

Subclinical Hypothyroidism: Management in Primary Care - To treat or not to treat?

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Received: November 2020; Accepted: December 2020; Published: January 1, 2021.

Citation: Sanjeewa Sumathipala. Subclinical Hypothyroidism: Management in Primary Care - To treat or not to treat? . World Family Medicine. 2021; 19(1): 151-156 DOI: 10.5742/MEWFM.2021.93962

Abstract

Subclinical hypothyroidism (SCH) is a relatively common condition, and it increases with age. A proportion of SCH patients will go on to develop overt hypothyroidism. Furthermore, there is concern that SCH increases the likelihood of extra thyroidal illness, such as cardiovascular disease. The diagnosis of SCH is a biochemical one, and given the common use of blood tests where thyroid function may be one component, the primary care clinician needs to understand what to do when a patient appears to have SCH. There are a variety of guidelines about the management of SCH for non-pregnant adults. The clinician needs to be aware that certain conditions can cause transient aberrations of thyroid blood test, and of those with persistent SCH, which patients might benefit from treatment and which would be better served with observation over time.

Key words: Subclinical hypothyroidism; Hypothyroidism; Levothyroxine

What is Subclinical hypothyroidism?

Subclinical hypothyroidism (SCH) is a biochemical diagnosis characterized by an elevated serum TSH but a normal free T4 [1]. It represents a compensated state in which increased TSH output is required to maintain normal circulating thyroid hormone levels [2].

SCH has been reported in 5–10% of the population, being more common in women and increasing with age [3]. It is thought to affect approximately 1% of people younger than 70 years of age and 6% of people by 80 years [4]. A study conducted in 2011 in Libya reported the prevalence of subclinical hypothyroidism as 2.3% [5] and the prevalence of subclinical hypothyroidism was 5.98% among females and 4.40% among males in Jordan [6].

The most common cause for SCH is chronic autoimmune thyroiditis [7] where thyroid peroxidase antibodies will be positive. Transient increases in TSH can occur in conditions like subacute thyroiditis, or during recovery from a non-thyroidal illness or when taking medication like lithium or amiodarone [3].

As symptoms are frequently absent in SCH, and free T4 is within the normal reference range, uncertainty exists as to whether there is any benefit from increasing those hormones with replacement therapy [4]. The International Classification of Diseases (ICD) does not provide a separate code for SCH; instead, it is usually labelled as “hypothyroidism, unspecified” [8].

TSH level

TSH is a frequently requested investigation. For instance, although the prevalence of hypothyroidism is estimated to lie between 1-2 % in the UK [9], approximately 25% of adults have thyroid function tests every year [10]. The normal reference range in non-pregnant patients is typically cited as between 0.4 and 4.0 mU/l [11]. By convention, a reference range usually only comprises 95% of a reference population, hence 5% of 'normal' will be outside of that range [2]. The reference range for TSH varies in different ethnic communities, pregnancy and by age [12].

SCH is generally classified into a mild version with TSH levels in the range 4.0 and 10.0 mU/l or a severe version with TSH greater than 10.0 mU/l [13]. 90% of cases of SCH occur in the serum TSH range of 4.0–10.0 mU/l [14]. TSH levels can return to normal in 6–35% of cases of SCH [13]. This reversion to normality is more likely within the first two years of diagnosis, and if the TSH level is less than 10mIU/l and there are no antithyroid antibodies [2].

The reference range used in pregnancy is different and varies according to the trimester [15] and discussion of the management of SCH in this subset of the population is outside the scope of this article.

Symptoms of SCH

The relationship between symptoms suggestive of thyroid hormone deficiency and the biochemical finding of subclinical hypothyroidism is not clear [1]. Symptoms attributable to hypothyroidism, such as weight gain and lethargy can occur in up to 25% of the healthy population, and approximately a third of patients with SCH have no symptoms at all [16]. Although the term subclinical implies that patients with SCH should be asymptomatic, this is difficult to assess, especially in patients with nonspecific complaints such as tiredness who undergo a TSH check [2]. The most frequent symptoms reported were problems with memory, constipation, slow thinking, tiredness, hoarse voice, puffy eyes, feeling colder, muscle weakness and cramps and dry skin [16].

Health consequences of SCH

In the general population, the lifetime risk for developing clinical hypothyroidism has been calculated to be 2.3%, with women having greater risk (3.5 vs 1.0% in men) [17]. Often symptoms develop insidiously, are non-specific and can remain unrecognized for prolonged periods [18]. Untreated hypothyroidism can lead to a variety of symptoms including hair loss, cold intolerance, weight gain, depression, constipation, lethargy, and outcomes like thyroid cancer and even death [19].

It is estimated that 5–8% of people with SCH per year will progress to overt hypothyroidism [13]. In a prospective study of 82 female patients with SCH, after a ten year

follow up, the incidences of overt hypothyroidism were 0%, 42.8%, and 76.9%, when the initial TSH was 4–6mU/L, >6-12 mU/L, >12 mU/L, respectively [20]. In patients who have circulating thyroid peroxidase antibodies, there is also a greater risk of progression from subclinical to overt hypothyroidism [21].

SCH may be associated with an increased risk of cardiovascular disease, especially when the serum TSH concentration is above 10 mU/L [22]. Epidemiological studies have demonstrated an association between coronary heart disease and SCH in younger people [23]. In a study of 1100 consecutive patients with heart failure, those patients with SCH, compared with those who were euthyroid, had impaired exercise capacity, higher pulmonary artery pressures, and increased cardiovascular events [24]. In a cross-sectional study of 25,862 participants (median age 56 years), patients with TSH between 5.1 and 10 mU/L had significantly higher mean total cholesterol concentrations than those with normal TSH levels [16].

In an observational study of 47,573 adults (3,451 had SCH) spanning fifty years, there was an increased risk of fatal stroke in the age groups 18-49 and 50-64 years, with a HR of 4.22 (95% CI, 1.08-16.55) and 2.86 (95% CI, 1.31-6.26), respectively (p trend 0.04). No increased risk was identified for those 65-79 years old (HR, 1.00; 95% CI, 0.86-1.18) or ≥80 years old (HR, 1.31; 95% CI, 0.79-2.18). There was a pattern of increased risk of fatal stroke with higher TSH levels [25].

In a cross-sectional study assessing nonalcoholic fatty liver disease (NAFLD), 30 and 36 percent of individuals with subclinical or overt hypothyroidism, respectively, had typical ultrasonographic findings of NAFLD (versus 20 percent of controls), while 20% and 26% of individuals with subclinical or overt hypothyroidism had abnormal liver enzymes [26].

However, in a recent systematic review and meta-analysis of RCTs in nonpregnant adults with subclinical hypothyroidism, thyroid hormone therapy was not associated with benefit regarding general quality of life, thyroid-related symptoms, depressive symptoms, fatigue/tiredness, cognitive function, muscle strength, blood pressure, or body mass index [27].

A case-control study in which patients 65 years or older with TSH levels of 4.2-10mU/L who died in the years 2012-2016 ('cases') were compared with matched individuals who did not die during this period ('controls'). Use of levothyroxine was compared between groups. On multivariate analysis, treatment with levothyroxine was associated with significantly increased mortality (HR=1.19 CI 1.03-1.38) [28].

A guideline panel recently issued a strong recommendation against thyroid hormones in adults with SCH. The recommendation does not apply to women who are trying to become pregnant or patients with TSH >20 mU/L, and the panelists considered the recommendation may not

apply to patients with severe symptoms or young adults (such as those ≤ 30 years old) [8].

Guidelines for managing SCH

There are several guidelines for the management of SCH in non-pregnant individuals [8]. Relatively recent guidelines have been produced by UpToDate [22], NICE [29] and the European Thyroid Association [30].

UpToDate

TSH less than 7mIU/L:

- Treat if aged less than 65 to 70 years with convincing symptoms of hypothyroidism.
- For patients who are older, the TSH values are considered age appropriate, and treatment not recommended,

TSH 7-9.9mIU/L:

- Treat if aged less than 65 to 70 years because of the reported increase in cardiovascular mortality with that level of TSH.
- Treat if older than 65 to 70 years only if there are convincing symptoms of hypothyroidism

TSH 10mIU/L or greater:

- Treatment is recommended due to the risk of progression to overt hypothyroidism and the association with atherosclerosis and myocardial infarction.

Treatment:

Aim to reduce patient's serum TSH concentration into the age-appropriate reference range.

There are two suggested regimes of LT4:

- Start at a low dose to avoid overtreatment, typically 25 to 50 mcg day. This approach is suggested for older adults or if there is underlying cardiovascular disease.

Or,

- Initiate treatment at slightly below full replacement doses (1.6 mcg/kg/day) depending on the cause of the subacute hypothyroidism.

Follow up:

- TSH is rechecked after 6 weeks and increments of 12.5 to 25mcg per day used to increase or decrease LT4 depending on whether the target TSH has been met.
 - Each adjustment of LT4 requires another TSH recheck after 6 weeks, and an annual check is required once the correct LT4 dose is found.
- For patients with SCH who are not treated with LT4, a six-monthly check of TSH and FT4 is required and annual checks can be undertaken when those levels are stable.

NICE Guidance for Thyroid disease: assessment and management. NICE guideline [NG145]

Referral or discussion with an endocrinologist is recommended if the person:

- Has suspected subacute thyroiditis.
- Has a goiter, nodule, or structural change in the thyroid gland.
- If malignancy is suspected, refer using a suspected cancer pathway.
- Has suspected associated endocrine disease, such as Addison's disease.
- Is female and is planning a pregnancy.
- Has atypical or difficult to interpret thyroid function tests.
- Has a suspected underlying cause of SCH, such as drug treatment with amiodarone or lithium.

In the absence of any of the above, then:

If TSH is greater than 10mIU/L:

- Treat if less than 70 years.
- Watch and wait if aged 70 years or more.

If TSH is 4-10mU/L:

- Consider a trial levothyroxine if age is less than 65 years.
- Watch and wait if aged 65 years or more

Follow up:

- NICE recommends 3 monthly review of the person and TSH levels, adjusting the dose according to symptoms and TFT results. FT4 should be rechecked if there are ongoing symptoms despite treatment.
 - Aim to resolve symptoms / signs of hypothyroidism.
 - Aim to maintain serum TSH and FT4 levels to within or close to the normal reference range.
 - If symptoms persist, consider adjusting the dose of LT4 further to achieve optimal wellbeing, taking care to avoid over-treatment.
 - Once the TSH level is stable (2 similar measurements within the reference range 3 months apart), check TSH annually.
 - If the person has untreated subclinical hypothyroidism or if LT4 therapy has been stopped, consider measuring TSH and FT4:
 - Annually if there are clinical features suggesting underlying thyroid disease, such as previous thyroid surgery or raised levels of thyroid peroxidase antibodies.
- Or,**
- Once every 2–3 years if there are no features suggesting underlying thyroid disease.

A referral to an endocrinologist should be considered if there are ongoing abnormal TFTs despite adequate LT4 treatment and possible underlying causes have been managed or excluded.

European Thyroid Association Management of Subclinical Hypothyroidism

If there is an elevated TSH with normal free T4 level: Repeat the measurement of TSH and free T4, and check for thyroid peroxidase antibodies, after a 2-to-3-month interval.

Individuals found to have positive antithyroid peroxidase or thyroglobulin antibodies, and/or those with a hypoechoic or an inhomogeneous echo pattern on thyroid US should have serum TSH measured.

Patients with persistent SCH and diffuse or nodular goiter should be treated with LT4 replacement with the aim to achieve serum TSH levels.

If TSH greater than 10mU/L

- Age less than 65-70 years: treat even if no symptoms of hypothyroidism
- Age over 70 years: consider treatment if clear symptoms or high cardiovascular risk

If TSH 4-10mU/L

- Age less than 65-70 years:
 - in the presence of symptoms, a trial of LT4 replacement therapy should be considered.
 - in the absence of symptoms, observe.
- Age greater than 70 years: observe

Treatment:

Daily oral LT4 is the treatment of choice.

- If LT4 therapy has been initiated, TSH should be re-checked after 2 months, and dosage adjustments made accordingly.
- The target TSH is in the lower half of the reference range (0.4–2.5 mU/l).
 - If there is no cardiac disease, a weight-related dose of LT4 should be used, approximating to 1.5 µg/kg/day (e.g. 75 or 100 µg/day for a woman, 100 or 125 µg for a man).
 - If there is cardiac disease and for the elderly, a small dose of LT4 should be started, 25 or 50 µg daily. The dose should be increased by 25 µg per day every 14–21 days until a full replacement dose is reached.
 - in the elderly, any treatment should be individualized, gradual and closely monitored.
 - for older patients (>70–75 years), a higher treatment target for serum TSH (around 1–5 mU/l) is acceptable.
 - For patients with mild SCH (serum TSH <10 mU/l) started on LT4 for symptoms attributed to SCH, the response to treatment should be reviewed 3 or 4 months after target TSH is reached. LT4 therapy should generally be stopped if there is no symptomatic improvement.

Follow up:

- Treated patients: TSH should be monitored at least annually.
 - in younger patients with symptoms, the aim is to alleviate their symptoms, with a target for a TSH in the lower half of the reference range (0.3–2.5 mU/l)
 - for older individuals, more relaxed targets are acceptable, with a target TSH between 1.0 and 5.0 mU/l in patients over 70 years of age.
- Untreated patients: repeat the thyroid function test within 8–12 weeks along with thyroid autoantibodies.
 - If thyroid function becomes normal: no further testing if asymptomatic, lack thyroid autoantibodies or do not have goiter.
 - If persistent SCH: thyroid function should be tested 6 monthly at least for the first 2 years and then annually.

Commonalities in guidelines

LT4 is the medication of choice in hypothyroidism, aiming to restore wellbeing and normalize serum TSH determined both by clinical and biochemical assessment, and avoiding detrimental health effects from inadequate or excessive treatment [2]. TSH is categorized into the range of 4 – 10 mU/L or the range greater than 10mU/L. The guidelines also divide people into an older or younger subgroup and management options are also differentiated by whether symptoms of hypothyroidism are present or not. Follow up with blood tests and / or observation is also recommended for those who receive treatment or do not.

To treat or not to treat

Arguments for and against treatment of SCV have been suggested [22]:

Arguments for treatment:

- To prevent progression to overt hypothyroidism, particularly when severe SCH (TSH is greater than 10 mU/L and in the presence of thyroid peroxidase antibodies.
- To possibly improve nonspecific symptoms of hypothyroidism and decrease the size of goiter, if present, in those with mild SCH.
- To possibly improve cardiac contractility and serum lipid concentrations

Arguments against treatment:

- The cost of medication and monitoring
- The commitment to lifelong daily medication in asymptomatic patients
- The potential risk of overtreatment

Suggested approach to a raised TSH with normal free T4

Take a careful history:

- What is the age and gender of the patient?
- Are there symptoms for overt hypothyroidism?
- Are there medications, such as amiodarone or lithium?
- Is there an intercurrent illness that could be causing a raised TSH?
- How long has the TSH been raised for - persistent SCH is more likely if duration is greater than 2 months?
- What is the level of TSH - is it in the mild or severe SCH range?
- Has presence of thyroid peroxidase antibodies been checked?
- Are there features to suggest significant co-morbidities eg cardiovascular disease or dyslipidemia?

Focused examination:

- Are there any signs of hypothyroidism?
- Is there a goiter?
- Are there signs to suggest significant co-morbidities e.g. cardiovascular disease or dyslipidemia?

Establish a clinical diagnosis:

- Do they have mild or severe SCH?
- Is it persistent SCH?
- Is further investigation or referral to a specialist required?
- Do they have features, eg age profile and co-morbidities to suggest whether levothyroxine therapy or observation is appropriate?

Partnership decision with the patient:

- Explain to the patient the doctor's suggested course of action.
- Establish with the patient what he or she would want to do.
- Agree on the best management.
- Follow up in primary care as appropriate.

Conclusion

Although the treatment of SCH continues to be debated, it is an ideal condition to be managed in the first instance in primary care. In the setting of family medicine, an individualized approach to each patient can then be undertaken and advice from specialist colleagues obtained, as necessary. The family medicine doctor can follow up the patient within existing guidelines, alert to any change to the patient's condition and any new understanding of SCH.

Learning Points

Subclinical hypothyroidism (SCH) is a common condition and is a biochemical diagnosis where the TSH is raised but FT4 is normal.

A proportion of SCH will progress to overt hypothyroidism and there is concern that SCH is associated, for some

patients, with an increased risk of adverse outcomes such as cardiovascular disease and non-alcoholic fatty liver disease.

Associated complications of SCH appear to be more likely for patients younger than 70 years of age and in severe SCH where the TSH is above 10mU/L.

There are several guidelines available to the primary care clinician to help guide the management of a patient diagnosed with SCH.

The guidelines agree that if treatment is proposed, levothyroxine is the medication of choice.

The patient and doctor will need to carefully weigh the risks and benefits of treatment versus a conservative approach, particular in the older population.

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