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Endocrinology

"SUBCLINICAL HYPOTHYROIDISM: EXPLORING THE HIDDEN SPECTRUM OF THYROID DYSFUNCTION"

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ABSTRACT Subclinical hypothyroidism (SCH) is characterized by elevated serum thyroid-stimulating hormone (TSH) levels with normal free thyroxine (T4) concentrations. Although most patients are asymptomatic, vague symptoms like fatigue and constipation may occur, necessitating laboratory-based diagnosis. SCH prevalence ranges from 4–15%, influenced by age, sex, ethnicity, and iodine intake. Common etiologies include chronic autoimmune thyroiditis, thyroiditis, thyroid injury, and drug-induced dysfunction. SCH progression to overt hypothyroidism occurs in 2–4% annually, with risk factors including elevated TSH (>12–15 mU/L) and anti-TPO antibodies. SCH is associated with cardiovascular risks, reproductive challenges, and potential neuropsychiatric and metabolic consequences. Management focuses on levothyroxine therapy for TSH ≥10 mU/L or younger symptomatic patients with TSH ≥7.0 mU/L. Treatment benefits include reducing progression risks and improving symptoms, though overtreatment poses challenges in older adults. Monitoring and individualized treatment strategies are essential to optimize outcomes in this subtle but clinically significant thyroid disorder.

KEYWORDS : Subclinical, Hypothyroidism, iodine, free t4

INTRODUCTION:

Subclinical hypothyroidism is characterized by elevated serum thyroid-stimulating hormone (TSH) levels with normal free thyroxine (T4) concentrations. While some patients may exhibit vague, nonspecific symptoms of hypothyroidism, clinical identification remains challenging, necessitating diagnosis through laboratory tests. This topic focuses on diagnosing and managing subclinical hypothyroidism. It excludes detailed discussions of overt hypothyroidism, as well as subclinical and overt hypothyroidism in pregnancy, which are addressed separately.

The prevalence of subclinical hypothyroidism ranges from 4–15%, varying with factors such as age, sex, ethnicity, and iodine intake. In the NHANES III study, 4.3% of 16,533 participants had subclinical hypothyroidism. Prevalence increases with age, is higher in females than males, and is lower in Black individuals compared to White individuals. Using age-specific TSH reference ranges significantly reduces prevalence estimates in older populations. In Europe, subclinical hypothyroidism is more common in iodine-sufficient areas, with rates ranging from 4.2% in iodine-deficient regions to 23.9% in iodine-rich areas, despite similar anti-TPO antibody levels. Diagnosis is influenced by TSH thresholds.

Etiology:

Causes of subclinical hypothyroidism include:

1. **Chronic Autoimmune Thyroiditis**: Associated with family or personal history of autoimmune diseases, Down syndrome, or Turner syndrome.
2. **Thyroiditis**: Persistent TSH elevation in subacute, postpartum, or painless thyroiditis.
3. **Thyroid Injury**: Partial thyroidectomy, radioactive iodine therapy, or external head/neck radiotherapy.
4. **Drugs**: Amiodarone, lithium, iodine-containing agents, interferon alfa, sulfonamides, and others.
5. **Inadequate Levothyroxine Therapy**: Due to low dosage, noncompliance, drug interactions, or malabsorption.
6. **Thyroid Infiltration**: Conditions like amyloidosis, sarcoidosis, or lymphoma.
7. **Genetic Factors**: TSH receptor or G-alpha gene mutations.
8. **Environmental toxins** and central hypothyroidism with impaired TSH bioactivity.

Clinical Findings

Most patients with subclinical hypothyroidism, particularly those with TSH levels <10 mU/L, are asymptomatic. Some may experience nonspecific symptoms such as fatigue or constipation, though clinical identification is unreliable. Older adults with subclinical hypothyroidism are typically asymptomatic, and symptoms like dry skin, low energy, or constipation are common in euthyroid older individuals.

Diagnosis

The diagnosis of subclinical hypothyroidism relies on biochemical findings of elevated TSH with normal free T4 levels, often confirmed by repeating TSH and free T4 testing after 1–3 months. For pregnant women or those undergoing infertility treatment, immediate retesting and treatment initiation are recommended. The definition of elevated TSH varies based on population, age, and clinical context, with controversies over the upper limit of normal.

Differential Diagnosis:

- Transient TSH elevation (e.g., recovery from illness or thyroiditis).
- Assay variability due to heterophilic antibodies, rheumatoid factors, or macro-TSH.
- Conditions like untreated adrenal insufficiency, TSH-secreting adenomas, thyroid hormone resistance, or TSH receptor mutations.
- Central hypothyroidism and obesity-related TSH elevations.

Careful evaluation is needed to differentiate true subclinical hypothyroidism from other causes of elevated TSH.

Identifying The Cause

To evaluate the cause of subclinical hypothyroidism:

1. **History And Physical Examination**: Check for hypothyroid symptoms, previous treatments for hyperthyroidism, a history of overt hypothyroidism, medications affecting thyroid function, and thyroid enlargement.
2. **Laboratory Testing**: Routine thyroid antibody testing is unnecessary. Anti-TPO antibodies are measured if the treatment decision is unclear, as they suggest Hashimoto's thyroiditis and predict progression to overt hypothyroidism. Antithyroglobulin antibodies are less specific and less predictive.
3. **Imaging**: Thyroid ultrasound is not routine unless nodules or goiter are detected, as it aids in evaluating these findings.

Progression and Consequences of Subclinical Hypothyroidism (SCH)

Progression to Overt Hypothyroidism

- **Incidence**: 33-55% within 10-20 years; annual progression rate of 2-4%.
- **Risk Factors**:
- Elevated TSH (>12-15 mU/L).
- Presence of anti-TPO antibodies.
- Underlying autoimmune disease, prior radioiodine therapy, or radiotherapy.
- **Spontaneous Recovery**: Occurs in up to 62%, particularly in patients with negative antibodies, TSH <10 mU/L, or within 2 years of diagnosis.

Cardiovascular Risks

- **CHD**: Increased risk in TSH ≥10 mU/L but not in mild elevations (4.5-6.9 mU/L).
- **Heart Failure**: Higher risk with TSH >10 mU/L; mild elevations show no significant risk.
- **Stroke**: No overall association, but increased risk in younger patients with higher TSH.
- **Lipid Changes**: Some studies show modest increases in LDL and total cholesterol with TSH elevation.

Mortality
- **Conflicting Results:**
- Increased cardiovascular mortality with TSH ≥10 mU/L.
- Older adults with TSH between 4.8-10 mU/L may have no increased or even reduced mortality.

Reproductive Effects
- **Women:** Unclear impact on fertility, but increased miscarriage risk in SCH and TPO antibody-positive euthyroid women.
- **Men**: Associated with increased sperm DNA fragmentation.

Other Potential Consequences
1. **Nonalcoholic Fatty Liver Disease (NAFLD)**: Higher prevalence of NAFLD, NASH, and fibrosis in SCH.
2. **Neuropsychiatric Symptoms**: Conflicting evidence; possible association with verbal memory defects, corrected by levothyroxine.
3. **Neuromuscular Symptoms**: Fatigue, weakness, and cramps in 64% of patients.
4. **Weight**: Slightly higher baseline weight but no significant weight changes with treatment.
5. **Alzheimer's Disease**: Increased risk in women but not men.
6. **Biliary Stones**: Linked to sphincter of Oddi dysfunction.
7. **Kidney Function**: Higher TSH levels associated with reduced eGFR.

Management Of Subclinical Hypothyroidism

1. **General Recommendations for Thyroid Hormone Replacement:**
- Administer levothyroxine (T4) only to patients with abnormal thyroid function tests.
- Avoid T4 therapy in patients with normal thyroid function tests, even if they present with hypothyroid-like symptoms.

Indications for T4 Replacement:
- **TSH ≥10 mU/L:**
- Strongly recommended for all patients due to the risk of progression to overt hypothyroidism and cardiovascular disease.
- Supported by guidelines from the American Thyroid Association (ATA), AACE, and European Thyroid Association.
- **TSH 7.0–9.9 mU/L:**
- **Patients <65–70 years:** Treatment suggested due to possible cardiovascular mortality reduction.
- **Patients >65–70 years:** Treatment only for those with significant hypothyroid symptoms; risks of overtreatment are higher in this group.
- **TSH ≤6.9 mU/L:**
- Treat younger patients (<65–70 years) with symptoms, high anti-TPO antibody titers, or goiter.
- Avoid treatment in older patients (>65–70 years) as TSH levels in this range may be age-appropriate.
- **Infertility Or Pregnancy Attempts:**
- Treat women with subclinical hypothyroidism (TSH above first-trimester-specific reference) and infertility or ovulatory dysfunction.

Arguments For and Against Treatment:
For Treatment:
- Prevents progression to overt hypothyroidism.
- May improve symptoms (fatigue, depression), decrease goiter size, and reduce cardiovascular risks (lipid profile, contractility).

Against Treatment:
- Risks include overtreatment, cost, and potential adverse effects (e.g., angina, arrhythmias).
- Higher TSH thresholds for older adults, as age-related TSH increases are normal.

Dosing And Monitoring:
- **Initiation:**
- Start with **25–50 mcg daily** (low dose) for older adults or those with cardiovascular disease.
- For younger patients without CVD, start near full replacement dose (1.6 mcg/kg/day).

- **Monitoring:**
- **Target TSH:**
- **0.5–2.5 mU/L** in younger patients.
- **3–6 mU/L** in patients ≥65–70 years.
- Reassess TSH 6 weeks after starting therapy or adjusting dose, then annually once stable.

Monitoring Untreated Patients:
- Repeat TSH and free T4 testing at **6 months**, then yearly if stable.

This structured approach balances the benefits and risks of treatment, particularly in older adults and those with mild subclinical hypothyroidism.

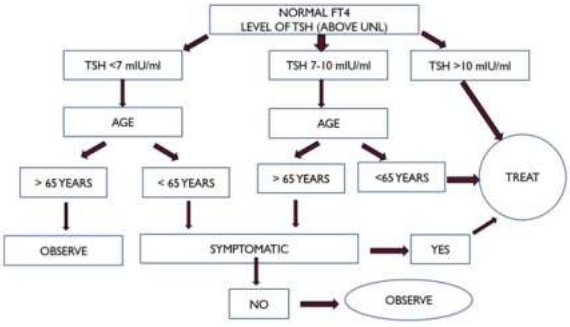

Figure.1 Outline for management of subclinical hypothyroidism.
Abbreviations: UNL, Upper Normal Limit; FT4, Free T4.

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