

# Subclinical Hypothyroidism – Whether and When To Start Treatment?

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## Abstract

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Subclinical hypothyroidism represents a state with increased values of thyroid stimulating hormone (TSH) and normal values of thyroxine (T4) and triiodothyronine (T3). The disorder is asymptomatic, and the diagnosis is made based on the results of laboratory findings when the level of TSH reaches values above 4.0 mU/l. It is still subject to debate whether patients with subclinical hypothyroidism are at increased risk of cardiovascular disease, neuropsychiatric and neuromuscular disorders. Studies have shown that the appearance of general symptoms and complications are more common in patients whose values of TSH are above 10 mU/l. Therefore, the initiation of therapy with levothyroxine, which is the foundation of substitution therapy, is advised in patients whose TSH is >10 mU/l. As for patients whose values of TSH are from 4.0 to 10.0 mU/l and who make up 90% of the patients with subclinical hypothyroidism, further research is needed to determine the effects of the disorder and levothyroxine therapy on the health. Until then, the introduction of the substitution therapy in patients with TSH which is <10 mU/l should be considered in the case of the presence of general symptoms, anti-thyroid antibodies, increased lipids and other risk factors, goitre, pregnancy, ovarian dysfunction and infertility.

## Introduction

Subclinical hypothyroidism (SH) is a very common disorder in the general population, especially among middle-aged and elderly patients. It represents a state with increased values of thyroid stimulating hormone (TSH) and normal values of thyroxine (T4) and triiodothyronine (T3) [1]. In most cases, patients with SH have no symptoms that would indicate this disorder, so diagnosis is made based on laboratory findings [2]. As the values of thyroid hormone are normal, increased level of TSH represents a compensatory mechanism that stimulates the thyroid gland to produce sufficient amounts of thyroid hormones. The disorder can eventually progress to overt hypothyroidism (OH) which is characterised by increased values of TSH but reduced values of thyroid hormones [3]. Since the SH is asymptomatic disorder

in which the values of thyroid hormones are normal, and it may be a prelude to a clinically manifest disease of the thyroid gland, the question is whether it should be treated. This paper aims to summarize the available data on the influence of this disorder on the health of patients, as well as data on the effects of treatment to answer the question whether SH should be treated and if so when to start the treatment.

## Subclinical hypothyroidism and clinical significance

Clinically OH and decreased production of the thyroid hormones is associated with an increased cardiovascular risk [4], but what about the SH where

the values of the thyroid hormones are still normal?

Values of TSH above 4.0 mU/l represent increased levels and by their increase the SH can be divided into a mild form (values from 4.0-10.0 mU/l) and a more severe form (values >10.0 mU/l). As long as the values of this hormone are over the limit, levels of thyroid hormones are not sufficient to provide the euthyroid state. If it weren't so, we would expect the value of TSH, whose half-life is 1h, to drop to normal values as soon as T4 and T3, whose half-life is seven days and 1 day, reach normal values. However, this does not happen in SH because the values of TSH remain increased even when T4 and T3 reach normal values [3].

SH is usually asymptomatic, but in some patients may still appear symptoms that would indicate hypothyroidism. In the US Colorado Thyroid Disease Prevalence Study, which included 20,862 examinees, patients with SH more frequently reported symptoms compared to euthyroid examinees but less frequently than patients with OH. The most common symptoms were dry skin, poor memory, slower thinking, weakness and muscle cramps, swollen face with periorbital oedema, fatigue, hoarseness, deep voice and constipation. The same study showed that in the majority of patients (74%) with SH the levels of TSH were between 5.1-10.0 mU/l, while in 26% were above ten mU/l [5]. This means that most of these patients have mainly a slight disturbance of the function of the thyroid gland which is the case in 90% of patients with SH in general population [6].

Although the appearance of these symptoms could mean that this disorder could have consequences for the health of patients, there is still no evidence for possible harmful effects on individual's health. Besides the ability to progress to clinically OH, some studies have shown that SH could be associated with increased risk of cardiovascular disease (CVD), mood disorders and cognitive dysfunction as well as impaired neuromuscular function [2, 3, 6, 7].

## **Subclinical hypothyroidism and cardiovascular system**

Thyroid hormones exert a direct influence on the heart and blood vessels. The deficit of these hormones leads to functional disorders of the CVS, so changes in cardiac frequency, cardiac output and systemic vascular resistance are closely related to the thyroid status [8, 9].

In SH there is a disruption of the systolic and diastolic function of the left ventricle. In the blood vessels, there are also changes in the form of increased vascular resistance, increased arterial

stiffness and endothelial dysfunction [6].

Thyroid hormones also influence the lipid status. Many studies have shown that patients with SH have increased the level of total cholesterol, as well as low-density lipoprotein (LDL) about the euthyroid patients [5, 10]. Despite these results, a clear connection between lipids and SH has not been established because some studies have shown that the lipid profiles of patients with SH were not significantly different compared to euthyroid patients [11]. However, the lipid profile was more impaired in patients whose TSH is >10 mU/l and in smokers [12]. Patients with SH are also believed to be at increased risk of atherosclerosis. That is shown in Rotterdam study that examined the connection between the atherosclerotic process and SH in 1,149 women aged over 55 years. In this study, patients with TSH >4 mU/l had an increased risk of atherosclerosis and occurrence of myocardial infarction [13].

Disturbed blood coagulation is also seen in patients with SH. The values of some coagulation factors are increased, and the whole fibrinolytic activity is decreased which might result in increased blood coagulation [12]. Bearing in mind the potential influence on the structure and function of the CV system and lipid status, Rodondi et al. examined 2,730 patients between 70 and 79 years, of whom 338 had SH, to investigate their risk of CV morbidity and mortality. They have shown that in patients with TSH levels  $\geq 7$ , there was an increased risk of chronic heart failure in comparison to other euthyroid patients, but there was no increased risk of other CV events and mortality. In examinees whose TSH values were between 4.5 and 6.9 mU/l an increased risk of CV morbidity and mortality has not been observed compared to euthyroid examinees [14]. The same author's analysis of 11 prospective studies that included 55,287 examinees showed that increase in levels of TSH increases the risk of CV events and CV mortality, especially among those whose TSH is >10 mU/l. The disadvantage in interpreting these results lies in the fact that some of these studies involved patients with the prior existence of CV disease [15, 16].

Due to the extreme heterogeneity of the studies, we cannot make accurate conclusions about the influence of SH on CV system, although we can conclude that there is no evidence that a mild form of SH (TSH values are from 4.0 to 10.0 mU/l) may have consequences for patient's CV system.

## **Subclinical hypothyroidism, mood and cognitive functions**

Some, but not all studies have shown the connection between anxiety and depressive disorders

with SH [17, 18]. In middle-aged patients with SH was observed the more frequent occurrence of depression and the occurrence of severe forms of depressive disorders compared to euthyroid examinees.

Although the deficit of thyroid hormones leads to disorder of affective and cognitive functions, the influence of SH on these functions is not yet fully understood. Given that in most cases the SH is caused by autoimmune process and associated with an increased titer of antibodies to thyroid peroxidase (TPO) and thyroglobulin, it should be noted that the presence of these antibodies can cause cerebral dysfunction known as Hashimoto encephalopathy [8].

### **Subclinical hypothyroidism and neuromuscular function**

The exact mechanism that would be placed by disorders of neuromuscular function is not fully understood, but it is thought that disorder in glycogen lysis, expression of heavy chains of myosin and the mitochondrial activity could be the reason for the appearance of these symptoms in patients with SH. One study examined 12 patients with SH who complained of neuromuscular ailments during rest and exercise. The amount of created lactates and pyruvates in skeletal muscles during exercise were significantly higher in patients with SH in comparison to the control group. Based on the results, it can be concluded that energy metabolism of muscles may be disturbed in patients with SH [12].

### **Subclinical hypothyroidism and the progression to clinical hypothyroidism**

SH is a disorder that occurs more frequently in women, the elderly and in areas where there is an increased intake of iodine. Prevalence rate ranges from 4 to 10% in the adult population, and if there is an increased intake of iodine, it is up to 24% [12, 19]. In 80% of patients with SH, there is an increased titer of anti-thyroid antibodies, which means that in most cases an autoimmune process is present [7].

The clinical course of SH can move in the direction of development of OH, as well as in the direction of normalisation of values of TSH. One of the prospective studies followed the clinical course in 82 women who had increased values of TSH and showed that after a period of 10 years, 28% of them developed OH (TSH > 20 mU/l and decreased levels of free T4), 68% of them still had a subclinical disorder, while 4% of them reached the normalization

of TSH levels [20].

Diez et al. examined the natural course of SH in 107 patients and have shown that patients with mild SH disorder (TSH levels from 5.0 to 9.9 mU/l) have more chances to have values of TSH normalised compared to patients whose TSH is > 10.0 mU/l. It was also shown that the value of TSH was the most important prognostic factor for the outcome of SH [21].

### **The effects of the treatment of patients with subclinical hypothyroidism**

Studies that dealt with the effects of therapy often researched its influence on the disorder of the lipid profile of patients, as a possible significant risk for future CV disease. In the report of the working group of the United States for the prevention (U.S. Preventive Services Task Force - USPSTF), seven studies examined the influence of treatment of SH on the values of lipids. Six of them showed that the treatment of SH does not lead to improvement in lipid parameters [16].

On the other hand, an analysis of 13 studies and a total of 247 examinees showed different results. All patients had a disorder of TSH levels, no matter if they had spontaneous SH or OH with an insufficient dose of levothyroxine to normalise the value of TSH. The mean value of TSH at the beginning was 10.8 mU/l, and after the treatment period (12 weeks to 3 months) it was 2.6 mU/l. In 11 out of 13 studies there has been a decrease in the value of total cholesterol (-0.20 mmol/L (-7.9 mg/dL, or 5%)) and 7 out of 9 there has been a decrease in the value of LDL (-0.26 mmol/L (-10 mg/dL)). Changes in values of HDL and triglycerides were not statistically significant. However, most of these studies included small samples, most of them were not randomised and did not include a control group [22].

Since it is known that thyroid hormones perform a substantial effect on the heart, some studies have examined the influence of levothyroxine therapy on the structure and function of the heart in patients with SH. One such, double-blind and placebo-controlled study was conducted by Monzani et al. and it showed that patients with SH had a disorder in systolic and diastolic function of the left ventricle and that the levothyroxine therapy led to complete regression of it [23].

Great retrospective study based on data from the Danish National Patient Registry has examined the influence of levothyroxine therapy in patients with SH on the risk of myocardial infarction, as well as cardiovascular and total mortality. No effect was seen on the risk of myocardial infarction or the CV mortality.

As for total mortality, the results showed that patients younger than 65 years could have some marginal benefit [24].

Substitution therapy had different effects regarding cognitive functions which may be because SH is not a disorder that leads to global cognitive dysfunction and its numerous domains, but the more subtle changes in specific domains such as memory and executive functions of the brain [25].

As for mood disorders, although there is evidence that in patients with affective disorders often occurs SH, there is no evidence that substitution therapy has favourable effects [8, 26].

Levothyroxine therapy can lead to a reduction and the complete disappearance of the present antibodies in hypothyroid patients with Hashimoto thyroiditis. Still, there is no clear evidence that the early initiation of therapy might affect the spontaneous course of SH [1, 12, 27].

## The negative effects of therapy

The most common negative consequence of levothyroxine therapy is the occurrence of subclinical hyperthyroidism and in some cases occurrence of iatrogenic hyperthyroidism [2, 27, 28]. Between 10% and 33% of patients who take levothyroxine have values of TSH below normal, and in more than half of these patients, TSH is less than 0.1 mU/L [27].

Other adverse effects are related to the effect of levothyroxine on the bones and heart. Studies that examined the effect of TSH suppression by levothyroxine on bone density did not provide specific conclusions whether the therapy could lead to an increased risk of osteoporosis [26, 27]. As for the effects on the heart, subclinical hyperthyroidism in people older than 60 years is associated with increased 10-year risk of developing atrial fibrillation [26].

## Whether and when to start treatment?

SH is considered to be a mild disorder which can have consequences for the health and introduction of substitution therapy may be beneficial in some patients. Most of these patients have values of TSH from 4.0 to 10.0 mU/l and minimal metabolic and physiological disorders. Therefore, starting substitution therapy in these patients isn't usually justified. They should be rather monitored and controlled every 6 to 12 months [7, 12, 27]. Therapy

should be considered if there are present antibodies on TPO, general symptoms that are suggestive of hypothyroidism, increased values of total and LDL cholesterol, nodular or diffuse enlargement of the thyroid gland, pregnancy or ovulatory dysfunction with infertility [12, 17].

The results of many studies have shown that treatment with substitution therapy should be initiated in patients with TSH values above ten mU/l because these patients are at increased risk of developing health disorders (dyslipidemia, CV events, psychiatric, neuromuscular disorders, and occurrence of general symptoms). Although there isn't enough evidence that levothyroxine therapy could lower the values of total and LDL cholesterol, its beneficial effects cannot be excluded. Clinicians are advised to decide on a case-by-case basis, particularly if patients are smokers and have other risk factors for cardiovascular disease (hypertension, insulin resistance and diabetes, renal failure, etc.) [27, 29].

High values of TSH also increase the risk of developing clinically OH. There is no evidence that treatment will postpone the progression of the disorder, but perhaps it could help coping with symptoms [30]. One of the strongest reasons why the treatment is proposed when TSH reaches values above 10.0 mU/l is that the favourable results of substitution therapy are more obvious in these patients [2, 6, 7, 12, 29, 30].

Treatment is initiated with levothyroxine. Usual doses 25-75 mg/day are sufficient to normalise levels of TSH in patients with SH. Doses should be carefully titrated until TSH reaches value between 1 and 2-3 mU/l in younger and middle-aged patients. When the optimum values are reached, TSH should be controlled every 6-12 months [12].

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