hypothyroid disease?

Evidence shows that 2.5% of patients with SCH progress to clinically overt hypothyroidism (OH) each year, and the progression rate is higher in patients with anti-thyroid peroxidase (anti-TPO) antibodies and higher levels of TSH.[13]

SCH may have subtle clinical manifestations and it is essential to develop rational laboratory strategies to differentiate the various conditions to guide the physician toward correct diagnosis and treatment.[10] The most frequent symptoms reported are memory impairment, slow thinking ability, muscle cramps, muscle weakness, tiredness, dry skin, feeling colder, hoarseness of voice, puffy eyes, and constipation.[10]

Studies have shown that adults with SCH experience higher rates of cognitive dysfunction, depression, and anxiety than euthyroid adults. Yet, the link between SCH and associated signs and symptoms remains ambiguous; only 10% of patients with these symptoms have SCH, and ~25% of people with normal thyroid function showed similar symptoms.[14]

The diagnosis of SCH is based on laboratory thyroid function tests which can identify clinically inapparent subclinical thyroid dysfunction.[15] Several physiological and demographic factors influence serum TSH levels that may affect the interpretation of laboratory thyroid function tests. It is therefore suggested to repeat the thyroid function tests at least 3 months apart to make a firm diagnosis.[16]

Table 1: Differential diagnosis of SCH[11,12]

Age
Impaired renal function
Transient SCH following subacute, painless, or postpartum thyroiditis
Laboratory analytical problem (assay variability, heterophilic antibodies)
Recovery phase of the euthyroid sick syndrome
After the withdrawal of thyroid hormone therapy in euthyroid patients
Untreated adrenal insufficiency
Isolated pituitary resistance to thyroid hormone
TSH-secreting pituitary adenoma
Intake of medications such as amiodarone, metoclopramide, amphetamine, and ritonavir

SCH: Subclinical hypothyroidism, TSH: Thyroid-stimulating hormone

Single elevated readings of TSH levels should be measured again after 4–6 weeks, as there is transient fluctuation in TSH in different medical/physiological conditions. Despite disagreement on the upper limit of TSH level, 4 mIU/L was considered the upper limit for the adult population. Moreover, for individuals aged >80 years, 6–8 mIU/L was considered the upper limit of the TSH level.[17]

SCH patients have a high rate of progression to clinically OH. However, some patients show no progression, and some experience normalization. A TSH level >10 mIU/L predicts a higher rate of progression, and a level <6 mIU/L predicts a lower likelihood of progression.[18]

In a study, the progression rate to OH was higher in patients with TSH >10 mIU/L than those with TSH <10 mIU/L. At the end of 2 years, the rate of resolution of SCH was higher in patients with TSH of 4.5–6.9 mIU/L versus patients with high TSH levels (10% for TSH of 7–9.9 mIU/L).[19]

In another study including patients older than 55 years with a mean follow–up of 32 months, 52% of patients with serum TSH levels <10 mIU/L had their TSH levels normalized.[20]

Imaizumi *et al*. reported that out of 63 patients with serum TSH levels <10 mIU/L, 38 (60.3%) of patients had their TSH levels normalized.[21]

Furthermore, patients with SCH have a high rate of progression to clinically OH, with an annual incidence of 2.6% in the absence of anti-TPO and 4.3% in their presence.[18]

A 2022 Indian study showed that the rate of progression to OH was higher in the anti-TPO positive group compared to the anti-TPO negative group ($P < 0.023$; odds ratio [OR]: 4.58; 95% confidence interval [CI]: 1.14, 18.28).[22]

SCH patients with elevated anti-TPO have a higher conversion to OH than those without, and hence, it is recommended that anti-TPO measurement should be an integral part of the diagnosis of SCH. Since patients with SCH develop OH at the rate of 5% per year, it is important to identify these patients at risk. Evidence suggests that both serum TSH and anti-TPO analyses are essential in determining thyroid status, particularly for the diagnosis of patients suspected of SCH.[23]

SCH is categorized into two on the basis of elevation in serum TSH level:[24]

- Grade 1: Serum TSH level is 4.0–10.0 mU/L. Grade 1 shows a mild increase in TSH level constituting around 90% of SCH cases on a population level

- Grade 2: Serum TSH level is >10 mU/L. Grade 2 shows severely increased TSH levels, and it is associated with increased risks of dyslipidemia, congestive heart failure, and coronary artery disease events.

Most studies suggest that symptoms, manifestations, and complications of SCH (including endothelial, lipid, and cardiovascular alterations) are related to the degree of TSH elevation. In a large cohort of older people (5316 subjects aged 70–82 years), increased heart failure events were reported only in those with a serum TSH >10 mU/L.[25] A meta-analysis of six prospective studies of community-dwelling older individuals confirmed that only patients with a serum TSH value >10 mU/L had an increased rate of heart failure.[26]

It is difficult to distinguish between transient disturbances of thyroid gland function and SCH. Only persistent or progressive SCH should be considered an early stage of thyroid disease.[12] Several non-thyroid factors transiently elevate TSH levels, leading to misdiagnosis as SCH. Such nonthyroid factors include transient SCH following subacute, painless, or postpartum thyroiditis, age, nonthyroidal illness, adrenal insufficiency, chronic renal failure, intake of medications such as metoclopramide, amphetamine, ritonavir, amiodarone, and St. John's Wort.[11] Other factors causing the elevation in serum TSH not associated with persistent SCH include laboratory analytical interferences such as assay variability, heterophilic antibodies), the recovery phase of euthyroid sick syndrome, condition after withdrawal of thyroid hormone therapy in euthyroid patients, TSH-secreting pituitary adenoma, and isolated pituitary resistance to thyroid hormone.[12]

Reassessing TSH concentration after 6–12 months of initial assessment can confirm the diagnosis of persistent SCH. This will ensure that only persistent or progressive disease is treated, and will also eliminate the possibility that abnormal values were the result of a laboratory error. Moreover, a high thyroid autoantibody titer associated with an increased persistent serum TSH concentration would be beneficial to identify individuals with autoimmune thyroid disease who are at increased risk of developing permanent hypothyroidism.[12]

The European thyroid association guideline mentions that identification of a transient increase of serum TSH is important and can be achieved by conducting repeated measurements of TSH. Also, waiting for the resolution of transient illness (a 2–3-month interval from the initial assessment of raised TSH) before repeating the serum TSH measurement is beneficial.[24]

Consensus statement

- A repeat thyroid function test is recommended in initial raised serum TSH with FT4 within the reference range. Both serum TSH and FT4, along with anti-TPO antibodies should be measured preferably after a 2- to 3-month interval for a firm diagnosis. (C/I)
- It is recommended to measure serum TSH concentration in patients with positive anti-TPO (C/I).
- Both serum TSH and anti-TPO measurement should be an integral part of the SCH diagnosis. (C/I)
- It is not recommended to repeat anti-TPO test.

Clinical question

Are the consequences of SCH serious enough for the patients to be treated?

Adverse cardiovascular endpoints (such as atherosclerotic disease and cardiovascular mortality), elevated total and low-density lipoprotein (LDL) cholesterol, systemic hypothyroid symptoms, neuropsychiatric symptoms, and the development of overt, symptomatic hypothyroidism are all potential consequences of SCH.[27]

Progression to overt hypothyroidism

Mild-to-moderate or Grade 1 SCH is diagnosed when the serum TSH level is between 4.5 and 9.9 mU/L, whereas severe or Grade 2 SCH is diagnosed when the serum TSH level is ≥10 mU/L. Patients with Grade 2 SCH are more likely to develop symptoms, progress to OH, and have poor long-term outcomes, and hence are more likely to benefit from treatment than those with Grade 1 SCH.[28]

Patients with SCH have a high rate of progression to clinically OH, with 2.6% progressing each year if TPO antibodies are absent and 4.3% progressing if they are present. However, some individuals do not progress and others experience normalization.[18] It is unclear why some SCH patients progress to OH while others remain in SCH or spontaneously regress to euthyroidism. Some individual or populational characteristics, such as population iodine level, sex, age, and initial TSH levels, appear to influence the natural course of SCH.[27]

The annual progression rate to OH, as reported by several studies, varies between 3% and 18%. Over a period of 10 years, researchers analyzed the natural history of SCH in 154 female patients; findings showed that 57% still experienced mild thyroid failure, 34% developed OH, and 9% had their TSH return to normal. In Wickham's study, TSH >6 (IU/L) predicted progression to OH with an OR of 14 (95% CI: 9–24) compared to TSH <6 (IU/L). Other risk factors for progression include the presence of antithyroid

antibodies, female gender, low-normal FT4, lithium medication, a history of radioiodine ablation for Graves' disease, and a history of external radiation therapy for nonthyroid malignancies.[22]

The first study from India to evaluate the spontaneous course of SCH, done in an endocrine clinic and hospital between 2018 and 2022, revealed that SCH had varied courses. The study demonstrated that Indian SCH patients had a high (18.97%) rate of progression to OH. Only the presence of anti-TPO antibody was predictive of OH in a cohort of 58 individuals followed for 1 year. Initial risk stratification can identify individuals with SCH who are at the highest risk for progression to OH, which requires mandatory therapy.[22]

Patients with OH should be treated regardless of their symptoms. Most people who have hypothyroidism have to take medication for the rest of their lives. As a result, it is generally considered to be good practice to verify the results with a second sample. Temporary thyroxine replacement may be required to maintain euthyroidism in some patients during the recovery phase of certain illnesses, such as thyroiditis or drug-induced hypothyroidism.[29]

When should we treat SCH?

Many patients with SCH may not require therapy, however, if treatment is required, oral levothyroxine (L-thyroxine) is the treatment of choice. L-thyroxine is efficient in restoring the biochemistry of an elevated blood TSH to the reference range, as proven by randomized clinical trials in SCH patients.[24]

A trial of L-thyroxine replacement treatment should be considered in younger SCH patients (<65 years; serum TSH <10 mU/l) with symptoms indicative of hypothyroidism. Even in the absence of symptoms, L-thyroxine replacement therapy is recommended for younger patients (<65 years) with serum TSH >10 mU/l. In elderly individuals aged 80–85 years or older with serum TSH ≤10 mU/L, a cautious "wait-and-see" approach is recommended, and hormonal treatment should generally be avoided. These individuals should be closely monitored.[24]

Treatment is not warranted in asymptomatic patients with a TSH <10 mu/L, although thyroid function should be evaluated annually in the presence of TPO-Ab and every 3 years in the absence of TPO-Ab.[24,30]

Consensus statement

- A trial of L-thyroxine replacement treatment should be considered in younger SCH patients (<65 years; serum TSH <10 mU/l) with symptoms indicative of hypothyroidism (A/I).
- Even in the absence of symptoms, L-thyroxine replacement therapy is recommended for younger patients (<65 years) with serum TSH >10 mU/l (A/I).
- In elderly individuals aged 80 to 85 years or older with serum TSH ≤10 mU/L, a cautious "wait-and-see" approach is recommended, and hormonal treatment should generally be avoided. These individuals should be closely monitored (A/I).
- Treatment is not warranted in asymptomatic patients with a TSH <10 mu/L, although thyroid function should be evaluated annually in the presence of TPO-Ab and every three years in the absence of TPO-Ab (C/I).

Cardiovascular disease

Thyroid hormones influence the heart via a variety of mechanisms. Thyroid hormones affect cardiac gene expression by acting on cardiomyocytes and altering the activity of ion channels in the cardiomyocyte cell membrane; thyroid hormones also have an impact on the cardiovascular system by affecting peripheral circulation. Thyroid hormone receptors are found in the myocardium and the vascular endothelium, allowing for the regulation of these tissue processes, such as endothelial nitric oxide production and vascular tone.[31]

SCH has been associated with several cardiovascular disease (CVD) risk factors including hypertension and dyslipidemia, functional cardiac abnormalities, such as left ventricular diastolic dysfunction, and reduced resting and exertional systolic function. Literature has also described an association between SCH and vascular abnormalities, such as increased vascular resistance, arterial stiffness, endothelial dysfunction, and atherosclerosis.[24,31]

In SCH, decreased thyroid hormone-mediated endothelial-dependent vasodilation may contribute to elevated blood pressure. Reduced activity of both lipoprotein lipase activity in adipose tissue and hepatic lipase activity in the liver is hypothesized to contribute to higher blood triglyceride levels in dyslipidemia. A decrease in the number of LDL receptors and impaired cholesterol breakdown may also explain the dyslipidemia seen in SCH. In addition to raising metabolic risk factors, SCH may significantly affect cardiac function, with studies suggesting a probable role of liothyronine (T3) in mitochondrial function and repair/damage, cardiac output, and peripheral vascular resistance with T3 administration. Other studies have shown that SCH is related to ejection fraction, decreased

arterial compliance, and increased risk of heart failure, perhaps through increased renin-angiotensin-aldosterone axis activation, increased vasoconstriction, increased sympathetic activity, reduced renal blood flow, and glomerular filtration rates.[31]

Numerous studies have examined the link between SCH and CVD, the third greatest cause of death worldwide. The associations between SCH, serum TSH levels, and CVD risk variables like blood pressure, glucose levels, and cholesterol levels have also been investigated.[31]

In a large individual-participant pooled analysis of prospective cohort studies (n = 55,287) by the Thyroid Studies Collaboration, SCH and coronary heart disease were positively associated in adults with TSH 10–19.9 mIU/L (hazard ratio [HR] 1.89, 95% CI 1.28–2.80) compared to those with normal TSH levels, the risk of which further increased higher the serum TSH level was ($P < 0.001$).[31]

A large cross-sectional and cohort studies were reviewed from 2000 to March 2006. The meta-analysis found a higher risk of prevalent coronary heart disease at baseline (relative risk [RR] 1.53, 95% CI 1.31–1.79; $P < 0.001$; 5 studies) and incident coronary heart disease (RR 1.19, 95% CI 1.02–1.38; $P = 0.05$; 3 studies). SCH was related to a greater risk of cardiovascular death (RR 1.28, 95% CI 1.02–1.60; $P = 0.05$; 3 studies) but not all-cause mortality (RR 1.12, 95% CI 0.99–1.26). Another research conducted showed that the prevalence of ischemic heart disease was 23% greater in SCH than in euthyroid patients (95% CI 1.02–1.48; $P = 0.03$; 12 studies). Due to heterogeneity, subgroup analyses were performed; these analyses showed that the elevated risk of ischemic heart disease was only present in the subgroup of individuals <65 years old (OR 1.57, 95% CI 1.19–2.06; $P = 0.001$; 7 studies) and not in the subgroup of individuals ≥65 years or older (OR 1.01, 95% CI 0.87–1.18; $P = 0.01$; 5 studies).[31]

A cross-sectional adult population survey was carried out on a total of 986 community-dwelling volunteers in Southern India to investigate the effect of SCH on cardiovascular health. The 10-year risk of an adverse cardiac event was calculated using the Framingham score algorithm. This sample had significant baseline rates of diabetes (19.5%), hypercholesterolemia (57.2%), and systolic hypertension (24%). SCH or increasing TSH did not affect Framingham's 10-year risk. While lipid profiles did not differ between groups, increased TSH was connected with modest lipid profile worsening.[32]

Kalra *et al*. conducted a prospective case-control study that aimed to compare beat-to-beat QT variability and vascular stiffness in female patients with SCH to age-and sex-matched normal controls. The study enrolled 58 patients with SH and 49 controls and used electrocardiogram and vascular indices measurements to assess cardiac repolarization and vascular function. The results showed that the patients with SH had a higher QT variability index, a higher ratio of sympathetic to parasympathetic regulation, and lower parasympathetic activity compared to the controls. The study's findings indicate that the elevated QT variability index in patients with SCH may be a sign of increased sympathetic activity and therefore may be an indirect indicator of an increased likelihood of CVD.[33]

Various pieces of evidence have demonstrated an increased risk of complications in untreated SCH patients:

- A study in heart failure patients revealed that a TSH value between 4.5 mIU/L and 10 mIU/L was associated with a 40% higher mortality, with pronounced increased risk in the untreated patients, compared with those within the normal range[34]
- In diabetes patients, untreated SCH was associated with a greater prevalence of diabetic nephropathy (OR, 3.15 [95% CI, 1.48–6.69]) and significantly increased risk of CV events ([admission as a result of angina, myocardial infarction, heart failure, acute coronary syndrome, and cerebrovascular disease] HR, 2.93; 95% CI, 1.15–7.48; $P = 0.024$)[35]
- SCH plays a critical role in age-related dyslipidemia; it worsens the effect of aging on serum lipid profiles. This has a major clinical consequence since aging is a non-modifiable factor for dyslipidemia. Every 1 mIU/L increase in TSH elevates TC and LDL-C levels in the elderly. Patients with significant SCH have a high prevalence of high TC and high LDL-C in individuals aged 60–69 years.[36]

According to the 2012 American Thyroid Association guidelines for hypothyroidism in adults treatment for primary hypothyroidism should commence when the serum TSH concentration exceeds 10 mIU/L. When the serum TSH falls within the range of 4.5–10 mIU/L, treatment may be considered in individuals with elevated CVD risk. Although limited data on the treatment outcomes of patients with TSH levels ranging between 2.5–4.5 mIU/L is available, studies have indicated that initiation of treatment in such patients can lead to improvement in markers of atherosclerosis risk, such as lipid levels, endothelial function, and intima-media thickness. For individuals with pre-existing CVD, the American Thyroid Association's 2014 guidelines recommend initiation of low-dose L-thyroxine therapy, followed by gradual dose escalation, and vigilant monitoring for the emergence of cardiac symptoms.[31]

Most international societal guidelines currently recommend that treatment decisions be individualized based on patient age, degree of serum TSH elevation, symptoms, CVD risk, and other co-morbidities. Treatment of SCH with L-thyroxine

must be initiated with caution in elderly patients. It should be noted that different reference intervals apply to specific subpopulations (the elderly and pregnant women), which may influence the decision to treat or not treat with L-thyroxine.[31]

Consensus statement

- SCH is associated with CVD risk factors including hypertension and dyslipidemia, functional cardiac abnormalities, such as left ventricular diastolic dysfunction, and reduced resting and exertional systolic function.
- Primary hypothyroidism should be treated when the serum TSH >10 mIU/L and considered in those with increased CVD risk when the serum TSH is 4.5–10 mIU/L. (A/I)
- In those with SCH and known CVD, treatment should be initiated at a low dose, increasing slowly as needed, and observed closely for the development of cardiac symptoms. (A/I)
- Treatment decisions be individualised based on patient age, degree of serum TSH elevation, symptoms, CVD risk, and other co-morbidities. (C/IIa)

Reproductive abnormalities

The thyroid gland regulates human physiology, including reproduction. Thyroid hormones modulate the hypothalamic-pituitary-gonadal axis, and clinically obvious thyroid abnormalities may impede ovulation and fertility. Women in the reproductive-age group often have thyroid problems. Both primary hyperthyroidism and hypothyroidism can cause gonadal dysfunction. Subclinical thyroid dysfunction and/or thyroid autoimmunity may be linked to infertility and spontaneous pregnancy loss.[37]

Infertile women were studied to see how thyroid disease affects fertility. Verma *et al*. conducted a prospective study on 394 infertile women (age group 20–40 years) attending the Gynecology department of a tertiary hospital in North India to determine the prevalence of clinical/sub-clinical hypothyroidism and the efficacy of hypothyroidism treatment on infertility. Of the 394 women included in the study, 19.29% had higher TSH levels solely, 13.7% had raised prolactin levels exclusively, and 4.57% had raised both TSH and PRL levels. Based on TSH levels, hypothyroid infertile women were further classified as subclinical (TSH 4–6 IU/ml) or clinical (TSH >6 IU/ml) hypothyroidism. It was found that 62.7% of hypothyroid infertile women had SCH, while 37.3% had clinical hypothyroidism. After hypothyroidism treatment, 76.6% of infertile women conceived within 6 weeks to 1 year.[38]

Priya *et al*. examined the prevalence of hypothyroidism in infertile women and the efficacy of hypothyroidism treatment on infertility. TSH was tested in 95 infertile women. Thyroxine doses ranging from 25 to 150 g were administered to infertile women with clinical/subclinical hypothyroidism. Of 95 infertile women, 53.7% were hypothyroid (TSH >4.6 IU/ml). After treatment with thyroxine, 33.3% of women with SCH conceived within 6 weeks to 2 years. The average gestational age was 14.5 ± 4.83 months. Hypothyroidism is a growing cause of female infertility, hence early therapy with L-thyroxine is justified in infertile women. Additionally, the study indicates that women with normal TSH levels and positive thyroid antibodies should be treated with L-thyroxine. Women who desire to conceive should be tested for serum TSH, T3, T4, and thyroid antibodies, especially TPO antibodies and thyroglobulin antibodies (TgAb).[39]

The 2021 European Thyroid Association Guideline on Thyroid Disorders before and during Assisted Reproduction recommends that all women seeking medical advice for subfertility should be screened for serum TSH and TPOAb. The inclusion of TgAb in the diagnostic evaluation should be based on local regulatory authority guidelines. Subfertile women with TSH >2.5 mIU/L, without elevated levels of TPOAb, should undergo TgAb screening if not previously done. Immediate initiation of L-thyroxine treatment is recommended in cases of overt thyroid dysfunction. The initiation of L-thyroxine treatment is recommended when TSH values exceed 4.0 mIU/L or the upper limit of the reference range.[40]

TSH testing is reasonable in infertile women attempting pregnancy, according to the data currently available. If TSH levels exceed the lab reference range for nonpregnant individuals (usually >4 mIU/L), patients should be treated with L-thyroxine to maintain levels below 2.5 mIU/L.[41]

Consensus statement

- It is reasonable to test TSH in infertile women attempting pregnancy. (A/I)
- Subfertile women with TSH >2.5 mIU/L, without elevated levels of TPOAb, should undergo TgAb screening if not previously done (A/I).
- Immediate initiation of L-thyroxine treatment is recommended in cases of overt thyroid dysfunction.
- The initiation of L-thyroxine treatment is recommended when TSH values exceed 4.0 mIU/L or the upper limit of the reference range (A/I).

Nonalcoholic fatty liver disease

Hypothyroidism is known to be associated with hypometabolism. It is distinguished by an increase in body

weight, a decrease in resting energy expenditure, and a decrease in gluconeogenesis and lipolysis. Obesity, poor lipid metabolism, and insulin resistance can be induced by THs dysfunction, which are all signs of metabolic syndrome in non-alcoholic fatty liver disease (NAFLD). Both overt and SCH is linked to NAFLD.[42]

In SCH, various mechanisms contribute to the progression of NAFLD, such as the physiology of TSH on the hepatocytes cell membrane, affecting hepatic triglyceride metabolism (increasing hepatic lipogenesis) via upregulating SREBP-1c activity. In addition, reduced thyroid hormone levels cause decreased glucose-sensing receptors in pancreatic beta cells. As a result, it lowers insulin secretion and lipolysis in adipose tissue while increasing FFA flow to the hepatic region.[42]

Hypothyroidism can cause atherogenic dyslipidemia. Hypothyroidism-induced hyperlipidemia is caused by a reduction in cholesterol excretion and a rise in apoB lipoproteins due to insufficient catabolism and turnover caused by a reduction in LDL receptors on hepatic cells. As a result, hypothyroid patients frequently have higher total and LDL cholesterol levels. In addition, hypothyroidism was associated with decreased triglyceride clearance from plasma and an increase in intermediate-density lipoproteins. Hypothyroidism can promote NAFLD due to high LDL and triglyceride levels in the liver. The lipids promote oxidative stress and inflammation in the liver.[42]

The 2018 meta-analysis investigated the association between hypothyroidism and NAFLD and Nonalcoholic Steatohepatitis (NASH) in a sample of 26 studies and 61,548 participants. The results indicated that patients with NAFLD/NASH had significantly higher levels of TSH compared to healthy controls and that this difference remained significant as the severity of NAFLD increased. The meta-analysis found that hypothyroidism was positively associated with the risk of developing NAFLD or NASH. However, the results were inconsistent when evaluated based on the degree of hypothyroidism, with a substantial correlation observed between SCH and the risk of NASH, but not with the risk of NAFLD. Conversely, a substantial correlation was observed between OH and the risk of NAFLD in adults, but not with the risk of NASH. These findings may be due to the limited number of studies included in the meta-analysis.[42]

Parikh, *et al*. assessed the prevalence of hypothyroidism in patients with NAFLD in patients attending a tertiary hospital in western India. The prevalence of hypothyroidism was higher among patients with NAFLD compared to the control group (16.8% vs. 1.3%; $P < 0.001$ respectively). Hypothyroidism was also found to be closely associated with NAFLD independently of known metabolic risk factors, confirming a significant clinical relationship between these two diseases.[43]

Liu *et al*. conducted a *post hoc* analysis of a randomized controlled trial and involved 33 significant and 330 mild SCH patients. All of the significant SCH patients received an L-thyroxine supplement. The mild SCH patients were grouped as L-thyroxine treated or not. The prevalence of NAFLD in each group was reevaluated after 15 months of follow-up. The prevalence of NAFLD in significant SCH patients decreased from 48.5% to 24.2% after treatment with L-thyroxine. L-thyroxine supplementation did not affect the prevalence of NAFLD or serum alanine aminotransferase (ALT) in mild SCH patients. Nonetheless, L-thyroxine treatment reduced the prevalence of NAFLD and serum ALT levels in mild SCH patients with dyslipidemia (for both). In contrast, in patients who were not treated, these parameters remained relatively stable. Thyroid hormone replacement therapy is beneficial for individuals with substantial SCH as well as mild SCH patients who also have dyslipidemia.[44]

Consensus statement

- Hypothyroidism was positively associated with the risk of NAFLD. The elevated TSH levels maybe a risk factor independently associated with NAFLD. (A/IIb)
- Thyroid hormone replacement therapy is beneficial for individuals with substantial SCH as well as mild SCH patients who also have dyslipidemia. (C/IIa)

Neuropsychiatric symptoms

Patients with SCH with clinical hypothyroidism have been observed to experience a range of neuropsychiatric and cognitive problems. These range from comorbid depression to depressive symptoms that may or may not be accompanied by anxiety. Patients in this population have been noted to have neuropsychiatric symptoms, such as learning and memory impairments, as well as defects in their executive functioning. It is now generally accepted that adult brains are susceptible to the effects of thyroid hormones, which can alter neuronal growth, modify the stress response, and influence neurotransmitters. Neuropsychiatric symptoms encompass a wide range of emotional and cognitive issues that can be traced back to changes in the brain as a result of several different causes.[45]

Kalra *et al*. carried out a prospective, case–controlled, hospital-based study in two tertiary care centers in Bangalore, India to explore the neuropsychological impairments in young patients with SCH and compare them with euthyroid controls. A total of 39 patients diagnosed with SCH between the ages of 18 and 45 were recruited. The controls were age, gender,

and education-matched euthyroid. The mean TSH value in cases and controls was 6.3 ± 1.3 mIU/L and 2.4 ± 1.03 mIU/L, respectively ($P < 0.001$). Visual memory delayed recall was impaired in 48.71% of cases and 21.7% of controls ($P = 0.03$). The category fluency test revealed impairment in more cases (35.9%) than in controls (13%; $P = 0.04$). Delayed visual memory recall and category fluency deficits, indicating prefrontal cortex and temporal lobe dysfunction in younger patients. These impairments may justify the use of replacement therapy in young SCH patients.[46]

A prospective, placebo-controlled, experimental research of L-thyroxine withdrawal in 19 women revealed impairments in declarative and working memory, in addition to motor learning, during SCH. This was demonstrated in two cross-sectional investigations involving 17 and 15 SCH patients with impaired memory and verbal fluency.[24]

Vishnoi *et al*. conducted a hospital-based case-control study to investigate the association of SCH with low mood and also investigated the effects of L-thyroxine therapy on the improvement of symptoms. The study included 300 patients with SCH and 300 age-and sex-matched healthy controls attending the endocrinology lab for hormonal evaluation in New Delhi, India. The Hamilton Depression Rating Scale (HAM-D) was used to assess baseline depression in all participants and in 133 individuals who had received L-thyroxine therapy for 2 months. SCH was associated with low mood, and there was a positive association between serum TSH levels and HAM-D ratings, according to the study. L-thyroxine therapy was related to a significant improvement in HAM-D scores. This stresses the significance of screening for thyroid abnormalities in all cases of depression and the usefulness of L-thyroxine treatment for such patients.[47]

No differences were observed in mood and cognitive function at baseline, or any consistent response during carefully titrated L-thyroxine replacement in subjects with TSH levels ranging from 3.5–10 mU/l. Similarly, using a battery of neurocognitive tests, two larger studies of elderly subjects (>65 years; $n = 164$ from Korea and $n = 94$ from the UK) found no significant improvements from L-thyroxine. The inconsistency of these studies' results could be attributed to differences in design, their small sample sizes, the diverse age groups recruited, and the wide range of neurocognitive tests used. There may be important differences if participants were preselected based on symptoms or biochemical screening of a population. However, it is likely that some younger patients with SCH have mild impairment of declarative memory, working memory, and mood, and that these symptoms improve with L-thyroxine therapy. No evidence that subjects over the age of 65 benefit from it.[24] Experts have emphasized that it is very important to be careful while treating patients with SCH.

Consensus statement

- In younger SCH patients, mild impairments in declarative memory, working memory, and mood may improve with thyroid replacement therapy. (C/IIa)

Clinical question

Should SCH patients be treated or not treated?

Treatment of SCH should include effective decision-making which involves incorporating all relevant clinical data for a thorough investigation of the patient's condition. Data such as age, TSH level, quality of life, comorbidities, cardiovascular risk, safety, and personal preferences should be considered. The patient should undergo an appropriate diagnosis in which only those with persistent SCH and without nonthyroidal causes of TSH elevation (obesity, physiological increase in elderly, untreated Addison's disease, recovery from nonthyroidal illness) should be considered for treatment. The severity of SCH and the age of the patient are important parameters that guide the decision-making process.[28]

Treatment of patients with SCH between 2.5 and 4.5 mIU/L

No clinical data have supported treating patients with SCH having TSH levels between 2.5 and 4.5 mIU/L. Exceptions may be pregnancy due to increased risk of complications in anti-thyroid antibody-negative women such as pregnancy loss, spontaneous miscarriage before 20 weeks gestation, and stillbirth after 20 weeks.[30]

Treatment of younger patients (<65 years of age)

All younger patients with TSH ≥ 10 mU/L should be treated to reduce the risk of long-term cardiovascular complications, progression to OH, and mortality.[28]

- Individuals with TSH 4.5–9.9 mU/L who are healthy and asymptomatic do not require treatment
- Individuals with TSH 4.5–9.9 mU/L at a higher risk of progression to OH (female gender, a progressive increase of TSH levels, positive TPOAb) can be considered for treatment.

Treatment of older patients (≥65 years of age)

Elderly patients with SCH should be treated with caution, as this subgroup of patients is at a higher risk of L-thyroxine overtreatment and are more susceptible to adverse consequences, such as reduction of bone mineral density, heart failure, and atrial fibrillation. Therefore, treatment of the elderly should be based on a careful balance between risks and benefits depending on the decision by the treating Physician, and an Endocrinologist.[16] Observation without treatment should be the strategy of choice in patients greater than 80–85 years old with SCH and serum TSH less than or equal to 10 mIU/L.[24]

A recently published 2022 study has shown that L-thyroxine treatment of SCH (4·5–7·0 mIU/L) in individuals aged ≥65 years did not improve the symptoms of hypothyroidism and cardiac and bone parameters. The data suggest that L-thyroxine should be considered for individuals aged ≥65 years with SCH when TSH concentration is persistently 7 mIU/L or higher. Treatment for those with TSH <7 mIU/L may not be of any benefit. The authors conclude that L-thyroxine doses should be personalized according to age, comorbidities, and life expectancy in the elderly aged ≥65 years.[48] As per the expert opinion, evidence is limited for the treatment of SCH in patients aged ≥65 years.

Existing guidelines on thyroid hormone replacement in SCH patients

Existing guidelines recommend thyroid hormone treatment for adults with TSH levels >10 mIU/L, however, treatment is recommended for the younger, symptomatic, or those with CVD or antibodies to TPO having lower TSH levels.[49] Table 2 lists several guidelines and the recommendations for treatment of SCH.

Table 2: Guideline recommendations for treatment of SCH

Guidelines	Recommendations for treatment
NICE CKS guidelines, 2018[49]	TSH >10 mIU/L Age <70 years, treat Age ≥70 years, watch and wait TSH 4-10 mIU/L Age <65 years with symptoms, consider trial Age ≥65 years, watch and wait
ETA, 2013[24]	Age <70 years TSH >10 mIU/L, treat TSH <10 mIU/L with symptoms, start a trial TSH <10 mIU/L without symptoms, observe Age >70 years TSH <10 mIU/L, observe TSH >10 mIU/L, consider treatment if clear symptoms or high CV risk
ATA, 2012[30]	TSH >10 mIU/L, consider treatment TSH <10 mIU/L, consider treatment if symptoms suggestive of hypothyroidism, positive antibodies to TPO, or evidence of ASCVD, heart failure, or risk factors for these diseases
British clinical practice guideline in 2019[49]	Lack of benefit from thyroid hormone treatment in nearly all those with SCH (does not apply to pregnant or women trying to conceive, those with severe symptoms, or those younger than 30 years), and specifically that asymptomatic SCH patients or those with nonspecific symptoms should not be treated The decision to initiate treatment should be individualized based on the degree of serum TSH elevation, symptoms, patient preference, and other factors

CV: Cardiovascular, ATA: American Thyroid Association, ETA: European Thyroid Association, NICE: National Institute for Health and Care Excellence, CKS: Clinical knowledge summaries, TSH: Thyroid stimulating hormone, SCH: Subclinical hypothyroidism, ASCVD: Atherosclerotic CV disease, TPO: Thyroid peroxidase

Consensus statement

- An approach of effective decision-making should be followed while deciding to treat SCH and all relevant clinical data such as the age of the patient, TSH level, quality of life, comorbidities, cardiovascular risk, safety, and personal preferences should be considered for a thorough investigation. (C/I)
- Patients (<65 years of age) with TSH 4.5-9.9 mU/L who are healthy and asymptomatic do not require treatment. (C/I)
- Treatment of older patients (≥65 years of age) should be based after weighing the risks and benefits as this category of patients are at a higher risk of overtreatment and are more susceptible to adverse consequences and depends on the decision by the treating Physician, and an Endocrinologist. (C/I)
- The dose of L-thyroxine should be personalised according to age, comorbidities, and life expectancy in elderly aged ≥65 years. (C/I)
- In individuals with TSH >10 mIU/L; treatment can be considered in those <65 years, whereas, a watch and wait approach can be followed or treatment can be considered if clear symptoms or high cardiovascular risk is present in the older population ≥65 years. (C/IIa)
- In individuals with TSH <10 mIU/L; treatment should be considered for <70 years with symptoms, whereas those without symptoms can be under observation, whereas those >70 years can be under observation. (C/IIa)

Clinical question

How to treat SCH patients and what dose of thyroid hormone replacement should be considered?

Oral L-thyroxine is the treatment of choice for managing SCH. L-thyroxine is shown to be effective in returning the biochemistry of a raised serum TSH within the reference range.[24]

As per the European Thyroid Association (ETA), there has been a substantial variability in the doses of L-thyroxine used, but typical regimens have started with 25 or 50 µg daily, with subsequent monthly or 2-monthly adjustments to maintain serum TSH within the reference range. L-thyroxine dose should be weight-based in patients without cardiac disease and start at a low amount (25 or 50 mcg daily) in those with cardiac disease and/or older age.[24]

As per the 2012 American Thyroid Association guidelines, the initial L-thyroxine dose is typically lower than that required in OH and suggests a daily dose of 25–75 mcg, depending on the degree of TSH elevation and to be adjusted based on symptoms and serum thyroid function test monitoring.[30]

For those with known CVD, the 2014 American Thyroid Association guidelines for the treatment of hypothyroidism recommend initiating L-thyroxine at a low dose, increasing slowly as needed, and observing closely for the development of cardiac symptoms.[50]

In the Thyroid Hormone Replacement for Untreated Older Adults with Subclinical Hypothyroidism, a placebo-controlled trial (TRUST) trial randomized adults with SCH aged 65 years old or older to a daily L-thyroxine dose of 25 or 50 mcg (then titrated by serum TSH level; median daily dose 50 mcg) or placebo. No difference was observed in the primary outcomes, namely, the mean change in the hypothyroid symptoms score and tiredness score on a thyroid-related quality-of-life questionnaire at 1 year.[51]

Another large cohort analysis of individuals over the age of 18 years with SCH (with comorbidities such as ischemic heart disease, heart failure, MI, and stroke) and having TSH levels divided into two categories 5.0–10.0 mIU/l and >10.0 mIU/l were initiated substitution treatment within the first 6 months after thyroid function tests. Reports showed that the average dose of L-thyroxine prescribed was 80 micrograms/day in these patients.[52]

Consensus statement

- The initial L-thyroxine dose is generally lower in SCH patients than what is required in the treatment of overt hypothyroidism. The daily dose can vary from 25 to 75 μg depending on the degree of TSH elevation with subsequent monthly or 2-monthly adjustments to maintain serum TSH within reference range. (B/I)

Clinical question

Is L-thyroxine treatment beneficial for SCH patients at risk of cardiovascular diseases?

Research has shown that the risk of CVD may be significantly elevated in younger individuals with SCH. Therefore, L-thyroxine treatment in SCH may show to improve CVD risk factors and markers of CVD risk.[31]

A reanalysis of the Whickham Survey has shown L-thyroxine to be beneficial in SCH patients. No difference was observed in ischemic heart disease events or ischemic heart disease-related mortality when the treated (n = 20) group was compared with not treated (n = 71) group, but a significant difference in all-cause mortality, with a 78% lower rate of death among those treated with L-thyroxine (P = 0.02) was observed.[53]

Another larger retrospective cohort analysis conducted has shown that L-thyroxine was associated with a significant reduction in fatal and nonfatal ischemic heart disease events, death due to circulatory diseases (ischemic heart disease, cerebrovascular disease, peripheral vascular disease), and all-cause mortality. However, these associations were seen only in younger subjects (age 40–70 years, n = 3,093) and not in older subjects (age greater than 70 years old, n = 1,642).[54]

Multiple small studies have suggested improvement in cholesterol parameters, blood pressure, and various markers of cardiac and vascular structure/function with L-thyroxine treatment in SCH.[55,56]

Data from larger trials like TRUST did not show any significant differences in fatal or nonfatal cardiovascular events (HR 0.89), new-onset atrial fibrillation (HR 0.80), or all-cause mortality (HR 1.91,) in those treated with L-thyroxine, compared with those in the placebo group. Overall event rates were so low for death from CVD and heart failure that HRs were not able to be calculated.[51]

Treatment with L-thyroxine was not associated with the incidence of myocardial infarction, CVD death, or all-cause mortality in this population. Sub-group analyses by younger/older individuals and grade 1/grade 2 SCH also did not demonstrate any significant differences with L-thyroxine treatment, except in patients less than 65 years old concerning all-cause mortality (incidence rate ratio 0.63). Therefore, L-thyroxine substitution in SCH patients does not indicate an association with lower mortality or decreased risk of MI.[52]

Researchers have opined that improvements in CVD risk factors and markers of CVD risk as indicated from smaller studies may suggest some benefit of L-thyroxine treatment in SCH; however, it is unclear if this risk reduction would ultimately confer a CVD or CVD mortality benefit. Larger observational and randomized studies have not yet shown convincing, and consistent evidence of the benefit of L-thyroxine treatment in reducing CVD outcomes.[31]

The National Heart, Lung, and Blood Institute convened a Working Group to develop priorities for future scientific research relating thyroid dysfunction to the progression of CVD. The results of this working group are published jointly by the American Heart Association and the American Thyroid Association [Table 3].[57]

The ETA suggests that for SCH patients with established ischemic heart disease, L-thyroxine lower doses should be started, with subsequent stepwise dose increases. Typically, in a patient with stable angina pectoris, a dose of 25 µg

Table 3: Recommendations for the screening and management of SCH coexistent with cardiovascular disease[57]

Conditions	Recommendations
Atrial fibrillation	Thyroid testing for a first episode and when the ventricular rate is difficult to control
Heart failure	Thyroid testing at the initial presentation
Dilated cardiomyopathy	Thyroid testing at the initial presentation
Amiodarone use	Thyroid testing before, within 3 months of initiation, and every 3–6 months Thyroid testing before, at 1 and 3 months after initiation, and every 3–6 months
SCH	Treat all patients or consider treatment with TSH level persistently >10 mIU/L Consider treatment For patients with TSH levels 4.5–10 mIU/L with atherosclerotic CVD, heart failure, or associated risk factors for these diseases For patients with TSH levels 4.5–10 mIU/L, for those patients <65 years with increased CV risk (previous CVD, diabetes, dyslipidemia, hypertension, metabolic syndrome), particularly with TSH level persistently >7 mIU/L

CV: Cardiovascular, CVD: CV disease, TSH: Thyroid-stimulating hormone, SCH: Subclinical hypothyroidism

L-thyroxine should be started and increased gradually by 25 μg every 2 or 3 weeks.[24]

Consensus statement

- L-thyroxine treatment in SCH may provide some benefit in improving the CVD risk factors and markers of CVD risk. (C/IIa)
- L-thyroxine should be initiated at a lower dose, typically a dose of 25 μg, with subsequent stepwise dose increase by 25 μg/day every 2-3 weeks until a full replacement dose is reached. (C/IIa)

Clinical question

Does L-thyroxine therapy have an effect on neuropsychiatric symptoms in SCH patients?

Reports have shown that the administration of L-thyroxine in Indian patients with SCH is associated with significant improvement in Hamilton Depression Rating Scale (HAM-D) scores. A positive correlation exists between the Hamilton scores and serum TSH levels which showed that higher values of TSH were associated with more severe depression as measured clinically by HAM-D. Therefore, since the administration of L-thyroxine therapy was associated with a significant decrease in HAM-D scores and TSH levels, the authors emphasize screening for thyroid disorders in all cases of depression and also the utility of L-thyroxine treatment in such cases.[47]

Consensus statement

- L-thyroxine treatment may be beneficial in SCH patients with neuropsychiatric symptoms. (B/IIa)

Clinical question

How are untreated and treated SCH patients followed up and monitored?

Researchers have confirmed that a single TSH above the reference range, but below 10 mU/l, should be followed by a confirmatory measurement of serum TSH, an estimate of T4, and a TPO-Ab. The majority of patients will most likely have a normal TSH on repeated testing, and further testing will be of little value.[58]

- The measurement of serum TSH and T4 is a cornerstone in monitoring SCH, but additional evaluation of symptoms and signs of hypothyroidism should be performed
- A validated assay with an appropriately established assay-specific reference interval should be used for T4. Change in the T4 estimation method during the monitoring should be avoided
- Initial diagnosis of SCH should be confirmed by the measurement of TSH, T4, and TPO-Ab after 8–12 weeks
  - If normal, no further evaluation is needed
  - If SCH is persistent, thyroid function should be evaluated every 6 months for the first 2 years, and then every year after 2 years.
- Patients without symptoms, TPO-A, b, or goiter can stop monitoring after 3 years
- After 3 years thyroid function should be evaluated if the patient gets pregnant, develop hypothyroid symptoms, or concomitantly with general health evaluations
- A decrease in thyroid function is suggested when:
  - TSH rises more than 40%[58]
  - T4 decreases by more than 15%.[58]

The European Thyroid Association (ETA) suggests that once treatment is commenced, thyroid function should be monitored 2–3 months later to ensure serum TSH is optimized and then at least annually later. The goal of treatment should be to alleviate their symptoms in younger patients with symptoms, aiming for a serum TSH in the lower half of the reference range (0.3–2.5 mU/l). If treatment is initiated for older patients, more relaxed targets are acceptable, aiming for a serum TSH between 1.0 and 5.0 mU/l in patients >70 years.[24]

Consensus statement

- Initial diagnosis of SCH should be confirmed by the measurement of TSH, T4, and TPO-Ab after 8–12 weeks. (C/IIa)
- If thyroid function has normalized, then no further testing is required in those who are asymptomatic, have negative thyroid autoantibodies or do not have goitre. If untreated SCH is persistent, thyroid function should be tested 6 monthly for the first 2 years and then yearly thereafter. (C/IIa)
- If L-thyroxine treatment is initiated in SCH patients, then serum TSH should be monitored at least annually thereafter. (C/I)

Clinical question

What is the impact of the timing of L-thyroxine treatment?

Non-compliance is a common reason for poor response to L-thyroxine therapy, which requires the need to take the drug daily on an empty stomach, as this approach accounts for optimal absorption. Studies have shown that consumption of L-thyroxine 60 min before breakfast led to optimal serum TSH control. However, L-thyroxine taken at bedtime was found to be superior to that taken 30 min before breakfast.[24]

Several food groups are reported to specifically impair L-thyroxine absorption, including milk (due to the calcium content), coffee, soya products, and papaya. Many medications including iron salts, calcium salts, antacids (including sucralfate, H2-receptor blockers, and proton pump inhibitors), cholestyramine, and raloxifene can also interfere with L-thyroxine absorption. Further, several gastrointestinal conditions such as atrophic gastritis/pernicious anemia and coeliac sprue and different forms of bariatric surgery are also shown to improve or impair L-thyroxine absorption.[24]

A randomized crossover design study conducted by Rajput and Pathak in Indian hypothyroid patients (mean age: 36 years) has shown that once-weekly L-thyroxine administration was as effective as conventional daily therapy in the maintenance of euthyroidism. Further, weekly therapy was also observed to show significant improvement in bodily pain, vitality, mental health, and social functioning vs. daily L-thyroxine administration. The authors suggest that in today's era of busy and hectic schedules, it is difficult to follow a rigid schedule, so once weekly L-thyroxine administration can provide an alternative approach for the treatment of hypothyroidism, especially in patients where compliance is a major issue.[59]

Another study by Rajput and Pathak has shown that the evening dose was as efficacious as the morning dose and can be considered as an alternate dosing regimen in hypothyroid patients. It was observed that euthyroidism was restored early (TSH <4.25 mIU/L) in the group receiving L-thyroxine as an evening dose. However, no statistically significant difference was seen at the end of 6 weeks and 12 weeks (P = 0.51 and 0.19). Improvement in thyroid profile (increase in fT3 and fT4 and decrease in TSH) at 6 weeks and 12 weeks was seen both in the morning group as well as in the evening, and it was highly significant in comparison with their baseline thyroid function ($P < 0.0001$). Further, the evening dose was as efficacious as the morning dose in the improvement of thyroid profile, reduction in total cholesterol levels, improvement of clinical signs and symptoms, and improvement in quality of life.[59]

Consensus statement

- L-thyroxine should ideally be taken 60 minutes before breakfast. An evening dose can be considered especially in patients where compliance is a major issue. Once weekly L-thyroxine administration can also be considered as an alternative approach for treatment of SCH. (A/I)

Clinical question

What is the clinical significance of screening for SCH?

Early detection of abnormal serum TSH levels with or without abnormal thyroxine levels and treatment in asymptomatic persons may be beneficial for the prevention of long-term morbidity and mortality from fractures, cancer, or CVD.[60] Table 4 elaborates on the advantages and recommendations for universal or targeted screening of hypothyroidism.

Table 4: Universal or targeted screening of hypothyroidism: Advantages and recommendations

Universal (routine) screening[61]	Targeted (case-based) screening[30]
Pros Routine screening in an asymptomatic population can help in detecting "abnormal" serum TSH levels	Evidence exists to support case finding for hypothyroidism in patients with Autoimmune diseases, such as type 1 diabetes Pernicious anemia A first-degree relative with autoimmune thyroid disease A history of neck radiation to the thyroid gland including radioactive iodine therapy for hyperthyroidism and external beam radiotherapy for head and neck malignancies A prior history of thyroid surgery or dysfunction An abnormal thyroid examination Psychiatric disorders Taking amiodarone or lithium
Cons The decision about appropriate cut-offs for the lower and upper boundaries of normal TSH levels in the general population and in the elderly where values differ from the overall population distribution is still under disagreement	
The discrepancies in measurement and the sensitivity of TSH secretion to conditions other than thyroid dysfunction further complicate accurate interpretation of serum TSH levels	
Widespread screening of asymptomatic individuals can cause harm due to false-positive results, overdiagnosis, and overtreatment of biochemically abnormal TSH levels (with or without abnormal serum T4 levels) that may eventually normalize, never progress, or never result in health problems, particularly in those with TSH <10 mIU/L	The ATA and the American Association of Clinical Endocrinologists recommend screening for hypothyroidism in patients older than 60 years, as well as "aggressive case finding" (but not universal screening) in persons who are at increased risk for hypothyroidism and in women who are planning pregnancy[30] Three British professional associations (the Association for Clinical Biochemistry, the British Thyroid Association, and the British Thyroid Foundation) jointly recommend aggressive case finding in women with nonspecific symptoms[61]

TSH: Thyroid-stimulating hormone, ATA: American Thyroid Association

Table 5: Recommendations of organizations regarding screening of asymptomatic adults for thyroid dysfunction[30]

Organization	Screening recommendations
ATA	Women and men >35 years of age should be screened every 5 years
American Association of Clinical Endocrinologists	Older patients, especially women, should be screened
American Academy of Family Physicians	Patients ≥60 years of age should be screened
American College of Physicians	Women ≥50 years of age with an incidental finding suggestive of symptomatic thyroid disease should be evaluated
U.S. Preventive Services Task Force	Insufficient evidence for or against screening
Royal College of Physicians of London	Screening of the healthy adult population unjustified

ATA: American Thyroid Association

Thyroid function tests for screening in asymptomatic individuals:[61]

- Thyroid function tests can be repeated in asymptomatic persons (over 3-to 6-month intervals) for confirmation of persistent dysfunction if the results are above or fall below-specified reference intervals before making a diagnosis or considering any treatment
- If the serum TSH level is >10.0 or <0.1 mIU/L, repeat TFTs may not be necessary
- Recommendations of organizations regarding screening of asymptomatic adults for thyroid dysfunction are listed in Table 5.

Consensus statement

- Universal screening for SCH in an asymptomatic population is associated with many discrepancies, and has inadequate evidence to determine its benefits. (C/IIb)
- Targeted screening for hypothyroidism can be considered for those at increased risk for hypothyroidism and in women who are planning pregnancy or with nonspecific symptoms. It should be considered in individual case to case depending on decision by the treating physician, or endocrinologists. (C/IIb)

Executive summary of the consensus statements

Diagnosis of SCH

- A repeat thyroid function test is recommended in initial raised serum TSH with FT4 within the reference range. Both serum TSH and FT4, along with anti-TPO antibodies should be measured preferably after a 2–3-month interval for a firm diagnosis (C/I)
- It is recommended to measure serum TSH concentration in patients with positive anti-TPO (C/I)
- Both serum TSH and anti-TPO measurement should be an integral part of the SCH diagnosis (C/I)
- It is not recommended to repeat the anti-TPO test

Consequences of SCH: To treat or not?

Progression to OH

- A trial of L-thyroxine replacement treatment should be considered in younger SCH patients (<65 years; serum TSH <10 mU/L) with symptoms indicative of hypothyroidism (A/I)
- Even in the absence of symptoms, L-thyroxine replacement therapy is recommended for younger patients (<65 years) with serum TSH >10 mU/L (A/I)
- In elderly individuals aged 80–85 years or older with serum TSH ≤10 mU/L, a cautious "wait-and-see" approach is recommended, and hormonal treatment should generally be avoided. These individuals should be closely monitored (A/I)
- Treatment is not warranted in asymptomatic patients with a TSH <10 mU/L, although thyroid function should be evaluated annually in the presence of TPO-Ab and every 3 years in the absence of TPO-Ab

CVD

- SCH is associated with CVD risk factors including hypertension and dyslipidemia, functional cardiac abnormalities, such as left ventricular diastolic dysfunction, and reduced resting and exertional systolic function
- Primary hypothyroidism should be treated when the serum TSH >10 mIU/L and considered in those with increased CVD risk when the serum TSH is 4.5–10 mIU/L (A/I)
- In those with SCH and known CVD, treatment should be initiated at a low dose, increasing slowly as needed, and observed closely for the development of cardiac symptoms (A/I)
- Treatment decisions be individualized based on patient age, degree of serum TSH elevation, symptoms, CVD risk, and other comorbidities (C/IIa)

Reproductive abnormalities

- It is reasonable to test TSH in infertile women attempting pregnancy (A/I)
- Subfertile women with TSH >2.5 mIU/L, without elevated levels of TPOAb, should undergo TgAb screening if not previously done (A/I)
- Immediate initiation of L-thyroxine treatment is recommended in cases of overt thyroid dysfunction
- The initiation of L-thyroxine treatment is recommended when TSH values exceed 4.0 mIU/L or the upper limit of the reference range (A/I)

NAFLD

- Hypothyroidism was positively associated with the risk of NAFLD. The elevated TSH levels may be a risk factor independently associated with NAFLD (A/IIb)
- Thyroid hormone replacement therapy is beneficial for individuals with substantial SCH as well as mild SCH patients who also have dyslipidemia (C/IIa)

Neuropsychiatric symptoms

- In younger SCH patients, mild impairments in declarative memory, working memory, and mood may improve with thyroid replacement therapy (C/IIa)

Treatment of SCH

- An approach of effective decision-making should be followed while deciding to treat SCH and all relevant clinical data such as the age of the patient, TSH level, quality of life, comorbidities, CV risk, safety, and personal preferences should be considered for a thorough investigation (C/I)
- Patients (<65 years of age) with TSH 4.5–9.9 mU/L who are healthy and asymptomatic do not require treatment
- Treatment of older patients (≥65 years of age) should be based on weighing the risks and benefits as this category of patients are at a higher risk of overtreatment and are more susceptible to adverse consequences and depends on the decision by the treating physician, and an endocrinologist (C/I)
- The dose of L-thyroxine should be personalized according to age, comorbidities, and life expectancy in elderly aged ≥65 years (C/I)
- In individuals with TSH >10 mIU/L; treatment can be considered in those <65 years, whereas, a watch-and-wait approach can be followed or treatment can be considered if clear symptoms or high CV risk is present in the older population ≥65 years (C/IIa)
- In individuals with TSH <10 mIU/L; treatment should be considered for <70 years with symptoms, whereas those without symptoms can be under observation, whereas those >70 years can be under observation (C/IIa)

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Dose of thyroid hormone replacement in SCH
- The initial L-thyroxine dose is generally lower in SCH patients than what is required in the treatment of OH. The daily dose can vary from 25 to 75 μg depending on the degree of TSH elevation with subsequent monthly or 2-monthly adjustments to maintain serum TSH within the reference range (B/I)

Benefits of L-thyroxine treatment in SCH patients with CVD risk
- L-thyroxine treatment in SCH may provide some benefit in improving the CVD risk factors and markers of CVD risk (C/IIa)
- L-thyroxine should be initiated at a lower dose, typically a dose of 25 μg, with subsequent stepwise dose increase by 25 μg/day every 2–3 weeks until a full replacement dose is reached (C/IIa)

Benefits of L-thyroxine treatment in SCH patients with neuropsychiatric symptoms
- L-thyroxine treatment may be beneficial in SCH patients with neuropsychiatric symptoms (B/IIa)

Follow-up of untreated and treated SCH patients
- Initial diagnosis of SCH should be confirmed by the measurement of TSH, T4, and TPO-Ab after 8–12 weeks (C/IIa)
- If thyroid function has normalized, then no further testing is required in those who are asymptomatic, have negative thyroid autoantibodies, or do not have a goiter. If untreated SCH is persistent, thyroid function should be tested 6 monthly for the first 2 years and then yearly thereafter (C/IIa)
- If L-thyroxine treatment is initiated in SCH patients, then serum TSH should be monitored at least annually thereafter

Impact of the timing of L-thyroxine treatment
- L-thyroxine should ideally be taken 60 min before breakfast. An evening dose can be considered especially in patients where compliance is a major issue. Once weekly L-thyroxine administration can also be considered as an alternative approach for the treatment of SCH (A/I)

Clinical significance of screening for SCH
- Universal screening for SCH in an asymptomatic population is associated with many discrepancies and has inadequate evidence to determine its benefits (C/IIb)
- Targeted screening for hypothyroidism can be considered for those at increased risk for hypothyroidism and in women who are planning a pregnancy or with nonspecific symptoms. It should be considered in an individual case to case depending on the decision by the treating physician or endocrinologists (C/IIb)

CV: Cardiovascular, SCH: Subclinical hypothyroidism, FT4: Free thyroxine, TPO: Thyroid peroxidase, CVD: CV disease, OH: Overt hypothyroidism, TgAb: Thyroglobulin antibodies, NAFLD: Nonalcoholic fatty liver disease

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Conflicts of interest

There are no conflicts of interest.

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