

# SUBCLINICAL THYROID DISEASE

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## REZUMAT

Hipertiroidismul subclinic este mai puțin frecvent decât hipotiroidismul subclinic, dar este asociat cu un risc crescut de fibrilație atrială, cu creșterea posibilă a mortalității generale și cu scăderea densității osoase, într-un studiu fiind citată și o predispoziție spre demență. Principalele preocupări în ceea ce privește hipotiroidismul subclinic sunt date de riscurile cardiovasculare și hiperlipidemia asociate cu acesta, precum și riscul ca acești pacienți să prezinte simptome neuropsihiatrice în cursul progresiei spre hipotiroidism manifest. Studiile clinice au demonstrat beneficiile tratamentului de substituție cu tiroxină (T4) asupra capacităților cognitive, a unor simptome precum senzația de uscăciune a pielii, precum și o îmbunătățire a lipidelor plasmatiche.

**Cuvinte cheie:** hipertiroidism subclinic, hipotiroidism subclinic, terapie de substituție cu tiroxină

## ABSTRACT

Subclinical hyperthyroidism is less common than subclinical hypothyroidism, but is associated with an increased risk of atrial fibrillation, possible increase in overall mortality and decreased bone density. A predisposition to dementia has also been noted in one study. The main concerns in the approach to subclinical hypothyroidism are the cardiovascular and hyperlipidaemic risks associated with this condition as well the risk that these patients have of developing neuropsychiatric features whilst progressing to overt hypothyroidism (OH). Randomized control trials (RCT's) and case-control studies have demonstrated the benefits of thyroxine (T4) replacement therapy on cognition, symptoms such as dry skin and low mood, on the cardiovascular system and have also shown an improvement in plasma lipids.

**Key Words:** subclinical hyperthyroidism, subclinical hypothyroidism, thyroxine replacement therapy

## SUBCLINICAL THYROID DISEASE

Both subclinical hyperthyroidism (SCHyper) and subclinical hypothyroidism (SCHypo), are increasingly being recognised as having significant health implications. In both conditions the serum concentration of circulating thyroid hormones thyroxine and triiodothyronine are within the normal reference ranges. TSH levels are low or suppressed in SCHyper and elevated in SCHypo. The prevalence of SCHyper is around 3% and that of SCHypo ranges from 5% to as much as 15% in certain areas.

## SUBCLINICAL HYPERTHYROIDISM

This may be associated with nodular goitre which may be single or multinodular but also may occur in the absence of goitre. It occurs in patients who are receiving T4 replacement therapy and are found to have a low or suppressed TSH. SCHyper does not include other causes of a low TSH such as steroid or dopamine administration or non thyroidal illness. As it is subclinical it is to be expected that patients will have no symptoms. While this is generally true some patients are found to have SCHyper following attendance because of palpitations and others are found after their bone density has been noted to be low. Otherwise asymptomatic patients with a low TSH have up to a 3 times risk of atrial fibrillation. Further it has been suggested that varying degrees of subnormal TSH are associated with an increased mortality. Several studies have examined bone density in patients with there are no data relating to fracture incidence in these cohorts. Nevertheless, a study by Faber reported return of bone density to control values following radioiodine treatment to SCHyper patients. In a population based prospective study Kalmijn et al noted that the risk of

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development of Alzheimers disease was significantly greater in a population with low TSH 2-4 years later.

What should our management strategy be in patients found to be SCHyper? At present there are no long-term randomised controlled trials of therapy in this condition although studies are in progress. It does not seem reasonable to treat an asymptomatic person with no cardiovascular or bone problems on the basis of a single low TSH. A full thyroid evaluation should be performed in this situation including thyroid ultrasound and measurement of thyroid antibodies.

The clinical background to subclinical hypothyroidism (SCHypo) and its treatment must be considered in relation to the action of thyroid hormone at the cell level. Briefly, triiodothyronine (T3) formed mainly by the outer ring peripheral deiodination of tetraiodothyronine (T4) acts through two nuclear thyroid hormone receptors  $\alpha$  and  $\beta$  to regulate appropriate tissue-specific protein synthesis. The situation is complicated by the fact that there is tissue specificity for the receptors and also differential isoform tissue distribution. Furthermore, the derivation of T3 also varies; for example, in the brain cellular T3 is derived from brain T4 whereas in other tissues circulating T3 is transported to the particular cell in question. This implies that even mild overt hypothyroidism (OH) i.e., elevated thyrotropin (TSH) and low levels of T4 may have significant effects on the efficiency of thyroid hormone action.

The most common cause of endogenous SCH is autoimmune (Hashimotos) thyroiditis which is usually associated with elevated levels of anti-thyroperoxidase antibodies (TPO abs). Other causes are listed in Table 1.

**Table 1.** Causes of endogenous SCH

**The risk of developing SCH is increased in persons:**

1. With a goiter in the family (e.g., inactivating mutations in TSH receptor);
2. Treated hyperthyroidism (Graves' disease);
3. With a history of post-partum thyroiditis;
4. With a history of neck irradiation;
5. With autoimmune disorders (type 1DM);
6. Treated with iodine-containing anti-arrhythmic agents (amiodarone);
7. Treated with lithium;
8. Treated with immune response modulators(interferon alfa);
9. After recovery from severe non-thyroidal illness;
10. With poor compliance of T<sub>4</sub> therapy.

Inadequately treated overt hypothyroidism is one of the most common causes of exogenous SCH and patients receiving radiotherapy for head and neck tumours can also develop the condition. When diagnosing endogenous SCH it is important that concurrent acute or chronic illnesses and thyroid hormone resistance are excluded and that there is no pharmacological interference from drugs such as

lithium, amiodarone, metoclopramide or domperidone. The "cut-off" values used in TSH assays also affects the prevalence. CH can progress to OH and we suggest that avoidance of this is an important benefit (*vida infra*) of early treatment. The assessment of the risks associated with SCHypo and the evaluation of the evidence available in favour of treatment can result in an informed decision about whether to proceed with treatment.

The benefits of treatment of subclinical hypothyroidism are to prevent the onset of overt hypothyroidism, to alleviate symptoms such as dry skin, lethargy and depression, to reduce serum cholesterol levels and to reduce cardiovascular risk.

SCH can be regarded as a stage in the development of OH and can be considered as subclinical thyroid failure. It has been previously noted in an epidemiological study examining the risk of progression of SCH to OH over a twenty-year period that there is a 4.3% risk at one year of developing OH in patients with SCH and antithyroid antibodies and a 38-fold increased risk compared with patients with a normal TSH level and no antibodies. However other studies have suggested that the risk of progression from SCH to OH would be as high as 18 % in patients studied over the same period during the first year after the demonstration of an elevated TSH OH can rarely lead to extreme morbidity with complications such as cardiac failure or myxoedema coma occurring in some patients.

## **ALLEVIATION OF SYMPTOMS OF SCH**

Although patients with SCH are presumed to be asymptomatic by the definition "subclinical" they can have subtle clinical manifestations and non-specific symptomatology. In a previous RCT dry skin, cold intolerance, constipation and easy fatigability were noted as the most common presenting symptoms but other signs and symptoms can be vague and hard to define; because of this, they are sometimes attributed to complaints associated with normal ageing.

However, patients usually present to a physician for one or more reasons. Canaris et al in a cross-sectional study involving 25,862 patients demonstrated that those with SCH had significantly more overall symptoms such as dry skin and lethargy than did euthyroid patients. Three double-blind placebo RCT's have demonstrated an improvement in symptoms with replacement T4 therapy. Different methods have been used to assess response; Meier et al used the Hypothyroidism Diagnostic Index of Billewicz and Zulewski scores demonstrating significant

improvement ( $p < 0.02$ ) in symptoms; other RCT's have used questionnaires and have also shown improvement with T4. The greatest improvement in patients' symptoms has been shown in those with a baseline TSH  $> 12\text{mUI}^{-1}$ . It has been suggested that mood disorders and disturbances in cognition and memory are associated with SCH. The lifetime frequency of depression is significantly higher in patients with SCH compared with patients with normal thyroid function, suggesting that SCH lowers the threshold for depression.

A case-control study has also supported these findings and showed that patients have significantly increased anxiety, somatic complaints and hysteria. Other abnormal mood disorders noted in SCH include an increased incidence of concurrent panic disorder in depressed patients with SCH and this might respond less well to antidepressant therapy. A previous study has shown significant decreases in logical memory evident in women with SCH compared with euthyroid individuals. A significant improvement of memory skills was induced by LT4 treatment in these patients.

Although OH is usually associated with dyslipidaemia, SCH has a less well recognized association. A previous review has demonstrated that SCH is two to three times more frequent in people with elevated total cholesterol (TC) levels. Caraccio et al found significant increases in TC and low density lipoprotein cholesterol (LDL-C) in patients compared with euthyroid controls and this statistical difference has also been confirmed in other case-control studies. Treatment of SCH could therefore potentially reduce serum cholesterol levels and retard the development of atherosclerosis. Three RCTs comparing T4 and placebo have shown statistically significant reductions in both plasma TC and LDL-C concentrations with improvement being shown to be of greatest benefit in those with higher initial pre-treatment TSH and cholesterol levels.

There is limited data on the effects of replacement T4 therapy on apolipoprotein A1 (Apo A1), apolipoprotein B (Apo B) and lipoprotein a (Lp(a)). Two studies have demonstrated significant reductions in Apo B following treatment if the initial TSH level is  $>10\text{mUI}^{-1}$ .

The effects of adding 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) in addition to replacement T4 have been assessed in postmenopausal women. A recent prospective study found that combination therapy caused significant reductions in TC, LDL-C and triglyceride (TG) and a significant increase in HDL-C levels at three months post treatment.

## **REDUCTION OF CARDIOVASCULAR RISK**

Cardiac abnormalities in hypothyroidism are well documented. More recently, several studies have investigated cardiac changes evident in SCH and even though SCH is considered as "mild thyroid failure" there is evidence to show that slight changes in thyroid hormone status do cause cardiac functional abnormalities. These include impairment of left ventricular diastolic function at rest (observed as slowing of relaxation of the left ventricle) and left ventricular systolic dysfunction. Other changes in left ventricular (LV) morphology include increased diastolic interventricular septum thickness, posterior wall thickness and left ventricular mass. Perhaps of most concern in one study was evidence of impaired intrinsic myocardial contractility. There is evidence that these abnormalities improve with T4 treatment, demonstrating that adequate thyroid hormone replacement improves cardiac output accompanied by a substantial decrease in systemic vascular resistance, a reversal of diastolic dysfunction, and importantly an improvement in left ventricular ejection fraction during exercise. Recently, the technique of pulsed tissue Doppler echocardiography (used to assess regional myocardial wall velocity) has been used to show that SCH is associated with significant prolongation of the pre-ejection, left ventricular ejection and isovolumetric times. This is related to the fact that the ATP-dependent calcium ion transport in the sarcoplasmic reticulum is controlled by thyroid hormone. Patients with SCH have more cardiovascular risk factors and are more likely to develop atherosclerosis and other cardiovascular disease. Endothelial dysfunction known to contribute to the development of atherosclerosis and detected by the use of flow mediated arteriolar dilatation has been shown in patients with SCH. In view of the clear structural and biological cardiovascular risks associated with the presence of SCH, treatment of this condition would certainly be expected to provide protection against the development of cardiovascular disease, although we admit that there are no published long term outcome studies demonstrating this.

## **PREGNANCY**

Thyroid dysfunction in pregnancy has been associated with both maternal and fetal problems. Neuro-intellectual developmental impairment of children born to mothers with SCH in pregnancy has been shown to be due to low fetal access to circulating maternal T4 during the first trimester. In this group of patients it is essential that treatment is advised and

that screening programmes are introduced. Even though screening may not be performed until after conception it is still important as the precise details of thyroid hormone on brain development have not yet been delineated. Although as yet there are no randomized controlled trials in this area, four cohort studies have been performed and Klein et al reported the inverse correlation between maternal hypothyroidism and the intelligence quotient (IQ) of the offspring and reinforced the need for a screening programme. Reproductive dysfunction or "subfertility" can remain unrecognized in patients with SCH and women being investigated for infertility should have their thyroid function tested. A variable rate of infertility has been noted in patients with SCH. One study has observed that patients with SCH have increased prolactin secretion although the impact of SCH on gonadal function and infertility is yet to be clarified.

## SCREENING

Screening depends upon the perceived benefits (once SCH is detected) of treating the condition, and ideally should be based on a rigorous cost benefit analysis. It has been previously suggested that although population-based screening programmes are generally not recommended, in certain high risk groups there is

evidence that screening is cost effective (e.g., in patients with type 1 diabetes mellitus, women over 40 years of age, those with a positive thyroid antibody status or during pregnancy). These focused target groups of patients (apart from pregnancy) would benefit from periodic screening (probably annually) with treatment instituted if SCH were to be documented. The American Thyroid Association recommended, in 2000, that adults be screened every five years from the age of 35 years by measurement of their TSH levels (Fig. 1). We are of the opinion that this option is too expensive and unproven in terms of population benefit at this time.

## THE FUTURE

To date there are few RCTs and longitudinal studies involving the treatment of SCH, and treatment studies are limited by the lack of placebo controls. Studies undertaken to date also usually involve predominately women. This, together with the small sample sizes used and variable definitions of SCH, limits the application of study findings and it is important that future RCTs assess the benefits of replacement  $T_4$  in larger groups of patients. With regular follow-up of patients and thyroid function tests performed periodically any risks of over replacement can be avoided.

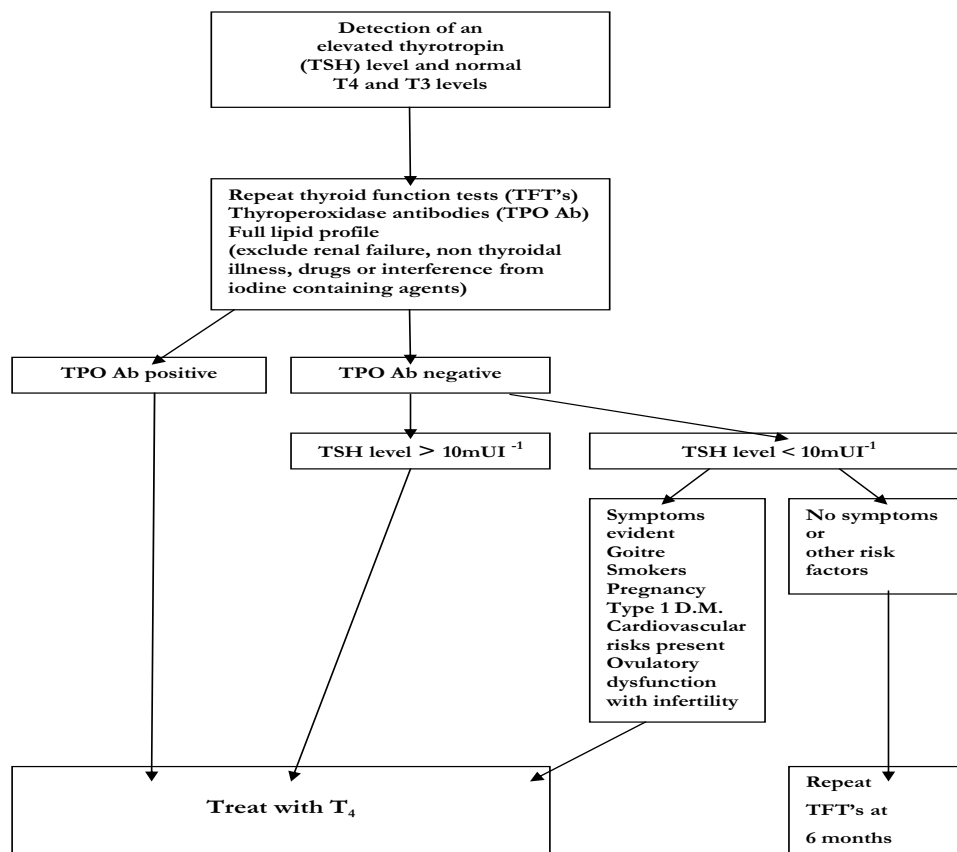


Figure 1. Screening algorithm for SCH

SCHypo should be treated, definitely in the “at risk” groups of patients, (Table 1) in view of the outcome data on cardiovascular disease and lipids. However, long term outcome data are not available in relation to many features of SCH but they are available for lipid abnormalities. Large, well controlled prospective studies are required to confirm the positive suggestive evidence already provided by the short-term RCTs, in order to extend the evidence basis for therapy.

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