The grey zone of thyroid function: Clinical significance and management controversies in subclinical hypothyroidism

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Abstract

Subclinical hypothyroidism (SCH) is defined by elevated serum thyroid-stimulating hormone (TSH) levels with normal thyroxine (T4) concentrations, representing a diagnostic grey zone in thyroid function. Its prevalence ranges from 4–10% among adults, particularly affecting women, yet it often eludes detection due to the subtlety of symptoms. This spectrum is notably heterogeneous: the majority of SCH cases (~3–8% of adults) exhibit mild disease with TSH levels between 4.5 and 10 mIU/L, whereas a smaller fraction (~0.5–1%) presents with severe SCH, characterised by TSH levels ≥ 10 mIU/L — a differentiation that entails significantly divergent prognostic and therapeutic consequences. This review investigates the complexities of SCH, including its potential associations with cardiovascular risk, neurocognitive changes, and progression to overt hypothyroidism (OH). The efficacy of levothyroxine therapy remains contentious, with conflicting studies regarding its role in symptom relief and cardiovascular event reduction. Additionally, the variability in clinical progression complicates the distinction between benign biochemical variations and clinically significant thyroid disorders. By highlighting special clinical scenarios and management controversies, we present approaches to inform clinical decision-making and promote individualised patient care.

Keywords: subclinical hypothyroidism, thyroid-stimulating hormone, levothyroxine, management controversies, age-specific considerations

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Introduction

The thyroid gland produces two main hormones, tetraiodothyronine (thyroxine, T4) and triiodothyronine (T3), that act on virtually all body tissue, affecting functions from metabolism, thermoregulation, and mental activity to bone maintenance. The pituitary gland secretes the thyroid-stimulating hormone (TSH), which regulates thyroid hormone production.[1] When circulating thyroid hormone levels fall, TSH rises to stimulate the thyroid gland. This compensatory mechanism forms the basis for diagnosing thyroid dysfunction. Hypothyroidism, characterised by elevated TSH and reduced circulating T4, has a well-established clinical profile and management pathway.[1-3] In Europe and the United States, hypothyroidism affects roughly 0.2–5.3% and 0.3–3.7% of adults, respectively, while long-term UK data show a higher annual incidence in women than men.[4] Other countries report similarly diverse patterns, and evidence shows a higher incidence of hypothyroidism with increasing age.[4]

However, beyond overt disease lies a less clearly defined group of individuals who fall within the biochemical and clinical "grey zone" of thyroid dysfunction. This condition is known as subclinical hypothyroidism (SCH), and it is characterised by elevated serum TSH levels with normal circulating T4 concentrations. Because individuals with SCH typically experience minimal or no symptoms of thyroid dysfunction, the condition is identified primarily through laboratory findings rather than clinical presentation. Its prevalence varies widely by age (about 4–10% of adults) but is generally reported to be higher in women.[5] Importantly, SCH is not a uniform condition: the majority of affected persons (~3–8%) exhibit mild SCH, characterised by TSH levels between 4.5 and 10 mIU/L, whereas a smaller fraction (~0.5–1%) presents with severe SCH, indicated by TSH levels ≥ 10 mIU/L. This distinction is clinically significant, as the risk of progression, cardiovascular consequences, and the therapeutic evidence vary considerably across these two groupings. A subset of patients (2–5%) with SCH progress to overt hypothyroidism (OH).[3,5] In some cases, however, studies have shown that TSH levels normalise in over 50% of participants within 32 months of follow-up.[5] The clinical relevance of SCH remains a subject of discussion. Some observational studies have linked SCH to adverse cardiovascular outcomes, dyslipidaemia, neurocognitive changes, infertility, and progression to OH, particularly in those with higher TSH levels or thyroid autoimmunity.[3,5] Conversely, several studies failed to demonstrate consistent symptomatic or cardiovascular benefit from levothyroxine (LT4) therapy, especially in older adults and those with mildly elevated TSH. These conflicting data have fuelled controversy regarding screening strategies, treatment thresholds, and long-term management.[5]

Despite decades of research, substantial gaps persist in the understanding and management of SCH. One major challenge lies in distinguishing a benign biochemical finding from an early stage of clinically meaningful thyroid disease. The progression of SCH is variable, with some evidence suggesting that individuals revert spontaneously to euthyroidism, and a proportion progress to OH.[3,5] There are inconsistencies in treatment recommendations, as conflicting evidence exists regarding the benefits of treating SCH. Clinical decision-making remains particularly challenging as clinicians must balance potential benefits, such as symptom

improvement, cardiovascular risk reduction, or prevention of progression, against risks including overtreatment, atrial fibrillation, and bone loss. This review offers a comprehensive and clinically focused analysis of SCH, examining the complexities associated with inconsistent data, biochemical abnormalities, symptom burden, and therapeutic uncertainty. While previous reviews have often addressed individual aspects of SCH in isolation, such as cardiovascular risk, treatment efficacy, or specific populations, the present review synthesises multisystem manifestations, age-specific considerations, special clinical scenarios, and emerging frameworks in personalised medicine within a unified narrative. This integrated approach aims to address the central clinical challenge of SCH: translating ambiguous biochemical findings into actionable, individualised management strategies. This area remains insufficiently explored in the current literature.

Defining the subclinical spectrum

Biochemical definition evolution

SCH is linked to various health issues, notably atherosclerosis, where it may lead to adverse lipid profiles, increased oxidative stress, and insulin resistance. This connection underscores the need to assess thyroid function in individuals at higher cardiometabolic risk. Still, it is crucial to use population-specific reference ranges to interpret thyroid function tests, as numerous factors can influence hormone levels. Iodine nutritional status is particularly significant, with low free thyroxine (FT4) levels often observed in iodine-deficient areas.[6] The TSH, which is inversely related to FT4, is the most sensitive marker for thyroid dysfunction; however, TSH values can vary due to diverse factors unrelated to age or ethnicity, such as lifestyle and geographic conditions.[6] This variation creates challenges in clinical decision-making, exacerbated by potential misapplication of LT4 therapy and inconsistent guideline recommendations on TSH screening. While some authorities suggest routine screening for the general population, others argue that the evidence is insufficient for universal screening, and there is disagreement about initiating LT4 therapy.[7]

Additionally, determining accurate reference ranges is complicated by interlaboratory variability in assay methods.[6] The reference range for TSH in adults is generally accepted as 0.35–4.5 mIU/L, with higher values indicating hypothyroidism;[8] however, pregnant women require trimester-specific ranges due to hormonal changes.[9] The consequences of untreated hypothyroidism include cardiovascular disease and other serious health implications, underscoring the importance of reliable TSH measurement for accurate diagnosis and treatment.[6]

A further complexity in thyroid function assessment is that TSH reference ranges are based on population-level data that do not account for individual thyroid hormone set points. Research indicates that everyone maintains a genetically influenced TSH set point that may vary significantly from population averages, influenced by factors including age, sex, body composition, seasonality, and genetic variations in thyroid hormone transport and metabolism.[10] Thus, a TSH level within the standard "normal" range could represent a significant deviation from an individual's optimal physiological level. At the same time, a mildly elevated TSH might be normal for certain patients.[10] This concept of individuality in set points has important clinical implications for SCH, as it explains why two patients with the same TSH levels may experience different symptom burdens. Consequently, relying solely on population-derived TSH cut-offs is inadequate for treatment decisions, underscoring the need to incorporate individual clinical context alongside biochemical results to prevent both undertreatment and overtreatment.

The TSH controversy

Modern assays can accurately measure TSH levels as low as 0.01 mIU/L, which benefits critically ill patients; however, there is ongoing debate regarding the clinically significant threshold for elevated TSH levels. Concentrations of TSH > 4.5 mIU/L and TSH ≥ 10 mIU/L are linked to increased mortality in conditions such as pulmonary arterial hypertension and postoperative complications in surgeries, namely, acute type A aortic dissection, respectively.[11] Notably, both low-normal (0.39–1.30 mIU/L) and high-normal (2.09–4.60 mIU/L) TSH values in euthyroid individuals have been associated with heightened risks of all-cause and cardiovascular mortality, especially in adults with diabetes.[11] In pregnancy, recommended upper reference limits are lower and trimester-specific: 2.5 mIU/L in the first trimester, 3.0 mIU/L in the second trimester, and 3.5 mIU/L in the third trimester. However, newer guidelines suggest an upper limit of ~4.0 mIU/L in early pregnancy.[9] These adjustments reflect physiological changes unique to gestation.

Multisystem clinical manifestations

The clinical consequences of SCH extend beyond its potential progression to OH. Its effects are multifactorial and interrelated, influencing the cardiovascular, endocrine, metabolic, neurological, and reproductive systems as outlined in Figure 1. These multisystem manifestations are discussed in detail below.

Cardiovascular system

Jankauskas et al.[12] reported a significant link between cardiovascular diseases and SCH, attributing these conditions to inadequate thyroid function. Decreased thyroid activity leads to reduced myocardial contractility at rest and during exercise, partly due to reduced expression of beta-adrenergic receptors, which are vital to heart function. Thyroid hormones enhance cardiac contractility by upregulating alpha myosin heavy chains (a-MHC) and sarcoplasmic reticulum calcium adenosine triphosphatase (SERCA2).[13] Furthermore, thyroid hormones facilitate vasodilation, promoting blood flow and reducing shear stress. Both OH and SCH contribute to arterial stiffness and atherosclerosis, primarily by diminishing nitric oxide (NO) production, a key vasodilator with anti-inflammatory properties.[13] The cardiovascular impact of subclinical hypothyroidism, though moderate, may potentially exacerbate aging-related cardiac changes and increase heart

failure risk. Population studies indicate a correlation between high TSH levels and heart failure occurrences, even when thyroid function appears normal.[14]

Metabolic and endocrine effects

SCH negatively impacts insulin and carbohydrate metabolism and is associated with increased Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) in non-diabetic patients.[15] The condition is linked to obesity, as thyroid hormones regulate fat metabolism, and lower T4 and higher TSH levels contribute to fat accumulation.[16] Reduced thyroid function lowers thermogenesis and energy expenditure, thereby increasing the risk of insulin resistance. Mechanisms may include elevated free fatty acids and disrupted leptin response. TSH correlates positively with insulin resistance and hyperglycaemia and contributes to hepatic glucose production.[16,17] Hypothyroidism also decreases bone turnover but there is insufficient evidence linking it to osteoporosis or skeletal growth issues in children.[17] Additionally, it affects adrenal gland development and the stress response, with high TSH levels associated with increased cortisol levels due to reduced hepatic clearance.[17]

Neuropsychiatric impact

Thyroid hormones significantly influence neuropsychiatric health by modulating adrenergic and serotonergic systems, contributing to conditions such as depression and anxiety.[18] Hypothyroidism is linked to resistant depression and cognitive decline, including memory deficit and lethargy.[18,19] Conversely, while hyperthyroidism is more commonly associated with psychosis, it can exhibit psychotic features as well. Hashimoto's disease, involving autoantibody production against thyroid hormones, is considered a neuropsychiatric disorder, with inflammation affecting the cerebrospinal fluid.[18] Evidence suggests a relationship between thyroid dysfunction and Alzheimer's disease, with hypothyroidism reducing brain-derived neurotrophic factor (BDNF) levels and impairing memory development due to alterations in glutamatergic and cholinergic systems.[19] Additionally, reduced cerebral blood flow in mild hypothyroidism may lead to cognitive impairments and increase the risk of dementia, particularly in the elderly, although findings are inconsistent.[17-19]

Reproductive and developmental

Thyroid function is essential for reproductive health, as it influences hormone balance and reproductive processes, particularly hypothyroidism, which is linked to various reproductive disorders, including irregular menstrual cycles and infertility.[9] Moreover, research indicates that hypothyroidism may lead to delayed ovulation and is prevalent among women facing fertility challenges. Thyroid hormones collaborate with follicle-stimulating hormones for follicle development and are vital for ovulation and corpus luteum formation.[9] High prolactin levels, resulting from untreated hypothyroidism or, in some cases, undiagnosed conditions, can contribute to fertility issues.[20] Elevated TSH can cause premature ovarian insufficiency and

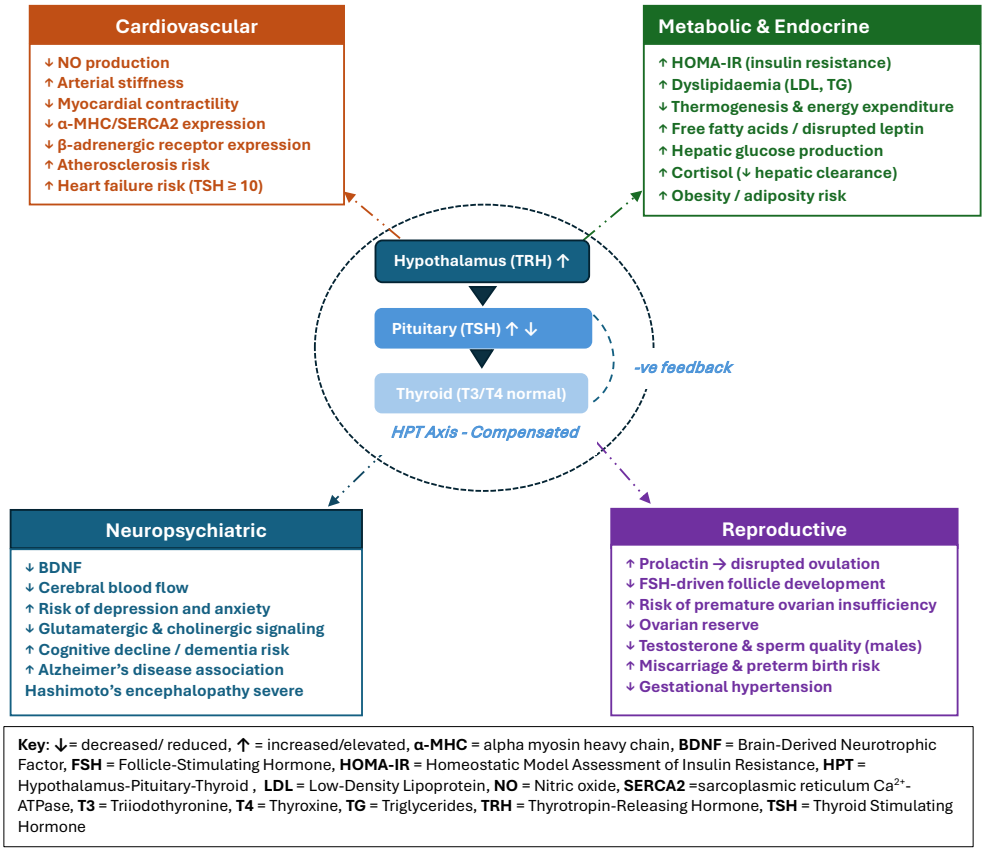

Figure 1: Pathophysiological Mechanisms Linking Subclinical Hypothyroidism (SCH) to Multisystem Effects[9, 12-21]

ovulatory dysfunction.[20,21] Lower ovarian reserve in women with OH or SCH hypothyroidism has been reported.[9,21]

Treatment

Current treatment guidelines

The management of SCH remains contentious within endocrinology, influenced by varying guidelines from prominent international organisations. The American Thyroid Association (ATA) 2014 guidelines suggest considering LT4 therapy for patients with TSH levels over 10 mIU/L due to associated increased risks of heart failure, cardiovascular mortality, and progression to OH. For TSH levels between 4.5 and 10 mIU/L, a personalised strategy is recommended, particularly for younger patients or those with symptoms, goitre, or positive anti-thyroid peroxidase (TPO) antibodies.[22] The European Thyroid Association (ETA) 2013 consensus indicates treatment for individuals under 70 years with persistently elevated TSH above 10 mIU/L, while routine treatment for levels between 4–10 mIU/L is discouraged unless specific risk factors are present.[23] The 2012 guidelines from the American Association of Clinical Endocrinologists (AACE) present a more permissive approach, suggesting the upper limit of normal TSH could be as high as 3.0 mIU/L in certain contexts.[24] Additionally, the 2019 ETA guidelines introduced age-adjusted TSH thresholds, recommending treatment only when TSH levels surpass age-specific reference ranges, particularly noting that elevated TSH in older adults may be physiological rather than indicative of pathology.[25]

Evidence from clinical trials

Randomized controlled trials

Numerous pivotal trials support the treatment of SCH, however these studies often yield contradictory findings. The TRUST trial, published in 2017, is the largest randomised controlled trial (RCT) to date, involving 737 adults aged 65 and older with persistent SCH (TSH 4.6-19.9 mIU/L). It concluded that LT4 therapy did not significantly improve hypothyroid symptoms after one year compared to placebo, as assessed by the Thyroid-Related Quality of Life questionnaire and the Tiredness score.[26] A systematic review by the Institute for Clinical Systems Improvement (ICSI) found limited evidence supporting cardiovascular health benefits of treatment.[27] However, smaller studies have produced mixed results; for instance, an observational study by Razvi et al.[28] reported a reduction in all-cause and cardiovascular mortality among younger patients (< 70 years) treated with levothyroxine, although it did not involve a RCT. Taken together, these findings suggest that a one-size-fits-all approach to the treatment of SCH, without recognising that biochemical correction does not always translate into clinical benefit, particularly in the elderly, may lead to overtreatment. However, the findings in younger patients are based solely on observational studies and do not include robust RCTs. As a result, it is impossible to conclude that treatment reliably improves clinical outcomes.

Meta-analyses findings

Feller et al.[29] conducted a meta-analysis of 21 RCTs involving 2192 participants, finding no significant improvements in quality of life, depressive symptoms, body mass index, or blood pressure with LT4 therapy. Subgroup analyses did not reveal benefits for patients with elevated TSH levels (> 10 mIU/L) or younger individuals. A Cochrane review by Villar et al.[30] on cardiovascular endpoints reported improvements in endothelial function and lipid profiles but did not show a decrease in clinical cardiovascular events. Additionally, a meta-analysis by Rugge et al.[31] published in the Annals of Internal Medicine, concluded that the evidence was insufficient to support routine treatment. These findings raise questions about the efficacy of SCH treatment as there is a disconnect between improved TSH levels and actual clinical outcomes. This suggests that the treatment approach needs to be tailored to improve symptoms rather than solely focusing on biochemical normalisation.

Cardiovascular outcome trials

The association between SCH and cardiovascular disease has been well studied,[13] notably by the Thyroid Studies Collaboration in 2010, which analysed data from 55287 patients. This investigation found a correlation between SCH and increased events and mortality from coronary heart disease (CHD), particularly in patients with TSH levels exceeding 10 mIU/L, as corroborated by Rodondi et al.[32] who reported hazard ratios of 1.89 for mortality in this group. However, intervention trials, such as the TRUST trial sub-study by Stott et al.,[26] have not shown cardiovascular benefits from therapy, suggesting that treatment does not reduce adverse cardiovascular outcomes despite observed associations with risk. This creates a challenge in treatment, as it is still unclear whether cardiovascular disease in SCH patients is a modifiable risk factor that can be improved with LT4 therapy or merely a marker of underlying risk. Therefore, a more multifaceted treatment approach that does not focus solely on biochemical normalisation with LT4 will be required to ensure that therapy leads to meaningful clinical outcomes.

Treatment decision framework

Risk stratification approaches

Current clinical practice in managing thyroid disorders emphasises individualised, risk-based decision-making due to conflicting evidence. ATA/ETA establishes a consensus approach for treatment stratification based on several criteria: TSH levels, with strong treatment considerations for levels above 10 mIU/L, and individualised approaches for levels between 4.5 to 10 mIU/L; age, generally favouring more liberal treatment for patients aged 65 to 70; hypothyroidism symptoms such as fatigue, cold intolerance, and constipation; the presence of thyroid peroxidase antibodies (TPOAb), which increases disease progression risk; cardiovascular risk factors including dyslipidaemia, hypertension, and atherosclerosis; and pregnancy status.[22,24] Additionally, Biondi and Cooper[33] proposed a widely accepted risk assessment model incorporating these factors (see Figure 2 for a comprehensive

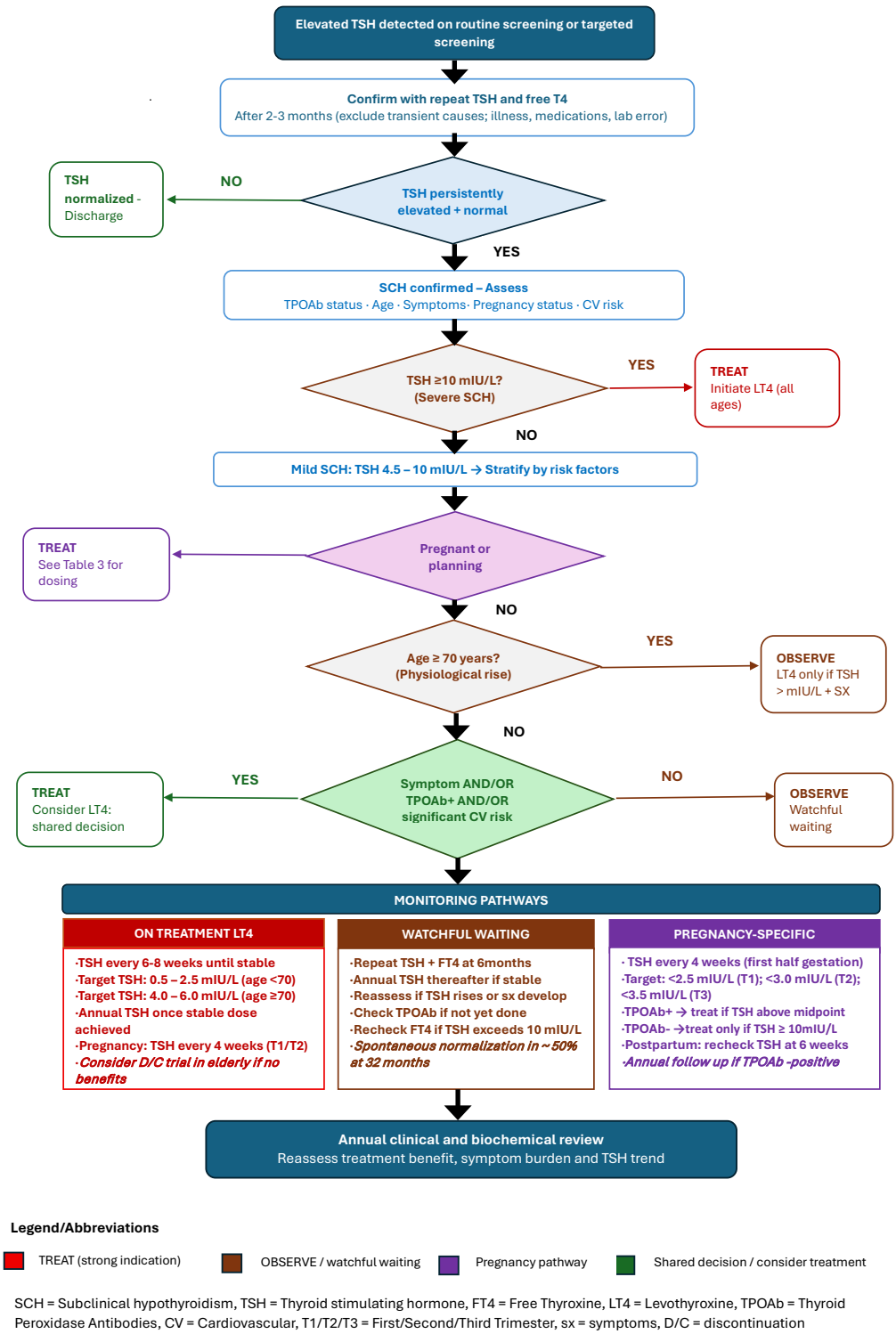

Figure 2: Clinical decision algorithm for the management of subclinical hypothyroidism (SCH), based on ATA 2014, ETA 2013/2019, and AACE 2012 Guideline Recommendations[22-25]

decision-making algorithm). The American College of Physicians recommended against routine treatment for individuals with TSH levels below 10 mIU/L and normal free T4 levels, emphasising the need for shared decision-making under certain conditions.[25]

Symptom assessment tools

Evaluating objective symptoms in thyroid-related conditions is challenging. The Thyroid-Related Quality of Life Patient-Reported Outcome (ThyPRO) questionnaire, validated by Watt et al.,[34] is a key tool for assessing thyroid-specific complaints. The TRUST trial indicates that many symptoms linked to SCH are non-specific and frequent in euthyroid patients, highlighting a complex relationship between thyroid biomarkers and patient-reported symptoms. The Zulewski Clinical Score has been used but lacks adequate sensitivity and specificity for subclinical cases,[35] and research by Canaris et al.[36] suggests poor correlation between symptoms and TSH levels in the subclinical range.

Monitoring strategies

Initial monitoring of patients starting treatment should involve TSH reassessment every 6 to 8 weeks until stabilisation, with a target TSH range of 0.5 to 2.5 mIU/L for younger adults and 4 to 6 mIU/L for those aged 70 or older. Long-term follow-up requires annual monitoring once dosage is stable, and treatment discontinuation trials should be considered for elderly patients without clear benefits. Special monitoring during pregnancy is advised, with TSH checks every 4 weeks in the first half of gestation.[22,37] The specific pathways for both treatment and watchful waiting are detailed in Figure 2.

Treatment is recommended for patients with persistently high TSH (> 10 mIU/L), those who are pregnant or planning pregnancy (target TSH < 2.5 mIU/L), individuals with goitre, rising TSH levels with TPO antibody positivity, significant hypothyroid symptoms, and young patients with TSH > 7–10 mIU/L (under 30–40 years).[9,17] Conversely, observation is preferred for elderly patients with lower TSH levels (< 10 mIU/L), asymptomatic individuals with TSH 4.5–7.0 mIU/L, and those with limited life expectancy or significant comorbidities,[17,38] as elevated TSH may normalise on its own, reducing the need for unnecessary long-term therapy.

Special clinical scenarios

Paediatric population

The incidence of SCH in children is low, primarily idiopathic and mild. It can be associated with conditions like Hashimoto's thyroiditis (HT), goitre, and Down syndrome.[39] Individuals with HT and elevated TSH levels (> 10 mIU/L) require closer monitoring and may need LT4 treatment, unlike asymptomatic children with mild, idiopathic SCH and negative TPO antibodies. Long-term untreated SCH can lead to cardiovascular issues, metabolic disturbances, and cognitive impairments, while growth and bone development typically remain unaffected.[17,39]

Elderly population

SCH is common among older adults and often presents unnoticed as thyroid function declines.[17] While this condition has been linked to cognitive decline and increased fracture risk, several studies do not consistently support these associations.[17,19,38] Higher TSH levels are associated with increased heart failure risk.[38] However, the management of elevated TSH in older adults, especially regarding treatment with LT4, is contentious due to potential risks, including cardiovascular issues and fractures.[17] Evidence suggests that LT4 therapy is most beneficial for those with TSH levels above 7.0 mIU/L, as lower levels do not show significant improvements in symptoms or health outcomes.[38]

Pregnancy and preconception

SCH during pregnancy and preconception poses clinical challenges due to the importance of thyroid hormones for foetal neurodevelopment and maternal health.[2,17] During pregnancy, TSH levels initially decrease due to human chorionic gonadotropin (hCG), then subsequently rise; diagnosis thresholds for SCH are trimester dependent.[9,17] SCH in pregnant women can lead to complications such as gestational hypertension and cognitive impairments in infants, warranting treatment with LT4 for women of childbearing age, especially those planning conception.[17] Monitoring thyroid peroxidase antibody (TPOAb) status is essential, as 50% of TPOAb-positive pregnant women are at higher risk and require LT4 to keep TSH levels below the midpoint range for their trimester.[17] TPOAb-negative women

Table I: Key dosing, TSH targets, and monitoring recommendations in pregnancy and postpartum

Clinical scenario	LT4 Dose (µg/kg/day)	TSH target (mIU/L)	Monitoring frequency	Rationale/Key consideration
Pre-existing hypothyroidism (on LT4 pre-conception)	Increase dose by 25–50% on confirmed pregnancy	< 2.5 (T1); < 3.0 (T2); < 3.5 (T3)	Every 4 weeks in the first half of pregnancy, every 4–6 weeks thereafter	hCG-driven rise in T4 demand increases LT4 requirement from the first trimester; undertreated OH risks foetal neurodevelopmental harm[2,17]
SCH, mild (TSH ≤ 4.2 mIU/L), TPOAb-positive	1.20	Below trimester midpoint: < 2.5 (T1); < 3.0 (T2/T3)	Every 4 weeks until 20 weeks; then every 4–6 weeks	TPOAb-positive women have ~50% higher risk of progression; treatment reduces miscarriage and preterm birth risk[17]
SCH, mild (TSH ≤ 4.2 mIU/L), TPOAb-negative	Observe: LT4 is not routinely recommended	≤ 4.0 (any trimester)	Every 4–6 weeks, recheck if symptoms develop	Evidence for benefit is limited in TPOAb-negative women with mild SCH; watchful monitoring is preferred[2, 37]
SCH, moderate–severe (TSH 4.2–10 mIU/L), any TPOAb status	1.42	< 2.5 (T1); < 3.0 (T2); < 3.5 (T3)	Every 4 weeks until 20 weeks; every 4–6 weeks thereafter	Gestational hypertension, cognitive impairment in offspring, and miscarriage risk are significantly elevated at this TSH range[9,17]
Overt hypothyroidism (TSH ≥10 mIU/L or suppressed FT4)	2.33	< 2.5 (T1); < 3.0 (T2); < 3.5 (T3)	Every 4 weeks until stable, then every 4–6 weeks	Untreated OH carries the highest risk of foetal harm; treatment is mandatory and urgent[2,3]
Postpartum SCH (TSH < 5 mIU/L), TPOAb-positive	Stop therapy; recheck TSH at 6 weeks postpartum	0.5–4.0 (non-pregnant range)	TSH at 6 weeks; if abnormal, repeat at 3 and 6 months; annual TSH thereafter	TPOAb-positive women face an elevated risk of postpartum thyroiditis and long-term hypothyroidism; annual follow-up is warranted[17]
Postpartum SCH, TPOAb-negative	Stop therapy; no routine LT4 required	0.5–4.0 (non-pregnant range)	Recheck TSH for 6 weeks; if normal, no further thyroid-specific follow-up required	Low risk of persistent hypothyroidism postpartum in the absence of autoimmune thyroid disease[17]

typically are initiated on treatment only if TSH exceeds 10 mIU/L. A 2019 meta-analysis by Biondi et al. [37] linked SCH to a higher risk of hypertensive disorders but found limited support for the benefits of LT4 treatment. This raises debates about universal versus targeted screening, with current guidelines favouring high-risk women, potentially missing many cases, especially in iodine-deficient populations with high autoimmune burden.[2] Most SCH cases during pregnancy are temporary, but women with positive TPO antibodies and elevated TSH levels may need persistent monitoring. If treatment is necessary, LT4 dosage is tailored to individual needs, with a focus on normalising thyroid levels preconception to mitigate adverse pregnancy outcomes, as summarised in Table I.[3]

Comorbid conditions

SCH's clinical implications are notably affected by comorbid conditions. SCH is linked to dyslipidaemia, endothelial dysfunction, and raised coronary event risks, particularly when TSH levels exceed 10 mIU/L.[17] In patients with cardiovascular issues, treatment must balance metabolic gains against risks. While LT4 may improve cardiovascular markers, conclusive outcome data are lacking, leading to uncertainty about screening and treatment thresholds.[17] In chronic kidney disease (CKD), SCH is common and may result from altered thyroid hormone metabolism, serving as an independent predictor of CKD progression.[17] Some guidelines suggest thyroid hormone replacement or treatment may slow eGFR decline and improve renal function.[40] Additionally, in polycystic ovary syndrome, SCH is significant due to its association with insulin resistance and other endocrine dysfunctions, suggesting treatment should be considered in select cases. However, prevalence estimates and treatment benefits vary. Further research is essential to determine the specific impact of SCH on metabolic outcomes in these populations.[41]

Drug-induced cases

Several medications, notably amiodarone, lithium, and tyrosine kinase inhibitors (TKIs), can induce SCH, approximately 20% of patients on amiodarone experience thyroid-related side effects, necessitating long-term thyroid function monitoring.[42] Lithium-induced hypothyroidism occurs more frequently in women and during the initial two years of medication. In numerous instances, an underlying factor of autoimmune thyroiditis is present. TKIs like sunitinib and sorafenib lead to hypothyroidism through destructive thyroiditis and reduced iodine uptake.[42] Management of drug-induced SCH requires an individualised approach, including regular TSH monitoring before initiating LT4. Decisions about discontinuing the causative medication can be complicated, and if the medication must be continued, LT4 is typically used to maintain thyroid function while preserving therapeutic benefits.[42]

Emerging perspectives and future directions

Personalised medicine approaches

Personalised medicine approaches aim to tailor treatments to individual symptoms and biology, moving away from generalised therapies. In hypothyroidism, while LT4 is commonly effective,

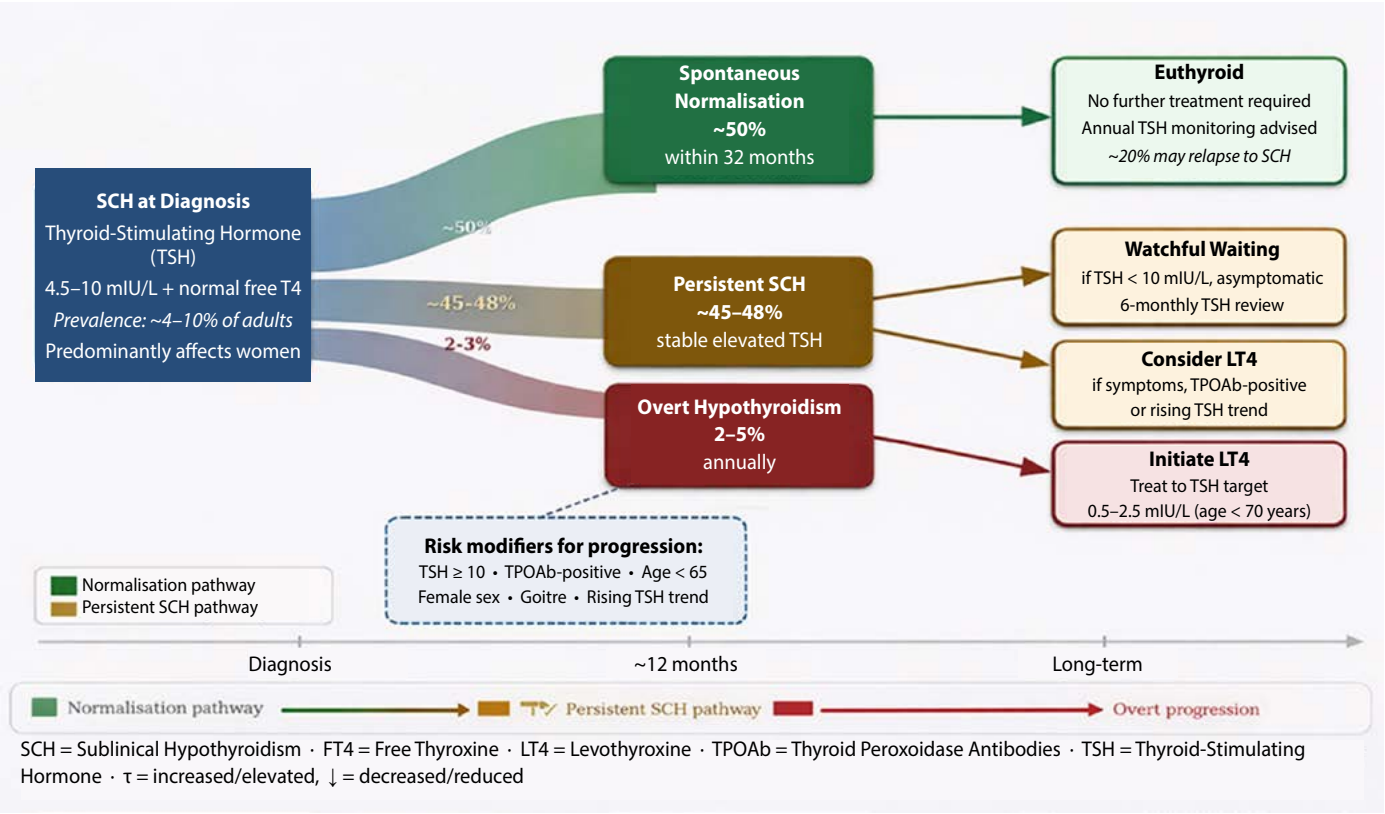

Figure 3: Natural history of subclinical clinical hypothyroidism – progress probabilities: SCH at diagnosis → over time → outcomes of (a) spontaneous normalisation (~50%), (b) persistent SCH, (c) progression to OH (2–5%)[3,5]

many patients remain symptomatic despite normal TSH levels.[43] Genetic variations, particularly in the DIO2 gene, dictate thyroid hormone metabolism, causing some individuals to respond better to combination T3 and T4 therapy.[44] Additionally, each person has a unique TSH set point, influenced by factors such as aging and seasonality, which complicates the ideal treatment approach.[10] TSH may not always reflect true thyroid hormone status, prompting exploration of serum T4 and FT3 levels as better biomarkers.[45] New research highlights the potential of metabolic biomarkers in diagnosing and managing hypothyroidism, with findings suggesting distinct metabolic profiles in hypothyroid individuals. Advances such as the Magnetic Chemiluminescent Immunoassay (MCLIA) kit for detecting thyroid autoantibodies offer promising auxiliary indicators for thyroid function assessment.[45]

Novel therapeutic options

Combination T4/T3 therapy is considered for patients still experiencing symptoms, such as fatigue and cognitive issues despite achieving normal TSH levels from LT4 monotherapy.[43] A systematic review by Nassar et al.[46] reported that individuals on combination therapy had lower serum FT4 and total T4 but higher total T3 levels, while TSH remained similar. Alternative formulations and targeted interventions, including tailored LT4 dosing based on individual profiles, are recommended. Notably, combination therapy may benefit individuals with specific gene polymorphisms and those with persistent symptoms, while special considerations for dosing are necessary in geriatrics and pregnant women.[44]

Research gaps

To improve long-term outcomes for patients undergoing LT3 and/or LT4 therapy, regular clinical and biochemical monitoring is crucial, as shown in Figure 3. An 18-month surveillance period is recommended, as 40% of patients may experience suboptimal dosing, leading to persistent symptoms or increased risks, such as atrial fibrillation.[47] Technological interventions for hypothyroidism diagnosis include AI-assisted ultrasound, the ACR Thyroid Imaging Reporting and Data System (TI-RADS), and digital health tools, which can improve patient stratification.[48] Currently, no validated serum biomarkers reflect tissue-specific thyroid hormone levels; however, potential markers include lipid derivatives and CD5L, which are linked to tissue hypothyroidism.[49] Lastly, while LT4 treatments are relatively low-cost, associated annual expenses can be significant, ranging from $460 to $2555 per patient, with higher costs observed in non-euthyroid patients.[50]

Limitations

The existing evidence base has certain limitations that must be acknowledged. Initially, several relationships outlined in this review, such as those connecting subclinical hypothyroidism (SCH) to cardiovascular risk, metabolic disturbances, and neurocognitive decline, are primarily based on observational studies, which are prone to confounding factors and are unable to demonstrate causality.[3,5,32] The Thyroid Studies Collaboration, conducted by Rodondi et al.,[32] provides the most comprehensive epidemiological data; however, both studies are constrained by their non-interventional design.[32] Secondly, notable heterogeneity is observed across the reviewed studies regarding the laboratory techniques employed to quantify TSH, with interlaboratory variability in assay platforms influencing the comparability of TSH thresholds and reference ranges across different populations.[6] This limits the generalisability of the findings and hinders direct comparisons across guideline recommendations from different organisations. Lastly, results from long-term randomised controlled trials are still limited. The aforementioned TRUST trial monitored patients for only 1 year, leaving the effects of LT4 on significant clinical endpoints, such as cardiovascular events, fractures, and cognitive outcomes, across 5 or more years essentially unexamined.[26] The meta-analyses compiled in this review[29-31] may be influenced by publication bias, as studies yielding null or negative outcomes for LT4 might be underrepresented in the available literature, thereby distorting pooled effect estimates. These limitations collectively highlight the necessity for sufficiently powered, long-term RCTs employing standardised TSH tests and patient-reported outcome measures to address the ongoing uncertainty in the therapy of SCH.

Conclusions

SCH presents a complex challenge within the realm of thyroid function and management. While it affects a significant proportion of the population, particularly women and older adults, the variability in its clinical manifestations and progression necessitates a nuanced approach to diagnosis and treatment. The association of SCH with various health risks, including cardiovascular complications and metabolic disorders, highlights the importance of careful evaluation and monitoring of thyroid function in at-risk individuals. However, the conflicting evidence surrounding the benefits of treatment raises critical questions about the appropriateness of intervention in this population. As the scientific community continues to explore the intricate relationship between thyroid hormones and overall health, there remains an urgent need for more robust research to clarify the long-term effects of SCH and to develop tailored management strategies. Ultimately, a balanced approach that considers individual patient profiles, symptomatology, and the potential risks and benefits of treatment is essential. By integrating emerging perspectives, such as personalised risk assessments and advanced biomarkers, clinicians can enhance their decision-making process, leading to improved outcomes for patients with SCH. Through ongoing dialogue and research, we can bridge the existing knowledge gaps and refine our understanding of this enigmatic condition. Until more definitive evidence emerges, a TSH threshold of ≥ 10 mIU/L remains the clearest indication for LT4 therapy, while shared decision-making is essential for the 4.5–10 mIU/L range.

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