Subclinical hypothyroidism: to treat or not to treat?

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Abstract

There is controversy on the treatment of subclinical hypothyroidism (SCH). While a number of guidelines from professional societies recommend treatment of SCH based on TSH levels, age, and presence of comorbidities, a recent guideline issued a recommendation against thyroid hormone treatment in adults with SCH. In this debate article, we explore this controversy by presenting two points of view about SCH and its treatment. Treatment of patients who are pregnant or trying to become pregnant will not be discussed.

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Introduction

Up to 12% of the adult population has subclinical hypothyroidism (SCH) (1, 2). SCH is a biochemical diagnosis, defined as an elevated serum thyroid-stimulating hormone (TSH) with normal circulating thyroid hormone levels; about 90% of all patients with SCH have TSH levels between 4 and 10 mIU/L (3, 4). SCH can be transient due to recovery from illness or acute thyroid inflammation, whereas the persistent form of SCH is most likely due to autoimmune thyroid disease (5). For them, SCH represents a mild form of thyroid failure, with few patients progressing to overt hypothyroidism (5, 6). Patients with SCH may experience non-specific symptoms suggestive of overt hypothyroidism (e.g. tiredness, fatigue, and cold intolerance) (7, 8). Studies have reported higher rates of cognitive dysfunction, depression, and anxiety among adults with SCH compared to euthyroid adults (9, 10). Yet, the association between SCH and symptoms remains unclear; only 10% of patients with these symptoms have SCH and ~25% of people with normal thyroid function report similar symptoms (11).

It is unclear whether patients with SCH should receive levothyroxine. Experts make recommendations for and against treatment. For example, using the same

body of evidence, a number of guidelines recommend treatment of SCH based on TSH levels, age, and presence of comorbidities (12, 13), while a recent guideline issued a strong recommendation against thyroid hormones in adults with SCH (14). At the core of this controversy is the lack of pragmatic clinical trials enrolling patients likely to benefit from therapy.

In this article, we explore this controversy by presenting two points of view about SCH and its treatment. To this end, we will focus our arguments on those patients with SCH in whom levothyroxine therapy is considered. To illustrate that there is a consensus on the treatment of SCH in the majority of cases, we will briefly start with two cases in which we agree regarding treatment. The debate will then focus on the third case. In this debate article, we will not address the role of treatment for patients with transient SCH or patients who are pregnant or trying to become pregnant.

Case A

A 62-year-old woman presents to the outpatient clinic with complaints of fatigue and difficulty concentrating.

She has a history of episodes with depressive symptoms, but feels that her current complaints are different. Her family history is negative for thyroid disease. General laboratory tests are normal, except a slightly elevated TSH (5.9 mIU/L, reference range: 0.4–4.3 mIU/L), whereas FT4 is normal (19 pmol/L, reference range: 11–25 pmol/L).

Should she be treated with LT4, if a repeat TSH is similar?

We found several reasons for not offering levothyroxine therapy. The first is that the patient may not have SCH. Her mildly elevated TSH values may be normal if we consider a TSH value range adjusted for her age. In addition, her FT4 of 19 pmol/L makes a relation with her complaints even more unlikely. The decision not to offer levothyroxine therapy at this moment will not be altered if the TPO antibodies are positive upon repeat testing, although patients with TPO antibodies have a two-fold increased risk of progression to overt hypothyroidism. Several randomized trials have shown that levothyroxine therapy will provide little or no benefit for patients like her. Given her past medical history, a potential plan of care is to review with her primary care or psychiatrist the possible association of symptoms with depression or antidepressant treatment.

Case B

A 68-year-old woman presents to the outpatient clinic with weight gain, constipation, cold intolerance and fatigue. Except mild rheumatoid arthritis, she has no other comorbidities. Both her daughters have been diagnosed with thyroid disease (Graves' disease in one, Hashimoto's thyroiditis in the other). Her TSH was 2.3 mIU/L when tested 6 years ago. Current laboratory testing shows no abnormalities in the general lab, but a clearly elevated TSH of 14 mIU/L with a normal FT4 (12 pmol/L, reference range: 11–25 pmol/L). Her TPO-antibodies are positive, according to the cut-off provided by the assay manufacturer.

Should she be treated with LT4, if a repeat TSH is similar?

We would treat this patient with LT4. The main reason is that there is a very high chance that she will develop overt hypothyroidism in the upcoming period. Although the overall risk of progression to overt hypothyroidism is about 2–6% per year, the risk is highest in those with higher TSH elevations, with thyroid peroxidase autoantibodies (TPO-ab's), female patients and those with low-normal FT4 levels

(15, 16, 17). So, she is already symptomatic with proven AITD and will very likely develop overt hypothyroidism in the next few years. Why wait with LT4 therapy until she is fully hypothyroid with even more complaints? A second argument may be that epidemiological evidence shows that a TSH > 10 mIU/L is associated with a higher risk of coronary heart disease events and mortality. Although we lack adequately powered RCTs that study the effects of LT4 treatment in SCH, observational studies suggest a lower all-cause mortality in LT4 treated patient younger than 65/70 years (4, 18, 19). However, these observational studies are subject to selection bias and confounding and must be interpreted with caution.

Case C

A 61-year-old woman presents to the outpatient clinic with fatigue and weight gain. She has no comorbidities. Her family history for thyroid disease is unknown. Both her parents died of myocardial infarction in recent years. Laboratory testing shows an LDL cholesterol of 3.2 mmol/L, which was 2.7 mmol/L 1 year ago. There are no abnormalities in the general lab, but her TSH is 8.2 mIU/L with a normal FT4 (13 pmol/L, reference range: 11–25 pmol/L). Her TPO-antibodies are not measured.

Should she be treated with LT4, if a repeat TSH remains this high?

Robin P Peeters

I would consider LT4 treatment in this patient, after carefully excluding other causes of her complaints. Particularly if the repeat TSH increases further and the FT4 remains in this low-normal range. However, her symptoms are aspecific and have been reported in many other conditions as well (11). For that reason, I will discuss with her that we will stop treatment if no clear improvement of symptoms occurs after 6 months (20). Two recent RCTs showed no beneficial effect on symptoms in elderly patients (21, 22), but both studies mainly included very mild SCH (median TSH of 5.7 and 5.8 mIU/L, respectively) with a mean age of 74 and 84 years, respectively, and normal symptom scores at baseline. I will try to obtain more circumstantial evidence pointing toward other symptoms of hypothyroidism. This information is currently lacking, except may be an increase in LDL. Together with the repeat TSH and FT4 after 2–3 months, I would measure TPO antibodies. Like patients with a low-normal FT4 and symptoms of hypothyroidism, patients with TPO antibodies have a two and three-fold

higher risk of progression to overt hypothyroidism (15, 17). The fact that she has a positive family history for cardiovascular disease does not influence my decision. Although several small-scale RCTs have shown beneficial effects of LT4 treatment on cardiovascular risk factors and lipid profile (4, 23, 24), this does not justify treatment since data on clinical outcome are lacking. If there would be an indication to lower her lipid levels, I would prefer to give a statin over LT4 if the statin is well-tolerated (muscle aches, CPK increase).

Altogether, I feel that there are arguments in favor of treatment in this patient with a TSH of 8.2 mIU/L and a low-normal FT4, particularly in case of more suggestive evidence of thyroid disease (i.e. TPOab positivity) or additional clinical symptoms of hypothyroidism. I would discuss those arguments with the patient. If she prefers treatment, but there is no clinical benefit, I will stop treatment after 6 months and switch to follow-up. Duration of follow-up depends on factors such as degree of TSH elevation, symptoms, and patient's preferences. For this particular patient, given the symptoms and elevation of TSH, I would continue to favor a 6-month follow up.

Juan P Brito

I would not offer levothyroxine therapy up front, but rather use the following approach. After understanding more about her symptoms and how they affect her quality of life, I would begin to exclude conditions typically associated with them. I would also describe to her what seems to be the only abnormality in her test results, and what it means for her to have an elevated TSH value, particularly the uncertainty about the association between the results and symptoms. Then, I would present different options, including (1) observation and close monitoring, (2) therapies targeting symptoms such as cognitive training for fatigue and weight loss interventions, and (3) initiation of levothyroxine. I would discuss the pros and cons of each care plan and how each fits her needs and values. For instance, regarding levothyroxine, I would explain what we know about the lack of effect that therapy has on her symptoms as well as the practical issues involved with thyroid replacement therapy (e.g. it must be taken away from food or multivitamins, frequent clinic appointments for monitoring with out-of-pocket and taking time off work to attend appointments). If the TSH lowering therapy becomes the option that makes sense for her situation, I would design a plan in which the lowest dose of thyroid replacement therapy is initiated to normalize TSH values and avoid side effects. Additionally, I would organize with the patient a follow-up time in

which we would decide on treatment discontinuation if treatment had shown to lack benefits.

Robin P Peeters for treatment

Part of the patients with SCH have true thyroid disease and should be treated with LT4

Denying treatment to all patients with SCH leaves a subgroup of patients with true thyroid disease untreated, resulting in a poor quality of life and a condition associated with a worse prognosis.

Subclinical hypothyroidism can be due to true thyroid disease

Serum TSH and FT4 show substantial variability between healthy individuals, whereas the variability within a healthy individual is usually in a much narrower range (25). This points toward a unique individual set point of the hypothalamic–pituitary–thyroid (HPT) axis, and likely explains why a TSH of 10 mU/L can be accompanied by normal FT4 in one, but by decreased FT4 in the other. In this respect, SCH can be interpreted as a mild form of thyroid failure, due to autoimmune thyroid disease in the majority of cases (20). This is supported by the high progression rate to overt hypothyroidism in patients with a clearly elevated TSH (15, 16). The severity of SCH is usually based on the level of TSH elevation, with a commonly used cut-off of 10 mU/L to distinguish between mild and more severe SCH (3, 4, 26). In patients < 70 years, most guidelines from professional societies recommend treatment of SCH when the TSH > 10 mIU/L (1, 13), whereas no routine treatment of SCH is recommended in patients with a TSH <10 mIU/L. Despite these conservative recommendations, prescriptions for levothyroxine have increased substantially in the last decade (27). This seems mainly due to the treatment of mild SCH, since the prevalence of overt hypothyroidism is stable and up to 90% of patients with SCH have a TSH <10 mU/L (3, 11). Against current recommendations, one-third of adults with SCH are offered treatment after a single TSH testing (28). Not all of these patients will have true SCH as TSH levels can be temporarily elevated due to other causes such as non-thyroidal illness or thyroiditis (29). Altogether, this suggests poor adherence to current guidelines recommending against routine treatment (1, 13).

In the context of increased levothyroxine prescriptions, the current guidelines have recently been challenged by a Rapid Recommendation published in the *British Medical Journal* (14), reporting 'a strong recommendation against thyroid hormone treatment in adults with SCH and a TSH <20 mIU/L'. Although it is important to decrease this overuse of levothyroxine in patients without a clear treatment indication, a recommendation not to treat any patient with SCH and a TSH < 20 mIU/L will leave the group of symptomatic patients with true thyroid disease untreated. This Rapid Recommendation was largely based on a systematic review and meta-analysis reporting no clear benefit of levothyroxine treatment for multiple outcomes (23). Whereas the authors of the systematic review acknowledged that the results of their meta-analyses 'may not be generalizable to patients with SCH and a TSH > 10 mIU/L', the authors of the Rapid Recommendation used the same evidence to formulate a recommendation against treatment in all patients with a TSH < 20 mIU/L (14). This cut-off has subsequently been challenged by many authors, including a recent analysis of the mean pooled baseline TSH values of patients included in the meta-analyses by Feller. This showed that the TSH ranged from 6.4 to 7.3 mIU/L, thereby confirming the lack of data on more severe SCH (30). Although the meta-analysis by Feller shows that treatment of very mild SCH is not beneficial in the vast majority of patients, we lack tools to identify the subgroups of patients that will benefit. In addition, we lack robust evidence on more severe SCH (i.e. TSH > 10 mIU/L). Particularly patients with more severe SCH are at risk of thyroid failure and to develop complications. Until we have better data for these subgroups, the decision to treat SCH is not a permanent choice between yes and no. In addition to the TSH, patient context should be taken into account so that treatment will not incorrectly be denied to symptomatic patients with clear SCH.

Patients with SCH have a poor quality of life and a worse prognosis

Patients with SCH more often report symptoms of overt hypothyroidism than age-matched controls, although symptoms are usually milder than in overt hypothyroidism. Number and severity of symptoms increase with higher TSH concentrations. Decreased quality of life, more depressive symptoms, decreased cognitive function and memory have been reported in patients with SCH, but not in all studies (11, 24, 31, 32). This is likely due to the selection of patients (biochemical

screening of a population vs a selection of patients with pre-existing symptoms, age of the patients, the severity of SCH, etc). Also, other symptoms associated with overt hypothyroidism such as fatigue, muscle weakness, weight gain, cold intolerance, and constipation occur more frequently in patients with SCH than in the normal population (4, 5). In those patients with SCH due to a mild form of thyroid failure, it is highly likely that the symptoms are causally related.

As discussed previously, patients with SCH have an increased risk of progression to overt hypothyroidism, with the highest risk in those with higher TSH elevations, with thyroid peroxidase autoantibodies (TPO-ab's) and with low-normal FT4 levels (15, 16, 17). Given the importance of thyroid hormone for various organ systems, the negative consequences of long-term SCH can be expected. This has best been studied for the cardiovascular system. An individual participant data-based meta-analysis from 11 prospective cohort studies ($n > 55\,000$ participants) showed an increased risk of fatal and non-fatal coronary heart disease events, which further increased with higher TSH levels (3). SCH, particularly at TSH levels > 7 mIU/L, has also been associated with congestive heart failure and fatal stroke in similar individual participant based meta-analyses (33, 34). SCH is also associated with a worse lipid profile and surrogate markers of cardiovascular disease, but it is currently unclear if lipid metabolism or other mechanisms mediate these effects on cardiovascular disease.

It is highly likely that patients with morbidities due to SCH will benefit from LT4 treatment

There is no doubt that the treatment of overt hypothyroidism improves clinical signs and symptoms of hypothyroidism (35). It is therefore highly likely that in those patients with SCH due to a mild form of thyroid failure (milder) signs and symptoms of hypothyroidism will improve as well. Multiple studies have shown a continuous relationship between FT4 concentrations, even within the normal range, and thyroid-related endpoints, such as cardiovascular disease and risk of diabetes (35). It is very unlogical to assume that a patient with a TSH of 12 mIU/L and an FT4 of 10 pmol/L (11–25 pmol/L) will benefit from LT4, whereas a patient with a TSH of 12 mIU/L and an FT4 of 11.5 pmol/L will not.

However, patients with other causes of an elevated TSH (i.e. recovery from non-thyroidal illness, recovery from thyroiditis, specific types of medication, assay interference due to for example macro-TSH or heterophilic

antibodies, severe obesity) will not benefit from treatment (20). It is, therefore, essential to make a distinction between true subclinical hypothyroidism and other causes of isolated hyperthyrotropenemia. This is even more important in elderly patients, since a widening of the reference range has been described in elderly persons living in regions with historical iodine sufficiency as part of the physiologic adaptation to aging (36, 37). For practical reasons, virtually all studies investigating the treatment of SCH use a purely biochemical diagnosis, without using an age-adjusted reference range for TSH for example (23). This may have contributed to the normal quality of life at baseline in subjects participating in the TRUST and IEMO trials (21, 22). For the above-mentioned reasons, it is essential to clearly establish a good clinical diagnosis and use the full patient context to interpret the biochemical results. This is particularly relevant in case of a mildly elevated TSH, since the majority of other causes mentioned above cause only a slightly elevated TSH.

A word of caution

Although LT4 treatment is relatively cheap and often considered harmless, a substantial proportion of hypothyroid patients treated with LT4 continue to have TSH levels outside the reference range in day-to-day clinical practice (28, 38). Five years after initiation of LT4 therapy, more than 10% of patients still have TSH levels > 10.0 mIU/L and almost 6% of patients have suppressed TSH levels < 0.1 mIU/L (28). Whereas undertreatment will mainly result in the lack of a possible beneficial effect, overtreatment (a suppressed TSH) should clearly be avoided since this is consistently associated with an increased risk of atrial fibrillation, osteoporosis and fractures, especially in the elderly (2, 39). Although the two most recent RCTs on SCH in the elderly, with a clear treatment protocol, showed no evidence for overtreatment or harms (21, 22), treatment should be stopped when there is a lack of clear clinical benefit.

Conclusion

Prescription rates of LT4 have increased substantially in recent years, without any evidence for an increased prevalence of overt hypothyroidism. This seems to be mainly due to treatment of mild SCH with a TSH < 10 mIU/L, and due to immediate treatment after a single elevated TSH. This demonstrates that adherence to current guidelines from scientific societies should be improved

(1, 13), but is no argument to relentlessly raise the TSH cut-off from 10 to 20 mIU/L. Just like the available evidence does not justify the treatment of all patients with SCH, it does not justify that no patients with SCH should be treated either. Based on the available evidence, physicians should aim to identify those patients who are likely to benefit from treatment, by considering all relevant contextual factors such as symptoms, comorbidities, patient preference, and safety issues. So I am not advocating treatment of all patients with SCH, but only in those with a TSH > 10 mIU/L or in those with a TSH between 7 and 10 mIU/L and a likely relation of the SCH with the patients' complaints. In those patients, a 6-month trial of LT4 treatment can be considered and discussed with the patient. If there is no clear clinical benefit, treatment should be stopped after this period.

Juan P Brito against treatment

There is little or no benefit of levothyroxine for patients with SCH

For patients with SCH to be better off with treatment, treatment must improve their quality of life and/or their prognosis.

Symptoms and quality of life

The body of randomized trial evidence has ruled out moderate-to-large symptomatic benefits with treatment for SCH (23). These randomized trials have included mostly women (46–100%) with a mean age of 50 (range 32–74), mean TSH at baseline of 6.6 (range 4.4–12.8 mU/L), and mild to moderate burden of symptoms. A meta-analysis of these trials showed no difference in hypothyroid symptoms (16.7 vs 16.5) or fatigue/tiredness (28.6 vs 29) as assessed using the ThyPRO self-reported instrument (scale 0–100, lower better), or in health-related quality of life, depression, cognitive function, or muscle strength (23). Most of the evidence came from the TRUST trial which included 737 participants 65 and older, with a mean TSH value of 6.4 ± 2 mU/L, a mean ThyPRO hypothyroid symptom score at baseline of 17, and a mean tiredness score of 25 (22). A sensitivity analysis showed that meta-analytic estimates were not dependent on the inclusion of this trial in the pooled estimates (40). These results are directly applicable to the vast majority of older patients with SCH contemplating treatment (3). A recent pooled analysis of two trials of patients 80 years

or older with a mean TSH of 6.4 mU/L also showed no significant improvement in hypothyroid symptoms or fatigue with treatment, extending the applicability of the evidence to the elderly (21). Clinical trials on the efficacy of levothyroxine treatment provided results that may not apply to the care of younger people with SCH, in whom even mild TSH value elevation is considered abnormal. Few trials included only patients younger than 50 and none of these trials assessed the impact of treatment on quality of life in this subgroup.

Prognosis – cardiovascular outcomes

Several observational studies have shown an association between severe forms of SCH (TSH ≥ 10 mU/L) and cardiovascular disease, particularly in patients younger than 65 and those with a high baseline cardiovascular risk (3, 34, 41). The strength of this association is, however, limited by misclassification of cases (many studies likely included only patients with transient TSH elevation), unmeasured confounders, and non-accounted for interventions that impact cardiovascular risk. Although there are no randomized clinical trials with sufficient power to examine the impact of thyroid hormone therapy on cardiovascular events, the TRUST study found that treatment of SCH did not impact the incidence of cardiovascular events within 1 year after initiation of therapy, HR 0.89 (95% CI, 0.47–1.69). Yet, confidence in these estimates should be low, given the low prevalence of events during follow-up (22).

Inconsistent observational evidence has suggested a possible association of high TSH levels with worse clinical outcomes in patients with heart failure. An individual patient data meta-analysis of 25 390 participants from six prospective cohorts in the United States and Europe, however, found no increased risk of incident heart failure in patients with TSH values between 4.5 and 9.9 mU/L (34). No randomized trial of levothyroxine in patients with SCH and heart failure has been conducted. There is also a reported association of SCH with cardiovascular risk factors; use of levothyroxine therapy may decrease these abnormalities. A randomized, cross-over study of patients with SCH (mean TSH 6.6 mU/L) found that compared to placebo, 100 µg of levothyroxine reduced triglycerides from 232 to 220 mg/dL; low-density lipoprotein cholesterol from 143 to 131 mg/dL, and waist-to-hip ratio from 0.83 to 0.81 (24). Although these changes were statistically significant, it is unclear if there are of clinical relevance.

Prognosis – progression to overt hypothyroidism

Large observational studies of the natural history of SCH have found that about 2% (in the absence of TPO-antibodies) and 4% (in the presence of TPO-antibodies) of patients with SCH and mild TSH elevation (4–10 mU/L) progress to overt hypothyroidism every year, while 60% see their TSH levels return to the normal range over 5 years without treatment (5, 6). These estimates strongly suggest that only a minority of patients with SCH will progress and most will improve without treatment. If we were to treat 100 patients with SCH with TSH elevations between 4 and 10 mU/L, we will potentially avoid the progression to hypothyroidism for 2–4 patients, but we will unnecessarily treat the rest.

Potential harms of treatment

In addition to producing no ostensible benefit, levothyroxine use may harm patients. Levothyroxine treatment requires modification of daily habits – for example, dosing 30–60 min before a meal, monitoring of effects, and frequent dose titration and clinic and laboratory visits. Also, treatment costs \$1600/year, and up to \$4100/year for patients requiring three or more dose adjustments (42). Although these (42) challenges could be mitigated in relatively healthy patients without affordability issues, they could be substantial in elderly patients with SCH. Elderly patients are at higher risk of multimorbidity and polypharmacy, and many struggle financially. Adding levothyroxine therapy to this group of patients could increase the burden of treatment, which in turn may lead to nonadherence and poor health outcomes (43, 44). Levothyroxine treatment may also expose patients to high thyroid hormone levels. Among patients older than 65 years taking levothyroxine, 40–50% had a TSH concentration below 0.45 mIU/L during the follow up (38, 45, 46). The Framingham study found that for people 60 years and older, a low TSH value was associated with a 3-fold increase in the risk of atrial fibrillation over a 10-year period compared to people with normal levels of TSH (45).

Levothyroxine overuse also burdens society. In the United States, the number of prescriptions for levothyroxine increased from 97 million in 2007 to 120 million in 2014; similarly, levothyroxine has become the third most prescribed drug in the UK (27, 47). Given that the prevalence of overt hypothyroidism has remained

stable, treatment for SCH must account for this increase in levothyroxine use. For instance, a population-based study showed that prevalence of treated SCH increased by 64% in women, and by 54% in men in 1995 and between 2006 and 2008 (48). Once levothyroxine is started for patients with SCH, about 90% continue levothyroxine indefinitely (28). The lack of benefit of levothyroxine treatment for patients with SCH and the potential harm of treatment strongly suggest that many patients with SCH are overtreated.

How to do better

The existing evidence, somehow, has not reduced clinicians' enthusiasm for treating patients with SCH. Besides issues of treatment effectiveness and harm, additional drivers of the decision to treat SCH may include: the lack of alternative explanations for symptoms (e.g. fatigue), the need for a therapeutic trial, presence of thyroid autoimmunity, additional comorbidities such as obesity or depression, or the impact of guidelines with recommendations at odds with the extant evidence reviewed here. The American Thyroid Association (ATA) and the American Association of Clinical Endocrinologists (AACE), for example, recommend that 'treatment based on individual factors for patients with TSH levels between the upper limit of a given laboratory's reference range and 10 mIU/L should be considered particularly if they have symptoms suggestive of hypothyroidism, positive (anti) thyroperoxidase antibodies, or evidence of atherosclerotic cardiovascular disease (or) heart failure, or have associated risk factors for these diseases' (12). Following this recommendation would result in treating 92% of all women with SCH. It remains unclear what research is needed to align clinical practice with the existing evidence of lack of benefit and potential harm of levothyroxine.

Avoid screening and reduce overtesting for thyroid dysfunction

Although there are limitations with the evidence and there is still uncertainty about whether levothyroxine treatment benefits subgroups of SCH patients, the majority of patients with SCH receive little or no benefit from levothyroxine treatment. This overuse of levothyroxine starts with the overtesting with TSH assays, particularly in asymptomatic patients. For instance, one study found that 71% of 135 243 persons (aged 20-year or older) without known thyroid disease had their TSH levels measured at least once over a 2-year period (49). In the United Kingdom,

up to 25% of all adults receive routine thyroid function testing each year (28). There is no known benefit of such screening for thyroid dysfunction such that the United States Preventative Services Task Force and the Canadian Task Force on Preventive Health Care have both issued recommendations against thyroid dysfunction screening (50). The implementation of these recommendations has the potential to reduce TSH overtesting.

Avoid misdiagnosis of SCH

Besides reducing the number of patients undergoing SCH screening, significant effort is needed to avoid SCH misdiagnosis. SCH diagnosis is based on a TSH test, the values of which are influenced by normal biological variations, medications, and analytical assay interference. A study following outpatients without thyroid disease over 5 years found that 62% of TSH values normalized without any intervention (6). To overcome this TSH variability, it is recommended that patients with one abnormal TSH value receive another test after a few weeks to confirm SCH (1). Despite this concern for false-positive results, one-third of patients receive treatment after only one abnormal TSH test result (28). Clinicians, including endocrinologists, need to understand the pitfalls of TSH testing to improve SCH diagnosis and avoid unnecessary treatment. Another factor that drives the misdiagnosis of SCH are euthyroid outliers (51); patients in whom high TSH could be still considered part of the normal range for their age. To correctly classify these patients, the TSH reference range may need to be tailored based on age group (52). In fact, some guidelines suggest increasing the upper limit of normal TSH from 5 to 6 mU/L to account for these patients (1, 13, 53). Based on the premises of potential SCH misdiagnosis several studies have aimed to assess the effect of levothyroxine discontinuation on SCH patients. These studies have consistently showed that 30–60% of the patients (with and without TPO-antibodies) remained euthyroid after levothyroxine withdrawal (54, 55, 56, 57).

Conclusion

There is significant evidence that supports the notion that levothyroxine has limited value for patients with SCH, and that its use has been increasing over time as a reflection of more SCH screening, SCH misdiagnosis, and lack of effective approaches to manage non-specific symptoms. Although this evidence suggests that levothyroxine should not be offered as treatment to these patients, it is

possible that uncertainty about the nature of symptoms could lead to a brief levothyroxine n-of-1 treatment trial.

Overall conclusion Juan P Brito and Robin P Peeters

Manage uncertainty and therapeutic restraint

How to care for a patient with SCH and mild symptoms remains puzzling. Failure to act and correct the laboratory abnormality may be perceived as uncaring, while acting on a laboratory test without assisting the patient and palliating their symptoms may be truly so. In order to stop the rise in unnecessary levothyroxine prescriptions, adherence to current guidelines from scientific societies should be improved and clinicians may need to become more expert in the management of symptoms without a clear pathological correlate, particularly in the case of mild elevations in TSH.

In patients younger than 70 years with a TSH > 10 mIU/L, SCH is a form of thyroid failure due to autoimmune thyroid disease in the vast majority of cases. It is for that reason that current ETA and ATA guidelines recommend (consideration of) treatment, particularly in the case of clear symptoms.

In the absence of alternative courses of action, and after reviewing the evidence described above, patient and clinician may opt to conduct a 6-month therapeutic trial, an n-of-1 trial, with the lowest dose of levothyroxine needed to normalize TSH. Symptoms should be reassessed periodically and treatment discontinued if and when no benefit becomes evident.

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