Consensus Statement on the Management of Subclinical Hypothyroidism

R.V. Jayakumar

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SECTION I

What is subclinical hypothyroidism?

Subclinical hypothyroidism or mild thyroid failure is a condition in which there is a persistent elevation in thyroid-stimulating hormone (TSH) (12 weeks or longer) in the setting of FT4/T4 concentrations that are repeatedly found within the reference interval.[1]

Patients with subclinical hypothyroidism 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).[2]

SECTION II

What is the natural history of (untreated) subclinical hypothyroidism?

The natural history of subclinical hypothyroidism depends on several other factors like underlying cause and the characteristics of each patient. It can be reversible or it can progress to overt hypothyroidism. Progression has been reported to occur in approximately 3–18% of affected patients per year.[3,4,5]

There is increased risk of progression to overt hypothyroidism in patients who are older, female, and positive for anti-TPO (thyroid peroxidase) antibodies. Other strong predictors of progression are serum TSH values >10 mIU/mL—a history of radioiodine ablation for Graves' disease, and a history of external radiation therapy for non-thyroid malignancies, chronic lithium treatment.[6,7,8,9]

High-dose iodine intake is also associated with an increased risk of progression to overt hypothyroidism.[10]

A TSH level >10 mIU/L predicts a higher rate of progression, and a level of <6 mIU/L predicts a lower likelihood of progression. In a study in men and women older than 55 years with a mean follow-up of 32 months, the TSH level normalized in 52% of those with a serum TSH of <10 mIU/L.[11]

SECTION III

What is the clinical impact of subclinical hypothyroidism?

By definition, subclinical hypothyroidism is asymptomatic. It is a biochemical diagnosis based on normal levels of free thyroid hormones and TSH levels that are elevated above the upper limit of normal. However the fact that thyroid hormones were estimated implies subjects presented with some symptoms—among those are poor quality of life, anxiety, depressive symptoms, impaired cognition, and memory.[12] Also, each individual could have a specific set point for the hypothalamopituitary thyroid axis, which is genetically determined. In terms of improvement of symptoms with thyroxine replacement, only tiredness appeared to be positively affected.[13]

The symptoms of hypothyroidism on the other hand are so vague and prevalent that it is difficult to have someone without at least one of them.

Of greater clinical interest is that subclinical hypothyroidism may be associated with cardiac dysfunction, heart failure and effect on the outcome of fetus in pregnancy and infertility.

In patients with TSH levels >10 mIU/L, there is increased cardiovascular mortality but not all-cause mortality

Subclinical hypothyroidism has been associated with increased cardiovascular risk by different mechanisms affecting serum cholesterol, heart rhythm and rate, ventricular function, risk of coronary artery disease and cardiovascular mortality. These operate by inducing left ventricular diastolic dysfunction, reduced systolic function, increased vascular resistance, stiffening of arteries and endothelial dysfunction.[12]

A meta-analysis of individual participant data from 11 prospective cohort studies has showed that subclinical hypothyroidism is associated with an increased risk of coronary heart disease events and CHD mortality in those with higher TSH levels, particularly in those with a TSH concentration of 10 mIU/L or greater.[14]

Re-analysis of data of Whickham survey cohort showed that in comparison to euthyroid patients, those patients with subclinical hypothyroidism had higher systolic and diastolic pressure, and higher cholesterol.

Subjects with subclinical hypothyroidism have an increased risk of progression of heart failure especially when the TSH is >10 mIU/L. Besides this risk of death increased among hospitalized patients with heart failure. A TSH value >10 mIU/L thus is an age-independent risk for future heart failure.[15]

In terms of coronary heart disease events, a large meta-analysis involving more than 50,000 subjects showed that mortality due to coronary heart disease increased in those with serum TSH > 7 mIU/L; risk was significantly higher with an elevation >10 mIU/L[L].[14] However in the absence of any randomized controlled trials showing benefit of intervention, it is questionable whether replacement with thyroxine should be advised for those aged above 60 years must be considered after evaluation of pre-existent risk factors, degree of TSH elevation, co-morbidity and frailty. Any decision must also consider intriguing evidence that in iodine-replete populations, extreme longevity is associated with increased TSH levels.[16]

Undetected subclinical hypothyroidism in pregnancy is a risk factor for miscarriage, low birthweight babies, and poor developmental outcome in the offspring

In a study done on 68 hypothyroid patients, with 45 of them with subclinical hypothyroidism, gestational hypertension—namely, eclampsia, pre-eclampsia, and pregnancy-induced hypertension were found to be more common in subclinical hypothyroid patients than in the general population, with rates of 22%, 15%, and 7.6%, respectively.[17] In a study done to evaluate the effect of hypothyroidism on maternal and fetal outcome, cesarean section rate for fetal distress was significantly higher among pregnant subclinical hypothyroid women.[18] In addition subclinical hypothyroidism could contribute to infertility.[19]

SECTION IV

Should subclinical hypothyroidism be treated at all?

Treatment of asymptomatic patients with serum TSH concentrations between 4.5 mIU/L and 10 mIU/L remains unclear

In 2002 the American Association of Clinical Endocrinologists (AACE), the US Endocrine Society and the American Thyroid Association (ATA) convened a panel to formulate evidence-based guidelines for the diagnosis, screening, and treatment of subclinical hypothyroidism.[20]

The panel recommended that only pregnant women and women contemplating pregnancy be treated for subclinical hypothyroidism and TSH concentrations ≤10 mIU/L. The panel recommended against routine treatment of patients with subclinical hypothyroidism and serum TSH ≤ 10 mIU/L, as available data did not support a clear-cut benefit for early treatment of these patients. However, in a separate consensus statement, these societies recommended that most subclinical hypothyroid patients be considered for treatment, with the key determinant being the clinical judgment of the provider.[21]

Evidence exists to recommend treatment in all patients with a TSH > 10 mIU/L

Patients whose serum TSH levels exceed 10 mIU/L are at increased risk for heart failure and cardiovascular mortality, and should be considered for treatment with L-thyroxine.[22,23]

Evidence is more compelling for the adverse effects of mild thyroid failure in this group. Studies have shown that levothyroxine therapy results in an 8-mg reduction in low-density lipoprotein (LDL) levels.[24]

Among the factors that predict response of lipid levels to levothyroxine therapy are higher levels of TSH, insulin resistance, higher levels of pretherapy cholesterol, and type III hyperlipidemia.

SECTION V

Are there subgroups of non-pregnant patients with TSH < 10 mIU/L in whom treatment is beneficial?

Patients with symptoms of hypothyroidism especially fatigue may be treated

Routine treatment of patients with subclinical hypothyroidism and serum TSH ≤10 mIU/L is not recommended as available data do not support a clear-cut benefit for early treatment of these patients. However, on the basis of clinical judgment treatment of subclinical hypothyroid patients can be considered especially fatigue.[21]

There is lack of evidence of the benefits of thyroxine replacements on lipid parameters in patients with TSH < 10 mIU/L

The Colorado Health Fair study showed that the mean total cholesterol level was 216 mg/dL for euthyroid patients and 224 mg/dL for patients with subclinical hypothyroidism (SCH).[25] Several randomized studies have shown reduction of low-density lipoprotein cholesterol (LDL-C) by levothyroxine therapy. However, most of the studies showing benefit are not categorized for serum TSH levels of 5.0–10.0 mIU/L. A meta-analysis of 13 studies concluded that the lipid profile improved with therapy.[24]

In a 2004 review, data were considered insufficient to show benefits of levothyroxine therapy on lipid levels.[20]

Patients with infertility, high titers of antibodies or goiter or patients with cardiovascular risk factors under the age of 70 may be candidates for therapy

Treatment is considered with recommended LT4 therapy in women who are pregnant, planning pregnancy, have ovulatory dysfunction, or are infertile; as well as in patients with symptoms, goiter, anti-TPO antibodies, and high background cardiovascular risk, including those with hypertension, hypercholesterolemia, insulin resistance or diabetes, isolated diastolic dysfunction, or evidence of impaired endothelial function. Current evidence suggests that middle-aged individuals are more likely to benefit from treatment than elderly individuals.[10,26]

Infants and children under the age of 3 may be started on therapy. Need for continued therapy may be re-assessed at the age of 3

In infants >1 month of age whose serum TSH concentration has failed to normalize, therapy with levothyroxine is recommended until 3 years of age when brain development is no longer thyroid hormone-dependent. At that time a trial off therapy can be performed to determine whether the hypothyroidism was transient or is permanent. In children with SCH >3 years of age in whom thyroid auto-antibodies are negative initially, regular monitoring of the serum TSH and TPOAb concentration is indicated. Because of the low risk of progression, monitoring can be performed in 1-year time, and less frequently thereafter if no worsening is observed.[27]

SECTION VI

How should patients with subclinical hypothyroidism who require treatment be treated?

Confirmation with a free T4 and TSH is recommended and a repeat FT4 and TSH in 8–12 weeks (except where there is a compelling evidence of benefit of immediate therapy such as pregnancy or infertility) is warranted before initiating therapy

It is necessary to distinguish subclinical hypothyroidism from other causes of physiological, artificial, or transiently increased serum TSH.

There are other conditions which should be excluded which causes false and transient increase in serum TSH. Misclassification can be avoided by taking into account the factor that reference range of TSH varies with age, race and body mass index[28] and poor compliance with treatment in primary hypothyroidism.[29] There can be transient increase in serum TSH in hospitalized patients during recovery from severe illness[30] or during recovery from destructive thyroiditis and untreated primary adrenal insufficiency.[31] Interfering heterophilic antibodies [e.g., human antimouse antibodies (HAMA)] in double-antibody immunoassays can also cause falsely high concentration of serum TSH.[32,33]

A laboratory profile of a high TSH and a normal free thyroxine T4/thyroxine FT4 /T4 may also be seen in overweight and obese persons. Normalization of TSH may occur in many of these patients when they lose weight.[34]

Serum TSH concentrations should be measured in 8–12 weeks.

The goal of therapy is to keep the TSH in the normal range. A TSH of 3–5 mIU/mL is desirable for the elderly

In the elderly, any treatment for SCH should be individualized, gradual and closely monitored. For older patients (> 70–75 years), a higher treatment target for serum TSH (around 1–5 mIU/L) is desirable.[35,36]

The lowest dose required to keep the TSH in the normal range is recommended

The rapidity with which the euthyroid state should be attained is dictated by several factors, notably the age of the patient, the duration and severity of hypothyroidism and the presence of other co-morbid conditions, specifically cardiac disease.

The goal of treatment is to restore the individual to a euthyroid state, with resolution of signs and symptoms of hypothyroidism. Chronic under- or over-replacement is common in clinical practice, with over-treatment occurring in about 20% of LT4-treated patients.[4,25]

After initiation of thyroid hormone therapy, the symptoms and signs of hypothyroidism should be assessed at each follow-up visit. The earliest clinical response to LT4 replacement is usually diuresis and weight loss, leading to mobilization of interstitial fluid as glycosaminoglycans are degraded. Weight loss is predominantly due to fluid loss, and is unlikely to exceed 5 kg, even in obese patients, especially if pre-treatment TSH concentrations were only modestly elevated. Two months after initiating therapy, the minimum time required for the pituitary-thyroid axis to re-set, the dose should be monitored by measuring serum TSH, with/without serum T4. Serum TSH should be maintained in the lower half of the normal range (0.5–2.0 mIU/L).[37]

Pregnant women with mild TSH increases require a starting dose of 1.2 µg/kg/d

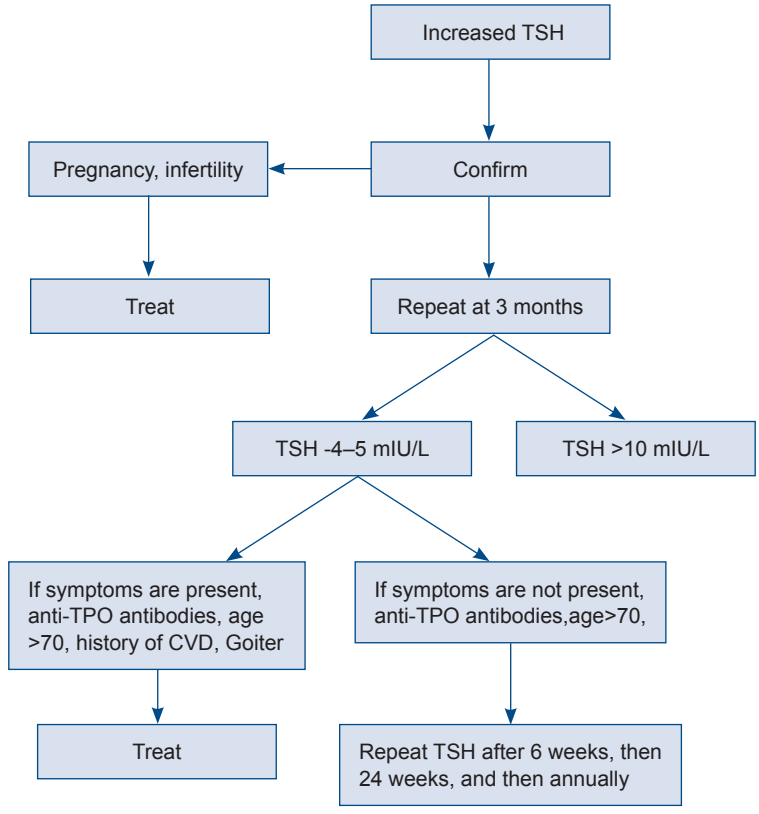
Subclinical hypothyroidism arising before conception or during gestation period should be treated with levothyroxine.

The recommended treatment of maternal hypothyroidism is administration of oral levothyroxine. In newly diagnosed patients with SCH in pregnancy, a starting dose of 1.20 µg/kg/day is advised.[27]

SECTION VII

How should patients who do not require treatment be followed?

1. In patients in whom treatment is withheld, a 6-monthly follow-up with TSH is recommended for the first 2 years and then annually. If the TSH normalizes further testing is not required unless clinically indicated.



Executive Summary

1. What is subclinical hypothyroidism?
   - Subclinical hypothyroidism is defined as an elevated TSH in the presence of a normal free T4.
2. What is the natural history of (untreated) subclinical hypothyroidism?
   - Progression to overt hypothyroidism over a long term is up to 50%. Patients with TSH > 10 mIU/L and/or anti-TPO antibodies have higher rates of progression. Conversely patients with TSH < 10 mIU/L have lower rates of progression.
3. What is the clinical impact of subclinical hypothyroidism?
   - In patients with TSH levels > 10 mIU/L there is increased cardiovascular mortality but not all cause mortality Undetected subclinical hypothyroidism in pregnancy is a risk factor for miscarriage, low birthweight babies, and poor developmental outcome in the offspring
4. Should subclinical hypothyroidism be treated at all?
   - Evidence exists to recommend treatment in all patients with a TSH > 10 mIU/L. The benefits of treating non-pregnant patients with TSH between 4.5 mIU/L and 10 mIU/L has not been clearly established
5. Are there subgroups of non-pregnant patients with TSH < 10 mIU/L in whom treatment is beneficial?
   - Patients with symptoms of hypothyroidism especially fatigue may be treated
   - There is lack of evidence of the benefits of thyroxine replacements on lipid parameters in patients with TSH < 10 mIU/L
   - Therapy is recommended in patients with infertility and TSH between 4 mIU/L and 10 mIU/mL
   - Patients with high titers of antibodies or goiter or patients with cardiovascular risk factors under the age of 70 may be candidates for therapy
   - Infants and children under the age of 3 years may be started on therapy. Need for continued therapy may be re-assessed at the age of 3.

6. How should patients with subclinical hypothyroidism who require treatment be treated?
   - Confirmation with a free T4 and TSH is recommended
   - A repeat FT4 and TSH in 8–12 weeks (except where there is a compelling evidence of benefit of immediate therapy such as pregnancy or infertility) is warranted before initiating therapy
   - The goal of therapy is to keep the TSH in the normal range. A TSH of 3–5 mIU/mL is desirable for the elderly
   - The lowest dose required to keep the TSH in the normal range is recommended
   - Pregnant women with mild TSH increases require a starting dose of 1.2 µg/kg/d
7. How should patients who do not require treatment be followed?
   - In patients in whom treatment is withheld, a 6-monthly follow-up with TSH is recommended for the first 2 years and then annually
   - If the TSH normalizes further testing is not required unless clinically indicated

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