

Management of Subclinical Hypothyroidism

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Abstract

Objective: To review current concepts in the management of subclinical hypothyroidism (SCH) in patients with non-specific symptoms. **Data sources:** A review of articles reported on overt hypothyroidism and subclinical hypothyroidism. **Summary of review:** In a patient with primary overt hypothyroidism, management is usually straightforward: treatment with thyroxine should be offered to anyone with characteristic clinical features, a raised serum thyroid stimulating hormone (TSH) concentration and a low serum thyroxine (T_4) concentration. More difficult is the management of a patient with subclinical hypothyroidism (SCH), in whom serum TSH is slightly raised (5-20 mIU/L) but T_3 , T_4 levels are normal, and who is either asymptomatic or has only non-specific symptoms. Left untreated, some of these patients will eventually develop overt hypothyroidism. This review will address the use of thyroxine in patients with subclinical hypothyroidism.

Key words: Subclinical hypothyroidism; TSH; T_3 ; T_4 .

INTRODUCTION

The term subclinical hypothyroidism is used to describe the finding of a mildly elevated serum TSH (5-20 mIU/L) but a normal free thyroxine (T_4).¹ T_3 is not a sensitive indicator for hypothyroidism¹. In the community, the most common etiology is chronic autoimmune thyroiditis¹.

Subclinical hypothyroidism or mild thyroid failure is a common problem, with a prevalence of 3% to 8% in the population without known thyroid disease². In the original Wickham survey in Northeast England, 8% of women (10% of women over 55 years of age) and 3% of men had subclinical hypothyroidism³. In the Colorado study, 9.4% of the subjects had a high-serum TSH concentration, of which 9.0% had subclinical hypothyroidism⁴. Among those with a high serum TSH concentration, 74% had a value between 5.1 and 10 mIU/L and 26% had a value >10 mIU/L. The percentage of subjects with a high-serum TSH concentration was higher for women than for men in each decade of age, and ranged from 4% to 21% in women and 3% to 16% in men. In the National Health and Nutritional Examination Survey (NHANES III) serum TSH concentrations increased with age in both men and women and were higher in whites than in blacks, independent of serum anti-thyroid antibody concentration⁵. Serum TSH greater than the population defined upper limit of the reference range of 4.5 mIU/L of whom only 40% were anti-thyroid antibody positive⁶. More recent data from Birmingham suggest that there is now an increased awareness of thyroid disease and testing of thyroid function and perhaps earlier use of levothyroxine in SCH⁷.

Spontaneous recovery has also been described in subjects with subclinical hypothyroidism, although the frequency of this phenomenon is unclear. In one study, 37% of patients normalized their serum TSH levels over a mean follow-up time of 32 months⁸. Normalization of serum TSH concentration is more likely to occur in patients with negative antithyroid antibodies and serum TSH levels <10 mIU/L, and within the first 2 years after diagnosis¹.

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NORMAL THYROID FUNCTION

There are two thyroid hormones, 3, 5, 3-triiodo-L-thyronine (T_3) and L-thyroxine (T_4). T_3 is the active hormone whereas T_4 functions as a circulating thyroid hormone store. T_3 binds to nuclear receptors to increase oxygen consumption (by stimulating Na^+ - K^+ -ATPase and activating mitochondrial metabolic pathway) and regulates lipid and carbohydrate metabolism and normal growth and maturation of tissues⁹.

Thyroid function is controlled by thyroid stimulating hormone, which in turn is controlled by thyrotropin releasing hormone (TRH). The major function of TRH is to release TSH from the adenohypophysis. TSH is released from adenohypophysis in response to TRH and the negative feedback effects of T_3 and T_4 . By binding to specific thyroid follicular cell surface receptors and activating adenylate cyclase, TSH stimulates synthesis and release of T_3 and T_4 from thyroid gland. Thyroid hormones circulate either free T_3 (FT_3) or free T_4 (FT_4) (i.e. the active form) or bound form. Approximately 99.98% of the circulating T_4 is bound and 99.8% of the circulating T_3 is bound¹⁰.

THYROID FUNCTION TESTS

Serum TSH: Extremely sensitive (fourth generation) TSH assays can detect TSH level $< \text{or} = 0.004$ mIU/L, but for practical purposes assays sensitive to $< \text{or} = 0.1$ mIU/L are sufficient. Using two specific monoclonal antibodies, the ultrasensitive TSH assay has improved the sensitivity of the TSH assay to the extent that both hypo and hyperthyroid states may be discriminated from the euthyroid state using this measurement¹¹⁻¹².

In secondary (i.e. pituitary) hypothyroidism, the circulating TSH levels may be within the normal range, although they are always low relative to the circulating FT_4 levels.¹³ The TSH levels are suppressed by adequate T_4 replacement in patients with primary hypothyroidism, but 4-6 weeks should be allowed after changing the doses of T_4 to allow adequate equilibration of thyroxine with tissues before measuring TSH levels¹³.

Free thyroxine: The FT_4 assay is a radioimmuno-assay that uses a T_4 tracer to measure the non-protein bound T_4 . The free hormone concentrations correlate well with the metabolic state and should always be used to assess thyroid status. It is often performed as a second-line test to investigate an abnormal TSH level. In early primary hypothyroidism, the TSH is a more sensitive test than the FT_4 , which may be within the normal range¹⁴.

Free triiodothyronine: The FT_3 assay is a radio-immunoassay that uses a T_3 analogue tracer to measure the non-protein bound T_3 fraction. The FT_3 estimation is not a useful test to detect hypothyroidism because low levels only occur late in the disease.

The normal, lower border line, upper border line and TSH, FT_3 and FT_4 levels diagnostic of primary hypothyroidism are listed in table -1¹⁴.

Table 1 : Free thyroid hormone levels in healthy and in primary hypothyroid

	Primary Hypothyroid	Lower Borderline	Normal	Upper borderline
TSH (mIU/L)	> 4.5	0.2-0.4	0.5-3.5	3.6-4.5
FT_4 (pmol/L)	<8	8-12	13-23	24-26

Total T_4 : The total T_4 measurement includes the protein bound as well as the FT_4 fraction, and is subject to false interpretation of the thyroid status when there are abnormalities of thyroid binding proteins¹⁴.

Other tests: Ultrasonography is usually performed first to assess thyroid masses, to detect whether the enlargement is cystic, solid or multinodular¹⁴.

BENEFITS OF LEVOTHYROXINE THERAPY IN NON-PREGNANT SUBJECTS

Although studies have pointed to some adverse effects of SCH, no consensus exists as to the clinical importance of the adverse effects and the benefits of levothyroxine therapy, particularly for the 80% of the patients with SCH who have a TSH of less than 10 mIU/L².

PROGRESSION TO OVERT HYPOTHYROIDISM

Patients with SCH have a high rate of progression to clinically overt hypothyroidism, 2.6% each year if thyroperoxidase (TPO) antibodies are absent and 4.3% if they are present. A TSH level greater than 10 mIU/L predicts a higher rate of progression, and a level of less than 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 less than 10 mIU/L².

SCREENING FOR SCH

Uniform national guidelines for screening for thyroid disease with serum TSH levels have not been established. However, because of the high prevalence of SCH and associated metabolic risk factors such as hyperlipidemia, the American Thyroid Association recommends screening by measurement of serum TSH beginning at age 35 years and every 5 years thereafter. The evidence in favour of screening is particularly compelling in women, but it can also be justified for men as a relatively cost-effective measure in the context of the periodic health examination. Before recommending routine screening of the general population, large-scale randomized trials are needed to prove that treatment will improve quality of life in otherwise healthy patients who have the mildly elevated TSH level (5-10 mIU/L) typical of most SCH cases. Many thyroidologists advocate routine screening before and during pregnancy². Screening of thyroid function and autoantibodies are not recommended for every women, but should be performed in first trimester, in those with a personal or family history of thyroid disease, goitre, other autoimmune disease including type I diabetes or when there is clinical suspicion of thyroid dysfunction¹.

MANAGEMENT OF SCH DURING PREGNANCY

One situation where opinion is consistent with regard to treatment of SCH with thyroxine is in the context of pregnancy or desire for conception. There is evidence that miscarriage rates and rates of premature delivery are lower if SCH is treated with thyroxine, and indeed some evidence that thyroxine treatment of biochemically euthyroid women with thyroid autoimmunity improves pregnancy outcome, which coupled with evidence that even mild thyroid hormone deficiency is associated with an adverse effect on childhood neurodevelopment, has led specialist associations and expert groups to support role of thyroxine treatment¹⁵⁻¹⁸.

Recent research suggests that inadequate maternal T₄ therapy is associated with impaired cognitive development in their offspring¹. Evidence of clinical benefit, though limited, broadly suggests that it is better to treat subclinical hypothyroidism before overt hypothyroidism develops. Such a strategy should reduce the risk of loss to follow-up and subsequent morbidity of a delayed diagnosis of profound hypothyroidism¹⁹. Unless contraindicated; iodine supplementation should be prescribed routinely in women planning a pregnancy. The National Health and Medical Research Council recommend an iodine supplement of 150 µg each day²⁰. Maternal thyroid functions during pregnancy changes in response to the increased metabolic requirements and the presence of the fetus. In addition, thyrotrophic activity of -hCG results in a decrease in TSH and increase in FT₄ and FT₃ in the first trimester^{1, 21}. In later pregnancy FT₄ and FT₃ are lower. Binding globulin levels are induced by estrogen, so total T₄ and T₃ levels are invariably high¹. The following ranges of TSH have been provided by the American Thyroid Association²¹.

- First trimester 0.1- 2.5 mIU/L
- Second trimester 0.2-3.0 mIU/L
- Third trimester 0.3- 3.0 mIU/L.

Table 2 : Definition and management of SCH during pregnancy

	Definition	Concern	Recommended Action ^{1,21}
Subclinical hypothyroidism (SCH) (Prevalence 2-2.5%)	TSH between 2.5-10 with normal T ₄	TPO Ab positivity may in itself be associated with fetal miscarriage and levothyroxine intervention in TPO antibody positive women with SCH may be beneficial ²² . Levothyroxine dose should be increase by 30-50% from early pregnancy ¹ .	Options include treatment with levothyroxine to normalize maternal serum TSH or 4 weekly monitoring of TSH. Obtain TPO Ab levels while awaiting specialist review. Monitoring to maintain TSH results within trimester specific reference range is recommended in early pregnancy and at least once in each trimester.

MANAGEMENT OF SCH IN NON-PREGNANT ADULTS

Serum TSH concentration of 3 to 5 mIU/L

Levels between 3 and 5 mIU/L are unlikely to indicate a clinically important abnormality, and levothyroxine therapy at these levels may or may not provide a benefit. Although persons with a serum TSH level of 3 to 5 mIU/L may be at higher risk of progression to hypothyroidism, no firm evidence of health consequences exists. In a randomized 12 week study of patients with symptoms suggestive of hypothyroidism with serum TSH in the upper normal range, no difference in cognitive and psychological function was observed between levothyroxine –treated and control groups. Given these findings, intervention cannot be recommended for this group, but follow-up by serum TSH measurement in 1 year would be a reasonable approach, particularly if antithyroid antibodies are detected².

Serum TSH concentration of 5-10 mIU/L

Where the TSH is consistently between 5-10 mIU/L and the patient is symptomatic, a 3-6 month trial of levothyroxine replacement is appropriate.

Treatment can be continued where there is symptomatic benefit. Where the TSH is between 5-10 mIU/L and there is the presence of anti-TPO antibodies, an alternative option to thyroxine therapy would be annual thyroid function tests for the early detection of progression to frank hypothyroidism. In contrast, where the patient is antithyroid antibody negative, 3yearly thyroid function tests are considered sufficient²³.

Serum TSH concentration greater than 10 mIU/L

Most thyroidologists agree that all patients with SCH and a serum TSH level above 10 mIU/L should be treated with levothyroxine^{2,24}. Studies have shown that levothyroxine therapy results in an 8-mg reduction in low-density lipoprotein levels. 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. Some evidence suggests nerve conduction, cardiac function, and cognitive and psychological function, with improvement after levothyroxine therapy². An algorithm for the management of subclinical hypothyroidism in the non-pregnant adult is shown in Figure 1.

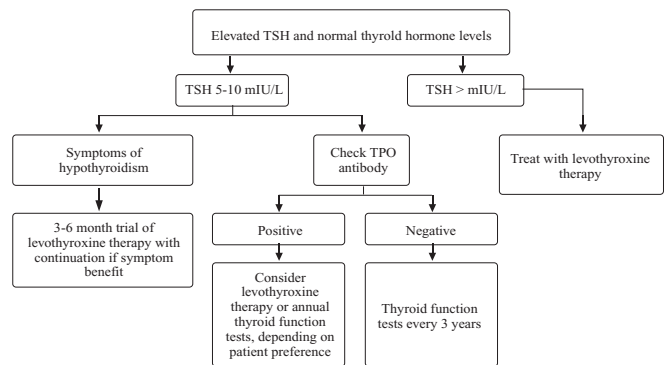


Figure 1 : Algorithm for management of subclinical hypothyroidism in the nonpregnant adult Adapted from Vaidya B, Pearce SHS. Management of hypothyroidism in adults. BMJ 2008; 337:284–289.

LEVOthyroxine THERAPY FOR SCH

Where treatment is commenced, an initial dose of levothyroxine of 25-50 µg/day can be used with a target TSH level between 1.0 and 3.0 mIU/L. The TSH level should be measured at 6-8 weeks after commencement of therapy as effect of levothyroxine on TSH lasts for 4-6 weeks^{2,25}.

CONCLUSION

Initiating levothyroxine replacement therapy is recommended for all patients of SCH with a TSH level greater than 10 mIU/L. However, treatment of patients with a serum TSH level between 5 and 10 mIU/L remains controversial. The strongest arguments for levothyroxine therapy are presence of anti-TPO antibodies, goitre, the possible improvement of quality of life, high risk of progression to overt hypothyroidism and the possibility that SCH is a cardiovascular risk factor. In patients who are antibody – negative warrants observation rather than immediate treatment as it may be a transient phenomenon. The aim of levothyroxine therapy should be to restore serum TSH concentration to within reference range: levels below this range are possibly associated with an increased risk of developing atrial fibrillation.

Serum TSH concentration of 3 to 5 mIU/L recommends follow up particularly if antithyroid antibody are detected. Management of SCH during pregnancy with TSH 3-5 mIU/L needs use of levothyroxine with or without positive TPO antibody, as the aim of treatment to keep TSH below 3 mIU/L and to prevent fetal loss in TPO antibody positive cases. All pregnant women with upper border range (TSH 3-5 mIU/L) should be treated with levothyroxine. Levothyroxine intervention in TPO antibody positive women with SCH is more beneficial to prevent fetal loss.

Suggested: Initiating levothyroxine replacement therapy is recommended for all patients of SCH with a TSH level greater than 10 mIU/L. However, treatment of patients with a serum TSH level between 5 and 10 mIU/L remains controversial. In patients who are antibody – negative warrants observation rather than immediate treatment. Serum TSH concentration of 3 to 5 mIU/L recommends follow up particularly if antithyroid antibody are detected. Management of SCH during pregnancy with TSH 3-5 mIU/L needs use of levothyroxine with or without positive TPO antibody, to keep TSH below 3 mIU/L and to prevent fetal loss in TPO antibody positive cases.

DISCLOSURE

All the authors declared no competing interest.

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