International Journal of Community Medicine and Public Health
Alharbi SA et al. Int J Community Med Public Health. 2026 Feb;13(2):1030-1033
http://www.ijcmph.com
pISSN 2394-6032 | eISSN 2394-6040

DOI: https://dx.doi.org/10.18203/2394-6040.ijcmph20260150

Review Article

Subclinical hypothyroidism and its clinical relevance in routine practice

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Received: 11 January 2026
Accepted: 25 January 2026

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ABSTRACT

Subclinical hypothyroidism is defined by elevated serum thyroid-stimulating hormone levels with normal circulating free thyroxine and is commonly identified through routine blood tests. Although patients are often asymptomatic, the condition has been associated with a range of systemic effects, including cardiovascular dysfunction, lipid abnormalities, cognitive changes, and subtle metabolic disturbances. These associations have raised concerns about potential long-term consequences, especially in populations with pre-existing risk factors. The diagnosis remains challenging due to inter-individual variation in TSH levels, age-related shifts in reference ranges, and the nonspecific nature of presenting symptoms. Interpretation of thyroid function tests must consider these variables to avoid overdiagnosis or unnecessary treatment. Evidence on whether levothyroxine therapy improves clinical outcomes in subclinical hypothyroidism remains mixed. While some studies suggest benefits in symptom relief, lipid profile improvement, or cardiovascular risk reduction, others show limited or no benefit, particularly in older adults. Treatment is more strongly supported in patients with TSH levels above 10 mIU/l, pregnant women, or those planning conception. In contrast, younger asymptomatic individuals with mild TSH elevations are often monitored without pharmacological intervention. Management strategies must balance potential benefits with the risk of overtreatment, including iatrogenic hyperthyroidism and its associated complications. Individualized care, guided by symptom profile, risk factors, and patient preferences, is increasingly recognized as the most appropriate approach. Clinical guidelines continue to evolve as more data emerge from randomized trials and longitudinal studies. Despite progress, significant gaps remain in understanding the natural history and optimal management of subclinical hypothyroidism. Future research focused on biomarkers of progression, patient-reported outcomes, and age-specific thresholds may help address these uncertainties and improve clinical decision-making.

Keywords: Subclinical hypothyroidism, Thyroid-stimulating hormone, Levothyroxine therapy, Cardiovascular risk, Clinical management

INTRODUCTION

Subclinical hypothyroidism (SCH) is defined as an elevated serum thyroid-stimulating hormone (TSH) concentration with normal levels of free thyroxine (FT4), and it represents a frequently encountered biochemical finding in clinical practice. Although it lacks the overt clinical features seen in primary hypothyroidism, its potential progression to overt disease and association with various systemic complications have made SCH a subject of clinical debate. The condition affects approximately 4 to 10 percent of the adult population, with higher prevalence in women and the elderly.[1]

The etiology of SCH varies but is most commonly linked to autoimmune thyroiditis, particularly Hashimoto's thyroiditis. Other causes include partial thyroidectomy, radioactive iodine therapy, or certain medications such as lithium and amiodarone. The detection of SCH often occurs incidentally during routine laboratory evaluations, as patients are generally asymptomatic or present with vague and nonspecific complaints such as fatigue, cold intolerance, or mild cognitive slowing. However, these symptoms often overlap with normal aging or other non-thyroidal illnesses, complicating clinical interpretation.[2]

Controversy persists regarding the clinical significance of SCH. While some studies suggest that untreated SCH may contribute to increased risk of cardiovascular disease, dyslipidemia, heart failure, and cognitive impairment, especially in older individuals, other studies show minimal clinical consequences. For example, increased serum LDL cholesterol and carotid intima-media thickness have been observed in some patients with SCH, potentially indicating early vascular changes.[3] Still, others argue that many of these associations diminish after adjusting for confounding variables, leading to ongoing debates about causality.

Another critical aspect of SCH lies in its natural course. In many cases, the condition remains stable or even reverses spontaneously, particularly when TSH elevations are mild (between 4.5 and 10 mIU/l). Progression to overt hypothyroidism occurs in only a subset of individuals, especially those with high TSH (>10 mIU/l), positive thyroid peroxidase antibodies, or structural thyroid abnormalities.[3,4]

REVIEW

Subclinical hypothyroidism presents a clinical challenge due to its variable natural history and the lack of consensus regarding treatment. While some individuals with elevated TSH levels remain asymptomatic and stable for years, others may progress to overt hypothyroidism or develop complications. This uncertainty has led to divergent practices in routine care. One area of concern is the cardiovascular impact of persistent SCH. Studies suggest that even mildly elevated TSH may be linked to endothelial dysfunction and increased cardiovascular risk, particularly in older adults or those with existing heart disease.[5] However, the evidence remains inconclusive, with some trials showing limited benefit from levothyroxine therapy in reducing cardiovascular events or improving lipid profiles in these patients.

Age and comorbidities play a critical role in treatment decisions. In elderly patients, overtreatment can lead to iatrogenic hyperthyroidism, increasing the risk of atrial fibrillation and bone loss. Therefore, careful evaluation of TSH thresholds and individual patient context is essential. Population-based screening for SCH remains controversial, as widespread testing may lead to unnecessary treatment without clear clinical advantage. As a result, current guidelines emphasize individualized care based on TSH levels, symptomatology, and patient risk profile.[6]

Diagnosis and clinical uncertainty

The diagnostic framework of SCH relies heavily on laboratory thresholds, particularly elevated TSH with normal FT4. Despite this biochemical definition, uncertainties frequently arise in real-world clinical settings. Small fluctuations in TSH, even within the same patient, challenge the notion that a single reading can reliably indicate thyroid dysfunction. Physiological variables such as age, body mass index, and transient illness influence TSH levels and often blur the line between normal variation and early thyroid failure.[7]

These complexities become more evident in primary care where routine testing might identify asymptomatic individuals with mildly elevated TSH. In some cases, repeat testing shows normalization without any intervention. This phenomenon contributes to doubts about the validity of a diagnosis based solely on a one-time test. There is also no universal agreement on the upper limit of normal for TSH, with laboratories and guidelines applying varying thresholds, particularly for older populations. The debate over whether age-specific reference ranges should be adopted remains unresolved and adds to the difficulty in classifying patients accurately.[8]

Diagnostic uncertainty further deepens when symptoms are considered. Many individuals labeled with SCH report fatigue, weight gain, or mood changes, yet these complaints are non-specific and overlap with common experiences or unrelated conditions. A patient presenting with such symptoms may prompt a clinician to check thyroid function, but a slightly raised TSH does not confirm a causal relationship. This raises the risk of misattribution, where coincidental lab abnormalities become the focus of treatment, while other underlying causes go unnoticed. Several reviews have highlighted that patient-reported symptoms do not consistently correlate with TSH levels in the SCH range, reinforcing the need for cautious interpretation.[9] Another diagnostic dilemma lies in the role of thyroid autoimmunity. The

presence of thyroid peroxidase antibodies (TPOAb) supports an autoimmune origin, such as Hashimoto thyroiditis, which is associated with a higher risk of progression to overt hypothyroidism. However, not all individuals with positive TPOAb will develop symptomatic disease. The predictive value of these antibodies, though statistically significant in population studies, is limited at the individual level. Clinicians are often left weighing risk factors with no definitive tools to predict outcomes. Moreover, imaging is not routinely recommended unless palpable nodules or structural abnormalities are present, limiting opportunities to clarify ambiguous cases.[10]

Systemic health implications

The influence of subclinical hypothyroidism extends well beyond the thyroid axis, with mounting evidence supporting its impact on multiple organ systems. One area of interest involves the cardiovascular system, where altered thyroid function appears to modulate vascular tone, lipid metabolism, and endothelial function. Observational data suggest that individuals with elevated TSH levels may exhibit increased systemic vascular resistance, contributing to hypertension and early atherosclerotic changes even in the absence of overt symptoms. This is particularly relevant in populations with coexisting metabolic risk factors such as hyperlipidemia and insulin resistance, which can amplify the cardiovascular burden associated with untreated subclinical dysfunction.[11]

Lipid abnormalities are another consistent finding, especially involving increased total cholesterol and low-density lipoprotein levels. Although the changes are often modest, they persist across large cohort studies and may act as cumulative stressors when combined with aging or sedentary lifestyle. Even in younger patients, untreated dyslipidemia contributes to subclinical vascular inflammation, which over time could elevate the risk of coronary artery disease. The interplay between thyroid-regulated hepatic enzymes and lipid clearance mechanisms highlights a biochemical pathway that connects endocrine disruption with cardiovascular pathology.[12]

Cognitive function also emerges as a domain of concern. Several meta-analyses and cohort studies have explored the relationship between elevated TSH and mild cognitive impairment, with a particular focus on executive function, memory, and information processing speed. The results, while variable, point to a trend where subtle thyroid imbalances may influence cerebral metabolism and neurotransmitter regulation. These effects appear more pronounced in elderly patients, possibly due to reduced neuronal plasticity and pre-existing cerebral vulnerability. However, younger adults with chronic SCH have also reported attention difficulties and fatigue that may reflect more subtle neuroendocrine disruptions.[13] From a metabolic perspective, thyroid hormones play a critical role in glucose homeostasis, energy expenditure, and mitochondrial activity. Even slight reductions in thyroxine availability can lead to alterations in basal metabolic rate, contributing to weight gain, insulin resistance, and altered appetite regulation. In some studies, patients with SCH have shown impaired fasting glucose or features of metabolic syndrome, although causality remains difficult to establish. These findings raise the possibility that undiagnosed or untreated subclinical hypothyroidism could subtly shift the metabolic balance, particularly in individuals predisposed to diabetes or obesity.[14]

MANAGEMENT AND TREATMENT

Managing subclinical hypothyroidism involves more than adjusting hormone levels. It begins with identifying which patients are most likely to benefit from treatment and which may fare better with monitoring alone. Guidelines generally recommend initiating levothyroxine therapy when TSH levels exceed 10 mIU/l, yet this threshold remains debated, especially for individuals who report nonspecific symptoms or have borderline values. The evolving consensus prioritizes context, weighing age, cardiovascular history, pregnancy status, and presence of thyroid autoimmunity when choosing whether to prescribe or observe.[15]

In younger adults, treatment decisions often rely on symptom burden. Some clinicians prescribe a low dose of levothyroxine based on reports of fatigue or poor concentration, hoping for subjective improvement. Trials have shown mixed outcomes in this regard. While some individuals report modest gains in energy or mood, these findings have not been consistent across larger randomized cohorts. The TRUST study, a well-designed multicenter trial, found that levothyroxine did not significantly improve quality of life or thyroid-related symptoms in older adults with subclinical hypothyroidism, prompting a reevaluation of automatic treatment in this age group.[16]

Pregnancy presents a different clinical scenario. In women planning conception or already pregnant, treatment thresholds are typically lower. Even mild thyroid dysfunction has been linked to adverse obstetric outcomes such as miscarriage and impaired neurodevelopment in offspring. As a result, international guidelines support early treatment in women with TSH levels above the trimester-specific range, particularly when thyroid autoantibodies are present. For clinicians working in fertility or obstetric care, this subgroup often represents the clearest indication for active intervention.[17]

In contrast, the management approach for elderly individuals tends to be more conservative. TSH levels naturally rise with age, and treatment with levothyroxine may increase risks of atrial fibrillation and bone loss, especially if overcorrected. Data from observational studies and meta-analyses suggest that treating mild TSH

elevation in patients over 70 rarely improves long-term outcomes and may introduce more harm than benefit. For this reason, some recommendations now advise against treating older adults unless TSH exceeds 10 mIU/l or symptoms are clearly attributable to thyroid dysfunction. The decision to treat in this population increasingly involves shared decision-making and individualized care planning.[18]

Even in those who meet treatment criteria, long-term follow-up and dosage adjustment remain essential. Overreplacement can result in suppressed TSH and the complications associated with subclinical hyperthyroidism. Conversely, undertreatment offers no symptomatic benefit and continues the risk of progression. Monitoring schedules typically include repeat TSH checks six to eight weeks after starting therapy and annually once stability is achieved. Adjustment may be more frequent in older adults or those on multiple interacting medications. While levothyroxine is effective in normalizing TSH, the clinical outcomes it produces vary significantly by population, making blanket policies insufficient.

CONCLUSION

Subclinical hypothyroidism remains a complex and frequently encountered condition in clinical practice. Its diagnosis, systemic impact, and treatment continue to spark debate due to variable patient presentations and outcomes. Current evidence supports an individualized approach rather than a universal protocol. Ongoing research and clearer guidelines are essential to refine management strategies.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Alharbi SA, Hassan WA, Al Rashoud AM, Alkhudhair SI, Altawash OJ, Shukr FA, et al. Subclinical hypothyroidism and its clinical relevance in routine practice. Int J Community Med Public Health 2026;13:1030-3.