Review Article

Review of the risks and/or benefits of thyroxine treatment in 'mild' subclinical hypothyroidism

Rachel Agius

Abstract

Subclinical hypothyroidism (SCH) is a form of mild thyroid failure and is a commonly encountered condition in clinical practice. It denotes the presence of a raised serum thyroid stimulating hormone (TSH) and normal serum free thyroid hormone concentrations (tri-iodothyronine [T3] and thyroxine [T4]). 'Mild' subclinical hypothyroidism is associated with a TSH level between 4.5-9mIU/L (0.4-4.2) whereas patients with a serum TSH level ≥10mIU/L are classified as having the 'severe' form. The clinical significance of this condition has aroused a lot of interest over the last decade, especially its effects on various health outcomes (namely cardiovascular disease, lipid metabolism, fertility, pregnancy outcomes and fetal neurocognitive function).

Unfortunately the unavailability of adequately powered, double-blind randomised controlled studies precludes the availability of clear cut guidelines as to how one should treat subclinical hypothyroidism. This review looks at the available evidence for and against treatment of SCH with levothyroixine. Most authors agree on the use of clinical judgement as well as individualising management based on the underlying unique patient characteristics when it comes to formulating a management plan for this condition.

Keywords

Subclinical hypothyroidism, prevalence, management, heart, lipids

Rachel Agius MD MRCP (UK)
Department of Medicine,
Mater Dei Hospital,
Malta
rachel.agius@gov.mt

Introduction

The term subclinical hypothyroidism (SCH) is used to describe the finding of a raised serum thyroid stimulating hormone (TSH) level above the defined upper limit of a reference range in conjunction with normal concentrations of free thyroid hormones [1-3]. By virtue of its very nature and due to the fact that patients with SCH exhibit few or no signs or symptoms of thyroid failure the diagnosis is a biochemical one. Thus, detection of SCH relies critically on the upper limit of the TSH reference range. Over the past few decades, the emergence of increasingly sensitive 3rd generation TSH immunometric assays have revolutionised thyroid testing, such that the upper reference limit has declined from about 10mIU/L to around 4.0-4.5mIU/L[1,4-5]. This reflects improved functional sensitivity and specificity of the immunometric assays used, the recognition that normal TSH values are log distributed and also improvements in the sensitivity and specificity of the thyroid antibody tests used to pre-screen subjects. In fact the third National Health and Nutrition Examination Survey (NHANES III),[6] specified a serum TSH range of 0.45-4.5mIU/L using the 2.5th -97.5th percentiles, however there are still controversies regarding the upper normal limit. The National Academy of Clinical Biochemistry, for example, has indicated that 95% of euthyroid volunteers have a serum TSH level of between 0.4-2.5mIU/L and thus argue that the upper TSH limit should be decreased to 2.5mIU/L.[1] Of course this is not without repercussions as lowering the upper limit for normal serum TSH values would increase the number of patients diagnosed with SCH and the economic burden of therapy as well as the possibility of overtreatment. Moreover, there are no studies to suggest that patients with a serum TSH of between 2.5 and 4.5mIU/L are at increased cardiovascular morbidity and mortality. These patients are at the very earliest stage of hypothyroidism and that apart from appropriate follow-up there is no compelling evidence stating the benefits of thyroxine treatment in such cases.[5] Thus the American Thyroid Association and the American Association of Clinical Endocrinology (ATA/AACE) guidelines advise that when reference ranges of 3rd generation TSH assays are not available, the clinician should use the NHANESIII reference population range.[1]

Prevalence and Aetiology

The prevalence of SCH varies between 4 and 20% of the adult population. This wide range reflects differences among the population studied with respect to age, race, gender, dietary iodine intake as well as the TSH cut off value used to define SCH.[3,7] In the Colorado study (which defined SCH as serum TSH >5.1mU/L), serum TSH concentrations were elevated in 9.5% of subjects, and it was found that this percentage increased with each decade of age in women but not in men. [3,9-11]

Around 60-80% of subjects with SCH have positive thyroid peroxidase antibodies making chronic autoimmune thyroiditis the commonest cause of SCH in iodine-replete communities.[9] It has also been shown that obese individuals, healthy elderly patients and the white population have higher serum TSH levels and this should be taken into consideration when interpreting thyroid function tests in these cohorts of patients.[3-4,7, 9,13] Thus, several authors recommend that serum TSH measurement should be repeated within 3 to 6 months after initial assessment (together with a free thyroxine [T4] level) in order to confirm the presence of a raised TSH level.[2-3,9]

It has been necessary to categorise SCH as either 'mild' in patients who have serum TSH levels of between 4.5-10mIU/L, and 'severe' if patients have a serum TSH of >10mIU/L.[2,7-8] This is important for a number of reasons. Patients with the severe form of SCH are at an increased risk of progressing to overt hypothyroidism, are more likely to be symptomatic and more likely to have adverse cardiovascular end points such as coronary heart disease, congestive heart failure and cardiovascular mortality.[7,14-16] In view of this, treatment with levothyroxine is generally recommended for patients with serum TSH levels 10mIU/L.[3,7] However, review of the literature shows conflicting data with regards to evaluation and management of mild SCH. While it is known that the majority of patients will have the mild form of SCH[7,9-10] and that thyroid hormone action has major effects on the cardiovascular system as well as lipids and other tissues [4], the available data shows conflicting results with respect to management of mild SCH.[2,4,7,9,11] These inconsistencies stem from the fact that the diagnosis of SCH is arbitrary, with different studies varying in their definition of SCH resulting in a wide degree of thyroid failure examined as well as heterogeneity with respect to age, gender and ethnicity of the examined subjects [8]. Thus several authors and expert panels recommend using clinical judgement as well as an individualised approach, taking into account the individual's unique situation when it comes to deciding the need for treatment of this condition.[1]

Natural history and progression of subclinical hypothyroidism

Both spontaneous recovery as well as progression towards overt hypothyroidism have been documented in several studies in patients with mildly raised serum TSH. The presence of antithyorid antibodies, female sex as well as higher serum TSH levels (≥10mIU/L) are associated with increased risk of progression.[3,4,18-19] In the 20 year follow-up of the Whickham study, the annual rate of progression to overt hypothyroidism was around 4% in females with a raised serum TSH level and positive antibodies, 3% if only serum TSH levels were raised and 2% in those with only positive antithyroid antibodies. At the 20-year follow up the respective cumulative rates of hypothyroidism were 55%, 33% and 27%.[15,20] On the other hand another study showed that in subjects older than 55 years with SCH and no previous history of thyroid disease. 37.4% of patients normalized their serum TSH level and only 26.8% developed overt hypothyroidism, with the only significant factor for progression to overt hypothyroidism being the serum TSH concentration. [18] These findings consolidate our knowledge that whilst some subjects do progress to overt hypothyroidism, a significant number will not and hence obviate the need for T4 treatment.

Subclinical hypothyroidism and its effects on cardiovascular disease and metabolism

The various effects of thyroid hormone on the cardiovascular system and metabolism are well known and hence it is reasonable to expect adverse cardiovascular effects in patients with SCH.[14] SCH has been associated with increased systemic vascular resistance, altered endothelial function, atherosclerosis, arterial stiffness, dyslipidaemia and altered coagulability. However, the association between SCH and coronary heart disease (CHD) events remain to be debated due to the divergent results of several observational studies.[3,12,14,21-23] The Rotterdam study found that SCH was an independent risk factor for aortic atherosclerosis and myocardial infarction and the risk was comparable to the known major risk factors for cardiovascular disease (such as smoking, diabetes and dyslipidaemia).[7,21] Also, a recent re-analysis of the original Whickham Survey (which defined SCH as a serum TSH between 6-15mIU/L and normal T4 levels) showed a positive association between SCH and the risk of CHD events and mortality and also suggests that treatment with thyroxine may reduce mortality as well as CHD events. A meta analyses has suggested that the incidence and prevalence of CHD events and mortality were modestly increased in participants with mild thyroid failure younger than 65 years of age but not in older individuals and that while prevalent CHD

was higher in both genders, it was statistically significant only in women.[24] Thus, it can be inferred that SCH is associated with an increased risk of CHD events and mortality particularly in those patients with a TSH concentration of 10mIU/L or greater.

Another important feature of SCH is its effects on cardiac function. SCH is associated with impaired left ventricular diastolic function at rest (often the earliest manifestation of heart disease in this setting) and systolic dysfunction on effort which may be associated with poor exercise capacity and impaired quality of life.[7,9,25] In the Cardiovascular Health Study of 3044 adults aged ≥ 65 years of age, an increased incidence of heart failure was only recorded in those patients with a TSH of ≥10mIU/L.[19] This risk was not increased in older subjects with TSH levels between 4.5 and 9.9mIU/L. Studies evaluating reversibility of cardiac dysfunction following levothyroxine therapy were positive suggesting that thyroxine therapy can normalise the hemodynamic alterations due to SCH, however, most of them were not blinded or placebo-controlled.[3,12]

The metabolic abnormalities linked with SCH include an increase in total and LDL cholesterol, but data on its effects on HDL cholesterol, triglycerides and lipoprotein(a) is still somewhat conflicting.[2,7,27] One meta-analysis showed that the beneficial effects of T4 therapy was proportional to the degree of hypothyroidism and the serum lipid level, such that reduction in serum lipids was significant in those with a TSH level >10m/IU/L and in those whose baseline serum cholesterol was >6.2mmol/L.[3,9,15,27-28] However, other studies did not show any relationship between SCH and raised cholesterol levels.[24,28]

Effects of replacement therapy

When it comes to the effects of treatment on symptoms, hypothyroid symptoms tended to improve only when the TSH level exceeded 10mIU/L.[29-30] In the Colorado study, patients with SCH reported more symptoms than euthyroid subjects but fewer symptoms than in the overtly hypothyroid patients.[10] Taking this into account, the available data does not confirm clear-cut benefits for routine thyroxine therapy in patients whose serum TSH level is <10mIU/L but serial monitoring of TSH levels at 6- to 12-month intervals with a 'watch-and-wait policy' is prudent and instituting therapy if the TSH levels worsens or if the patient has symptoms compatible with hypothyroidism.[2-3,9]

Subclinical hypothyroidism and pregnancy

Another important issue to consider is the finding of SCH in pregnant women or those women contemplating pregnancy. The importance of thyroid hormone (especially in the first trimester) for foetal brain development and maturation is well known. [3,31] It has been shown that the prevalence of SCH in women of reproductive age is between 0.5-5%.[3,6,10,17] Trimester-specific reference ranges for TSH should be applied, this is because there is strong evidence in the literature to suggest that both the upper and lower normal limits of TSH levels are lower in the pregnancy state when compared to the non-pregnant state.[32] Several studies have shown an association between SCH and increased risk of adverse pregnancy outcomes. However, even here data is also conflicting. The commonly reported adverse effects include increased rates of miscarriages, placental abruption, preeclampsia and premature delivery.[31,33-34] One study found an association between inadequately treated women with SCH and foetal neurocognitive development. This study (which mainly recruited overtly hypothyroid pregnancies) demonstrated a reduction in intelligence quotient as well as delays in motor, language and attention in off-spring of mothers with thyroid hormone insufficiency. Thus, the ATA taskforce state that the available high-quality evidence is enough to associate SCH with increased risk of adverse pregnancy outcomes.[32] Overall, these data show that the potential benefits of levothyroxine treatment outweigh the risks in pregnant women and hence justify its use.

Risks of replacement therapy

Finally one should also keep in mind the risks of thyroxine therapy. It has been shown that around 50% of patients on thyroxine replacement have serum TSH levels either above or below the reference range, implying that a considerable number of patients are either under- or over-treated.[10,15,20] The consequences of over-treatment are iatrogenic hyperthyroidism which has been associated with two important adverse outcomes, namely osteopenia and atrial fibrillation.[2,18,36] Two meta-analyses of cross-sectional studies on postmenopausal women both found that suppressed TSH values with thyroxine treatment were associated with significant reduction in bone mass. On the other hand, in the Framingham study, the risk of developing atrial fibrillation in patients with low serum TSH levels was increased threefold in subjects aged ≥60 years compared to those with normal TSH levels.[8,20] Moreover, in elderly subjects with mild SCH, treatment is not always beneficial.[3] As has been stated previously, mild increases in serum TSH levels in elderly subjects does not always imply true thyroid hormone deficiency and that mild thyroid failure may be associated with longevity.[2,7] Studies have also shown that CHD events and mortality were lower in older patients with mild SCH.[24] Hence, routine treatment with thyroxine in elderly subjects is not advocated by

many authors and that treatment should be individualised based on the presence of associated co-morbidities, symptoms, cognitive function and overall quality of life.[3,7] When treating this cohort of patients, lower doses of thyroxine therapy are often adequate and clinicians should set higher target serum levels for TSH then in younger subjects in a bid to mimic physiological values.

Another important issue to consider when contemplating thyroxine replacement in patients with autoimmune thyroid disease is hypocortisolaemia. The association of autoimmune thyroid disease and Addison's disease is well described. Thus, it is prudent to exclude adrenal insufficiency before starting thyroxine replacement in order to avoid a potentially fatal adrenal crisis. Moreover, it has also been shown that adrenal insufficiency per se may be associated with raised TSH levels which normalise when glucocorticoid deficiency is corrected. [37]

Conclusion

SCH is a commonly encountered condition in clinical practice. However, as one can see the myriad of differences encountered in study results as well as the paucity of evidence in certain situations makes management of SCH somewhat difficult. Most authors advise use of clinical judgement as well as individualising management on a case-by-case basis. Until the availability of large, double-blinded randomised controlled trials upon which to base unequivocal recommendations, clinicians should base their management strategy on the underlying unique patient characteristics (such as age, gender, presence of hypothyroid symptoms, cognitive, metabolic and cardiovascular risk factors as well as quality of life) in order to have sufficient grounds for or against treatment.

References

1. Garber J, Cobin R, Gharib H, Hennessey J, Klein I, Mechanick J *et al.* Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American association of clinical endocrinologists and the American thyroid association. *Endocrine Practice* 2012; 18(6): 988-1028.
2. Gillett M. Subclinical Hypothyroidism: Subclinical Thyroid Disease: Scientific review and guidelines for diagnosis and management. *Clin Biochem Rev.* 2004; 25(3): 191–194.
3. Cooper D and Biondi B. Subclinical thyroid disease. *Lancet* 2012; 379: 1142–54.
4. Biondi B and Cooper D. The Clinical Significance of Subclinical Thyroid Dysfunction. Endocrine Reviews 2008; 29(1): 76–131.
5. SurksM, Goswami G and Daniels G. The thyrothropin reference range should remain unchanged. J Clin Endocrinol Metab 2005; 90(9): 5489-96.
6. Hollowell J, Staehling N, Flanders W, Hannon W, Gunter E, Spencer C *et al*. Serum TSH, T4, and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endcrinol Metab* 2002; 87: 489–9.
7. Biondi B. Natural history, diagnosis and management of subclinical thyroid dysfunction. *Best Practice & Research Clinical Endocrinology & Metabolism* 2012; 26: 431–446.
8. Chu J and Crapo L. The Treatment of Subclinical Hypothyroidism Is Seldom Necessary. *J Clin Endocrinol Metab* 2001; 86(10): 4591–9.
9. Vanderpump M. How should we manage patients with mildly increased serum thyrotropin concentrations? *Clinical Endocrinology* 2010; 72: 436–40.
10. Canaris G, Manowitz N, Mayor G, and Ridgway C. The Colorado thyroid disease prevalence study. *Archives of Internal Medicin*e. 2000; 160: 526–34.
11. McDermott M and Chester Ridgway E. Subclinical hypothyroidism is mild thyroid failure and should be treated. *Journal of Clin Endocrinol Metab* 2001; 86(10): 4585–4590.
12. Biondi B. Thyroid and obesity: an intriguing relationship. *J Clin Endocrinol Metab* 2010; 95: 3614–7.
13. Huber G, Staub J, Meier C, Mitrache C, Guglielmetti M, Huber P *et al.* Prospective study of the spontaneous course of subclinical hypothyroidism: prognostic value of thyrotropin, thyroid reserve, and thyroid antibodies. *J Clin Endocrinol Metab* 2002; 87(7): 3221–36.
14. Rodondi N, Elsen W, Bauer D, Cappola A, Razvi S, Walsh J *et al.* Subclinical hypothyroidism and the risk of coronary heart disease and mortality. *JAMA* 2010; 304 (12): 1365-74.
15. Vanderpump M, Tunbridge W, French J,*Appleton D, Bates D, Clark F et al.* The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. *Clin Endocrinol (Oxf)* 1995; 43: 55-68.
16. Meyerovitch J, Rotman-Pikielny P, Sherf M, Battat E, Levy V and Surks M. Serum thyrotrophin measurements in the community: five-year follow-up in a large network of primary care physicians. Archives of Internal Medicine 2007; 167: 1533–8.
17. Gharib H, Tuttle R, Baskin H, Fish L, Singer P and McDermott M. Consensus Statement: Subclinical thyroid dysfunction: a joint statement on management from the American Association of Clinical Endocrinologists, the American Thyroid Association, and The Endocrine Society. *J Clin Endocrinol Metab* 2005; 90(1): 581–5.
18. Diez J and Iglesias P. Spontaneous Subclinical Hypothyroidism in Patients Older than 55 Years: An Analysis of Natural Course and Risk Factors for the Development of Overt Thyroid Failure. *J Clin Endocrinol Metab* 2004; 89(10): 4890–7.
19. Rodondi N, Bauer D, Cappola A, Cornuz J, Robbins J Fried L *et al.* Subclinical thyroid dysfunction, cardiac function, and the risk of heart failure. The Cardiovascular Health Study. *Journal of the American College of Cardiology* 2008; 52: 1152–9.
20. Vanderpump M. Subclinical hypothyroidism: the case against treatment. *Trends in Endocrinology and Metabolism* 2003; 14 (6): 262-6.
21. Hak A, Pols H, Visser T, Drexhage H, Hofman A and Witteman J. Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam study. *Ann Intern Med* 2000; 132: 270-8.
22. Klein I and Danzi S. Thyroid disease and the heart. *Circulation* 2007; 116(15): 1725-35.

23. Monzani F, Caraccio N, Kozàkowà M, Dardano A, Vittone F, Virdis A *et al.* Effect of levothyroxine replacement on lipid profile and intima-media thickness in subclinical hypothyroidism. *J Clin Endocrinol Metab* 2004; 89(5): 2099-2106.
24. Razvi S, Shakoor A, Vanderpump M.Weaver J and Pearce S. The influence of age on the relationship between subclinical hypothyroidism and ischemic heart disease: A meta-analysis. *J Clin Endocrinol Metab* 2008; 93: 2998–3007.
25. Biondi B, Palmieri E, Lombardi G and Fazio. Effects of Subclinical Thyroid Dysfunction on the Heart. *Ann Intern Med.* 2002; 137: 904-14.
26. Razvi S, Weaver J, Vanderpump M, and Pearce S. The incidence of ischemic heart disease and mortality in people with subclinical hypothyroidism: Reanalysis of the Whickham survey cohort. *J Clin Endocrinol Metab* 2010; 95(4): 1734–40.
27. Danese M, Ladenson P, Meinert C and Powe N. Effect of thyroxine therapy on serum lipoproteins in patients with mild thyroid failure: a quantitative review of the literature. *J Clin Endocrinol Metab* 2000; 85: 2993-3001.
28. Vierhapper H, Nardi A, Grosser P, Raber W and Gessi A. Low-density lipoprotein cholesterol in subclinical hypothyroidism. *Thyroid* 2000; 10: 981–4.
29. Meier C, Roth CB, Huber G, Guglielmetti M, Huber P, Staub JJ. Clinical and metabolic effects of thyroxine replacement in patients with mild thyroid failure: results from a double-blind placebo-controlled study. Proceedings of the 82nd Annual Meeting of The Endocrine Society, Toronto, Canada, 2000; 2372:573
30. Kong W, Shiekh M, Lumb P, Naoumova R, Freedman D and Finer N. A 6-month randomized trial of thyroxine treatment in women with mild subclinical hypothyroidism. *Am J Med* 2002; 112: 348-54.
31. Schneuer FJ, Nassar N, Tassevski V, Morris J and Roberts C. Association and predictive accuracy of high TSH serum levels in first trimester and adverse pregnancy outcomes. *J clin Endocrinol Metab* 2012; 97(9): 3115-22.
32. Stagnaro-Green A, Abalovich M, Alexander E, Azizi F, Mestman J, Negro R *et al.* Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. *Thyroid* 2011; 21(10): 1081-1125.
33. Casey B, Dashe J, Wells E, McIntire D, Byrd W, Leveno K *et al.* Subclinical hypothyroidism and pregnancy outcomes. *Obstetrics and Gynecology* 2005; 105 (2):239-245.
34. Abalovich M, Gutierrez S, Alcaraz G, Maccallini G, Garcia A and Levalle O. Overt and subclinical hypothyroidism complicating pregnancy. *Thyroid* 2002; 12 (1) 63-8.
35. Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med 1999; 341: 549 –55.
36. Marqusee E, Haden S and Utiger R. Subclinical thyrotoxicosis. *Endocrin Metab Clin North Am* 1998; 27: 37-49.
37. Osman I and Leslie P. Adrenal insufficiency should be excluded before thyroxine replacement is started. *BMJ* 1996;313:427.1.