

Subclinical Hypothyroidism

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Subclinical hypothyroidism (SCH) is defined as a normal serum FT₄ and a high serum thyrotropin (TSH) concentration. Up to 30% of patients with SCH may have vague, non-specific symptoms of hypothyroidism, but attempts to identify the patients on the basis of clinical findings have not been successful, so the diagnosis can only be made with laboratory testing.

The causes of SCH are the same as those of overt hypothyroidism. Most patients have Hashimoto's thyroiditis. The worldwide prevalence of SCH ranges from 1-10%. A substantial proportion of patients with SCH develop overt hypothyroidism. Serum TSH concentration and positive antithyroid antibodies (ATA) are significant predictors of progression to clinical hypothyroidism. Some patients with SCH have some symptoms of hypothyroidism, while some studies show significant improvement in hypothyroid symptom scores and psychometric testing; others found no improvement in symptoms with levothyroxine therapy.

There is consensus that SCH in pregnancy is a risk factor for poor developmental outcomes in the offspring and the condition should be treated in women who wish to become pregnant. There is also agreement that patients with SCH and TSH levels over 10 mU/L, or with goiter should be treated. Population-based screening for SCH is not warranted, but thyroid function should be tested in high risk groups, e.g. in women aged over 60 yr, persons with previous radiation therapy of thyroid gland or external

radiation, those with previous thyroid surgery of thyroid dysfunction, type 1 diabetes mellitus patients and those with a family history of autoimmune disease. Evidence documenting routine determination of TSH in pregnant women or women planning to become pregnant are insufficient, and it would be reasonable to consider TSH measurement in those at high risk for thyroid dysfunction.

Key Words: Subclinical, Hypothyroidism, Thyrotropin, Thyroiditis, Antithyroid antibodies

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Introduction

Subclinical hypothyroidism is defined as a normal serum free thyroxine (T₄) concentration and a slightly high serum thyrotropin (TSH) concentration. Patients with SCH may have vague, non-specific symptoms of hypothyroidism, but it is not easy to identify these patients on the basis of such non-specific symptoms and signs. Thus this disorder can only be diagnosed on the basis of laboratory test results.

Etiology: The causes of SCH and overt hypothyroidism are the same. The most common cause is chronic autoimmune thyroiditis with high serum antithyroid antibodies concentrations. Hashimoto's thyroiditis was found in 54% of patients with SCH in one study,¹ while in another study, 67% of

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women and 40% of men with SCH had chronic autoimmune thyroiditis.²

Ablative therapy of thyrotoxicosis caused by Graves' disease is another important cause of SCH and accounts for 40% of the cases in the United States.¹ It has been reported that up to two-thirds of patients with Graves' disease treated surgically develop SCH.³⁻⁴ Inadequate T₄ replacement therapy for overt hypothyroidism is another common cause of SCH, confirmed in a study where 37% of patients had SCH following thyroxine replacement therapy.⁵

Epidemiology: SCH is a common disorder with a prevalence ranging from 1-10% among the of adult population in most community studies,²⁻⁶ and up to 20% in women aged over 60 y⁶³. In two population-based studies, the prevalence of SCH was 7.5-8.5 percent in women and 2.8 to 4.4% in men.^{2,7} An age-dependent increase in TSH concentration was detected in women, which was not found when those with high serum antithyroid antibody concentrations were eliminated from the analysis.

In the National Health and Examination Survey (NHANES III), conducted in the United States, 4.3% of 16533 individuals had SCH.⁸ The prevalence of SCH is about 15% in women over the age of 60 years²⁻⁹ and about 8% in elderly men.⁹ SCH is more common in patients with type1 diabetes¹⁰ and probably also in those with other autoimmune diseases, in contrast to the normal population. In areas of iodine sufficiency, SCH is more prevalent. In one study in Europe, the prevalence of SCH ranged from 4.2% in iodine-deficient areas to 23.9% in an area of abundant iodine intake.¹¹

Natural History: The Wickham survey involved approximately 2800 randomly selected adults in whom thyroid function was assessed.² After 20 years of follow up, a high risk of overt hypothyroidism was found in women who had both elevated serum levels of TSH and antithyroid antibodies at baseline (4.3% per year).¹² Moreover a high serum

TSH alone or antithyroid antibodies alone at baseline also conferred an increased risk of overt hypothyroidism (2.6% per year and 2.1% per year respectively).

In a study evaluating patients aged over 60 years,¹³ the risk of progression of SCH to overt hypothyroidism was related to initial laboratory findings. All patients with an initial serum TSH concentration >20 mU/l, 80% of those with serum antithyroid microsomal antibody titers of 1: 1600 or higher, but none with titers of less than 1: 1600 developed overt hypothyroidism.

In another study of 107 patients, it was found that serum TSH concentration was the only significant predictor of progression to overt hypothyroidism, subjects with serum TSH concentrations under 10 mU/L, or between 15 and 19 mU/L were associated with 1.76 and 73.47 cases of overt hypothyroidism per 100 patient years, respectively.¹⁴

Symptoms: SCH is often asymptomatic; however, nearly 30% of patients may have symptoms suggestive of thyroid hormone deficiency.^{15,16} The Colorado Thyroid Disease Prevalence Study¹⁵ surveyed over 25000 state residents, by measuring serum TSH concentrations and conducting symptoms surveys. SCH was detected in 2336 of cases (9.5%), and 114 subjects were overt hypothyroids. In response to a validated survey concerning symptoms of thyroid hormone deficiency, patients with SCH as compared to euthyroid subjects, more often reported dry skin (28%; p<0.001), poor memory (24%; p<0.001), slow thinking (22%; p<0.001), muscle weakness (22%; p<0.001), fatigue (18%; p<0.01), muscle cramps (17%; p<0.001), cold intolerance (15%; p<0.001), puffy eyes (12%; p<0.05), constipation (8%; p<0.05), and hoarseness (7%; p<0.05). Compared with euthyroid cases, the total symptoms reported were significantly higher for both SCH patients (p<0.05) and those with overt hypothyroidism (p<0.05) (Fig.1). However other cross-sectional¹⁷⁻¹⁸ and case-control studies¹⁶ did not confirm these observations.

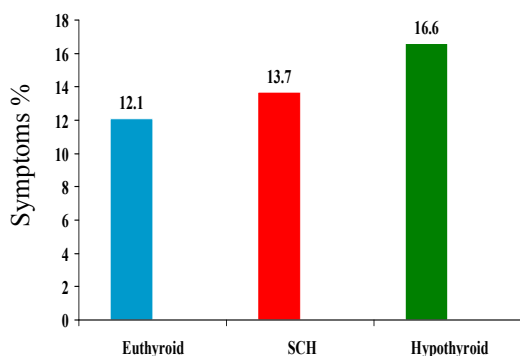


Fig.1. Hypothyroid symptoms: Compared with the euthyroid subjects, total symptoms reported were significantly higher for both SCH patients ($p < 0.05$) and those with overt hypothyroidism ($p < 0.05$)

Effects of therapy on symptoms: In a double-blind cross over study in which patients received either T_4 or placebo, each for 6 months, hypothyroid symptom scores and psychometric test results improved during T_4 -treatment period, as compared with the placebo period.¹⁹ In another RCT, patients with SCH, some of whom had symptoms such as dry skin, low energy and cold intolerance, were treated with T_4 or placebo for one year.²⁰ The dose of T_4 was adjusted to normalize the serum TSH concentrations. During treatment, one half of the patients in the T_4 group, but none in the placebo group, had fewer symptoms, as assessed by a standardized hypothyroid diagnostic index.²¹ The two RCTs mentioned were restricted to subjects with TSH level < 10 mU/L, and found no improvement in symptoms of hypothyroidism with T_4 therapy.²²⁻²³

According to the American Association of Clinical Endocrinologists (AACE), the American Thyroid Association (ATA), and the Endocrine Society consensus panel on SCH,²⁴ routine levothyroxine treatment is not recommended for patients with TSH levels between 4.5-10 mU/L. The panel realized that some patients with TSH levels in these

ranges have symptoms compatible with hypothyroidism and therefore a several-month trial of levothyroxine may be used, while monitoring for improvement in symptoms; decision for continuation of therapy should be made based on clear symptomatic benefit. The panel considered the likelihood of improvement small, and felt it must be balanced against the inconvenience, expense and potential risks of therapy.

Neuropsychiatric disease: Several reports suggest that SCH is associated with neuropsychiatric disease. Patients with SCH have a higher lifetime frequency of depression than do euthyroid subjects.²⁵ In one study, women with SCH and goiter had increased rate of free-flowing anxiety, somatic complaints, depressive features, hysteria and abnormal psychometric testing as compared with euthyroid patients with goiter. These problems improved with T_4 treatment.²⁶

In a placebo-controlled double blind clinical trial conducted on subjects with SCH and TSH levels between 3, 5-10 mU/L, there was no neuropsychological dysfunction, and compared with healthy controls, there were no differences in symptoms related to hypothyroidism.²⁷

According to the SCH consensus panel, there is insufficient evidence to support association of SCH and neuropsychiatric disease or benefits of T_4 therapy.²⁴

Serum lipids: The effects of SCH on serum lipids remain controversial.²⁴ In the Colorado Study¹⁵ the mean total cholesterol levels in 22,847 euthyroid subjects and 2,336 mild thyroid failure subjects with TSH ranges between 5.1-10 mU/L, and 114 subjects with overt hypothyroidism were, 224 mg/dL, and 251 mg/dL respectively. Both thyroid disease groups had statistically higher total cholesterol levels and LDL cholesterol than did the euthyroid controls (Fig.2).

In some studies, patients with SCH had high serum LDL-cholesterol,²⁸⁻³⁴ and low HDL-cholesterol concentration.³¹⁻³⁵

In contrast to these findings, many cross-sectional studies have found that serum total

cholesterol concentrations in patients with SCH were similar to those of normal subjects,³⁶⁻³⁸ and T₄ therapy did not consistently decrease these concentrations.^{19,20,28-30,35,39-41}

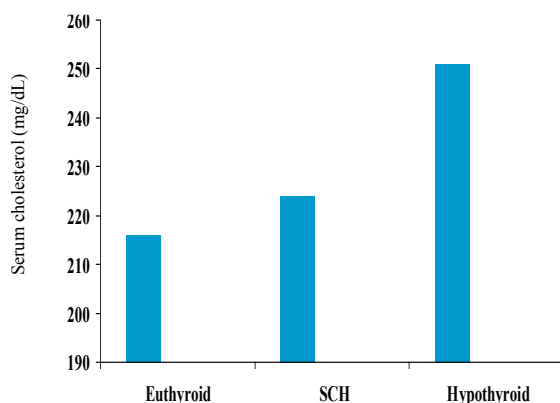


Fig.2. Total cholesterol levels: Both thyroid disease groups had statistically higher total cholesterol levels than did the euthyroid controls (p=<0.001)

A meta-analysis of 247 patients in 13 studies of SCH found that T₄ therapy resulted in significant reductions in serum total cholesterol (8 mg/dL), while serum LDL-cholesterol (10mg/dL), the mean serum HDL-cholesterol and triglyceride concentrations did not change.⁴² In this meta-analysis, reductions in serum cholesterol were only seen in patients with levels > 240 mg/dL at baseline. In two other studies, only serum total and LDL-cholesterol concentrations decreased after levothyroxine treatment.^{28,43}

However evidence that therapy will reduce serum total cholesterol and LDL-cholesterol in SCH patients is inconclusive.²⁴

Cardiac function: Some patients with SCH have diastolic dysfunction and increased peripheral vascular resistance, as noted in patients with overt hypothyroidism and in these, cardiac output increased and systemic vascular resistance decreased following T₄ treatment.⁴⁴ Another case-control study⁴⁶ reported that arterial stiffness was increased in SCH and improved with L-thyroxine, whereas myocardial functional re-

serve was similar to controls and remained unchanged after treatment.

Elevated levels of inflammatory markers, such as C-reactive protein (CRP) have been directly related to the risk of myocardial infarction.^{47,48} Similarly, recent evidence has established hyperhomocysteinaemia as an independent risk factor for cardiovascular disease.^{49,50} In a large population-based study conducted on 1608 individuals, hs-CRP and homocysteine levels did not differ for patients with SCH, as compared to euthyroid cases.⁵¹ In contrast, in another study,³⁴ patients with SCH, irrespective of gender, had higher serum hs-CRP levels than did healthy subjects.⁵² However according to the consensus panel, it remains to be determined whether cardiac dysfunction can be expected in SCH.²⁴

Cardiovascular disease/all-cause mortality: As with overt hypothyroidism, SCH may also be associated with an increased risk of cardiovascular disease (CVD), congestive heart failure, and possibly, all-cause mortality.⁵²⁻⁵⁴

Data from the Rotterdam study, a population-based survey, designed to examine the determinants of chronic disease in postmenopausal women, reported that SCH (defined as TSH.4 mU/L) was associated with a significantly increased risk of both aortic atherosclerosis (odds ratio 1.7) and myocardial infarction (odds ratio 2.3).⁵³ Another population-based study from Australia (all ages) found SCH in 119 out of 2108 subjects.⁵⁵ There was a significantly increased risk of coronary artery disease (CAD) at baseline (odds ratio 1.8). During a 20-year follow up of patients without baseline CAD, the hazard ratio for coronary events was 1.5, if TSH was <10 mU/L and 2.2, if TSH was >10 mU/L; the risk of cardiovascular mortality was also increased (HR 1.5). In another study, an increase in all-cause mortality was found in patients with SCH at 6 years, but was no longer present 10 years after diagnosis.⁵⁶ In an English study⁵⁴ patients with SCH following ra-

dioiodine therapy for hyperthyroidism had 2-fold increased mortality from CAD.

The follow-up Whickham survey⁵⁷ found no association between elevated serum TSH and increased risk of ischemic heart disease or dyslipidemia. A large cross-sectional survey of 3410 elderly subjects noted significantly elevated LDL cholesterol in subjects with SCH, but only for those with TSH over than 10 mU/L;⁵⁸ no increased frequency of diagnosed atherosclerosis was found in this entire cohort of SCH subjects. An Italian review article concludes that, the actual effectiveness of thyroid hormone substitution in reducing the risk of cardiovascular events remains to be elucidated.⁵⁹

According to the consensus panel,²⁴ the question whether untreated SCH affects important cardiovascular outcomes such as angina pectoris, myocardial infarction, and cardiovascular death remains unanswered.

Subclinical hypothyroidism during pregnancy: Undetected SCH during pregnancy may adversely affect the neuropsychological development⁶⁰ and survival⁶¹ of the fetus and may be associated with hypertension and toxemia.⁶² According to the consensus panel²⁴ SCH should be treated in pregnant women and in those planning to become pregnant.

Screening: The consensus statement recommends against population-based screening and suggests aggressive case finding in high risk groups.^{24,63} Thyroid dysfunction is more prevalent in certain population groups including women aged over 60 years, those with history of radiation therapy of the thyroid or thyroid surgery, or past history or family history of thyroid dysfunction, past history of autoimmune disease, and type1 diabetes mellitus.²⁴ The panel recommends screening only

in pregnant women at high risk of thyroid dysfunction.^{24,63}

Recommendations

- Routine T₄ therapy of SCH patients with TSH levels of 4.5-10 mU/l is not indicated, but thyroid function tests should be repeated at 6-12 months to monitor for improvement or worsening in TSH levels.^{24,63}
- In symptomatic patients with TSH levels between 4.5-10 mU/L, a several-month trial of T₄ therapy may be used, and continuation of therapy should be based on clear symptomatic benefit.²⁴
- Treatment of patients with TSH levels between 4.5-10 mU/L and cardiovascular risk factors is suggested.⁵⁹
- Lack of definitive evidence for a benefit does not equate to evidence for lack of benefit.
- Most patients with TSH levels of 4.5-10 mU/L should be considered for treatment according to the judgment of the physician in consultation with the patient.⁶³
- The best clinical practice regarding treatment of patients with SCH and serum TSH levels between 4.5-10mU/L is clinical judgment and patient preferences.
- T₄ therapy is reasonable for patients with SCH and goiter and / or serum TSH concentration >10mU/L.^{24,63}
- SCH should be treated in pregnant women and those planning to become pregnant.^{24,63}
- Routine screening for SCH is indicated in all pregnant women and those contemplating pregnancy.⁶³
- Many societies endorse the use of anti-TPO antibody determination in management of SCH patients.⁶³

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