

SUBCLINICAL HYPOTHYROIDISM: WHEN SHOULD TREATMENT BE INITIATED?

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Abstract

Subclinical hypothyroidism (SCH) is a common endocrine disorder characterized by elevated serum thyroid-stimulating hormone (TSH) levels with normal circulating free thyroxine (fT4) concentrations. Despite its high prevalence, particularly among women and the elderly, the management of SCH remains controversial. While some patients progress to overt hypothyroidism or develop cardiovascular and metabolic complications, others remain stable or even revert to euthyroidism without intervention. Recent studies have produced conflicting results regarding the benefits of levothyroxine therapy, especially in mild forms of the disease. This review aims to summarize current knowledge on the epidemiology, pathophysiology, clinical implications, diagnostic approach, and treatment strategies of subclinical hypothyroidism, with a particular focus on identifying patients who may benefit from pharmacological intervention.

Keywords

subclinical hypothyroidism, TSH, levothyroxine, thyroid disorders, treatment indications.

Introduction

Thyroid dysfunction represents one of the most prevalent endocrine disorders worldwide. Among these conditions, subclinical hypothyroidism occupies a unique and challenging position due to its biochemical nature and often subtle or absent clinical manifestations. SCH is frequently detected during routine laboratory testing, raising questions regarding its clinical significance and optimal management.

Over the past two decades, increasing attention has been paid to the potential associations between SCH and cardiovascular disease, dyslipidemia, neuropsychiatric symptoms, infertility, and adverse pregnancy outcomes. However, the decision to initiate treatment remains debated, particularly in patients with mildly elevated TSH levels. This article reviews the current evidence and provides a practical framework for clinical decision-making.

Definition and Classification

Subclinical hypothyroidism is defined biochemically by:

- Elevated serum TSH concentration above the upper reference limit
- Normal serum free thyroxine (fT4) levels

Based on TSH values, SCH is commonly classified into:

- Mild (Grade 1) SCH: TSH 4.5–10 mIU/L
- Severe (Grade 2) SCH: TSH >10 mIU/L

This classification is clinically relevant, as the risk of progression and the potential benefit of treatment increase with higher TSH levels.

Epidemiology

The prevalence of SCH varies depending on age, sex, iodine intake, and population characteristics. Large population-based studies estimate a prevalence of 4–10% in the general population, with higher rates observed in:

- Women
- Elderly individuals
- Populations with sufficient or excessive iodine intake

Autoimmune thyroid disease remains the most common underlying cause, particularly in iodine-sufficient regions.

Etiology and Pathophysiology

Etiological Factors

Common causes of subclinical hypothyroidism include:

- Hashimoto's thyroiditis (autoimmune thyroid disease)
- Iodine deficiency or excess
- Thyroid surgery or radioiodine therapy
- Medications (e.g., amiodarone, lithium, interferon- α)
- Aging-related alterations in TSH regulation

Pathophysiological Mechanisms

SCH reflects early thyroid failure, in which the thyroid gland maintains normal hormone production at the expense of increased pituitary stimulation. Elevated TSH acts as a compensatory mechanism to preserve euthyroidism. Over time, continued autoimmune destruction or reduced thyroid reserve may lead to overt hypothyroidism.

Clinical Manifestations

Although many patients with SCH are asymptomatic, subtle symptoms may occur, including:

- Fatigue and reduced energy
- Cold intolerance
- Weight gain
- Cognitive slowing
- Depressive symptoms

These manifestations are often nonspecific and may overlap with aging or comorbid conditions, complicating clinical assessment.

Cardiovascular and Metabolic Implications

Cardiovascular Risk

Numerous observational studies have linked SCH to:

- Dyslipidemia (increased LDL cholesterol)
- Endothelial dysfunction
- Increased arterial stiffness
- Higher risk of coronary heart disease, particularly with TSH >10 mIU/L

However, randomized controlled trials have shown inconsistent benefits of levothyroxine therapy on cardiovascular outcomes, especially in older adults with mild SCH.

Metabolic Effects

SCH has been associated with insulin resistance, weight gain, and metabolic syndrome, although causality remains uncertain.

Reproductive Health and Pregnancy

In women of reproductive age, SCH has been associated with:

- Menstrual irregularities
- Anovulation
- Infertility
- Increased risk of miscarriage and preterm delivery

Current guidelines generally recommend treatment in pregnant women or those planning pregnancy, even in mild SCH, particularly when thyroid autoantibodies are present.

Diagnostic Approach

Diagnosis of SCH should not rely on a single laboratory measurement. Recommended steps include:

- Repeat TSH and fT4 testing after 6–8 weeks
- Measurement of thyroid peroxidase antibodies (TPOAb)
- Thyroid ultrasound in selected cases

Transient TSH elevation due to non-thyroidal illness, medications, or laboratory variability should be excluded.

Management: when should treatment be initiated?

Indications for Treatment

Most guidelines recommend initiating levothyroxine therapy in the following situations:

- TSH >10 mIU/L
- Presence of hypothyroid symptoms
- Positive thyroid autoantibodies
- Pregnancy or pregnancy planning
- Increased cardiovascular risk or established cardiovascular disease

Observation and Monitoring

In patients with TSH 4.5–10 mIU/L who are asymptomatic and without significant risk factors, a watchful waiting approach with periodic monitoring is often appropriate.

Treatment Strategies

Levothyroxine remains the treatment of choice.

- Initial dose: 25–50 µg/day
- Lower starting doses in elderly patients or those with cardiac disease
- TSH monitoring every 6–8 weeks until stable

The goal of therapy is normalization of TSH and improvement of symptoms, while avoiding overtreatment.

Controversies and Recent Evidence

Recent large randomized trials, particularly in older populations, have questioned the symptomatic and cardiovascular benefits of levothyroxine therapy in mild SCH. These findings have shifted clinical practice toward a more conservative, individualized approach.

The concept of precision medicine is increasingly emphasized, integrating biochemical data, clinical presentation, patient preferences, and long-term risk assessment.

Conclusion

Subclinical hypothyroidism is a heterogeneous condition with variable clinical significance. While treatment is clearly indicated in selected high-risk groups, routine therapy for all patients with mildly elevated TSH is not supported by current evidence. Individualized decision-making

remains the cornerstone of effective management, balancing potential benefits against the risks of overtreatment.

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