Best Practice & Research Clinical Endocrinology & Metabolism 26 (2012) 431–446

Contents lists available at SciVerse ScienceDirect

Best Practice & Research Clinical Endocrinology & Metabolism

journal homepage: www.elsevier.com/locate/beem

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Natural history, diagnosis and management of subclinical thyroid dysfunction

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Keywords:
subclinical thyroid dysfunction
subclinical hyperthyroidism (exogenous and endogenous)
subclinical hypothyroidism
thyrotropin
L-thyroxine
replacement therapy
thyroid cancer
thyroid autonomy
thyrotropin suppression
prevalence
progression
cardiovascular risk
heart
bone
osteoporosis
symptoms
elderly
anti-thyroid drugs
radioiodine

Subclinical thyroid dysfunction (STD) represents a condition of slight thyroid hormone excess or deficiency, which may be associated with important adverse effects.

This review will focus on the natural history, diagnosis and management of subclinical thyroid dysfunction.

Since STD is only detected as a thyroid stimulating hormone (TSH) abnormality, it is essential to exclude transient causes of abnormal serum TSH before treating this disorder.

Treatment of subclinical hyperthyroidism (SHyper) is recommended in elderly patients with undetectable serum TSH for the increased risk of atrial fibrillation, osteoporosis and bone fractures and for the higher risk of progression to overt disease.

Treatment of subclinical hypothyroidism should be considered in patients with serum TSH above 10 mU/L for the increased risk of progression to overt hypothyroidism and the increased risk of coronary heart disease and heart failure events, which have been documented in patients with TSH increase above 10 mU/L.

About 75% of patients with STD have mild dysfunction. The mild form of STD (low but detectable serum TSH in SHyper and mild increased serum TSH between 5 and 9 mU/L in SHypo is associated with a minor risk of disease progression to overt dysfunction. The best treatment for STD remains controversial. Treatment of the mild form of STD should be considered after evaluating the patients' age, the adverse risk factors, the potential beneficial effects of treating this disorder and any underlying co-morbidities. Mild SHypo should be treated in infertile and pregnant women.

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doi:10.1016/j.beem.2011.12.004

Introduction

Subclinical thyroid dysfunction (STD) is an early condition of mild thyroid hormone excess (subclinical hyperthyroidism) or deficiency (subclinical hypothyroidism), characterized by abnormal serum thyroid stimulating hormone (TSH) and normal free thyroxine (FT_4) and free tri-iodothyronine (FT_3).[1,2]

The upper limit of the normal range has progressively decreased in the last decades from 10–7.0 mU/L to 4.0–5 mU/L, with the use of thyroid antibody tests.

Subclinical hypothyroidism (SHypo) is characterized by elevated serum TSH and thyroid hormone levels at the lower limit but within their respective reference range.[1–4] It is necessary to distinguish between patients with mildly increased serum TSH levels (5–9 mU/L) and patients with more severely increased serum TSH levels (≥10 mU/L) (Table 1). About 75% of all SHypo patients have mild disease.

The enhanced sensitivity of the TSH assay with the second and the third generation immunometric evaluation has helped differentiate the lower limit of the normal range from complete and incomplete TSH suppression.[1–3]

Subclinical Hyperthyroidism (SHyper) is defined as low-undetectable serum TSH and thyroid hormone (FT_4 and FT_3) concentrations in the upper limit but within their respective reference range.[1–4] Clinicians usually distinguish mild SHyper when the serum TSH level is low, but still detectable (0.1–0.4 mU/L), from a more severe condition in which TSH is undetectable and fully suppressed (Table 1).

Mild SHyper is the prevalent form of this dysfunction because it is present in about 75% of patients.[2]

The high frequency and the various implications of STD require the need to establish a correct diagnosis, clinical assessment and treatment of this disorder.[4,5]

Subclinical hypothyroidism

Prevalence and etiology

The prevalence of SHypo has been reported to be between 4 and 20% of the adult population samples.[1,2,6] This wide range reflects some important differences among the populations studied in terms of race and dietary iodine intake, the dissimilar characteristics among the patients evaluated (age, gender, body mass index) and the different methods of TSH evaluation (TSH cut-off values used to define SHypo).[1,2,7]

Hashimoto thyroiditis, an autoimmune disorder of the thyroid gland is the most frequent cause of progressive thyroid destruction, inducing thyroid hormone deficiency in adults.[1,2,8] It is associated in 15% of cases with systemic autoimmune disorders.[1,2] The incidence of Hashimoto thyroiditis is more frequent in females with a peak at 30–50 years of age; the overall incidence increases with age in both sexes, reaching 18–20% in the ninth decade of life.[1,2]

Acquired thyroid hormone deficiency frequently develops after partial thyroidectomy, radioiodine (RAI) treatment and after external radiotherapy of the head and neck.[1,2,8] Transient or persistent increases in serum TSH may occur after subacute, post-partum or painless thyroiditis and after an infiltrative disease (Riedel's thyroiditis, amyloidosis, hemochromatosis and cystinosis) or infectious disorder of the thyroid gland.[1,2,8]

Several drugs can induce persistent or transient subclinical or overt hypothyroidism, particularly in patients with underlying autoimmune thyroiditis (iodine-containing compounds, lithium carbonate, cytokines and interferon, tyrosine-kinase inhibitors).[1,2,8]

Table 1
Definition of subclinical thyroid disease.

Subclinical Hypothyroidism and Minimally Increased TSH
■ Patients with mild disease (serum TSH levels 5–9 mU/L)
■ Patients with more severe subclinical hypothyroidism (serum TSH levels >10 mU/L)
Subclinical Hyperthyroidism and Minimally Suppressed TSH
• Patients with mild disease (low but still detectable serum TSH 0.1–0.4 mU/L)
• Patients with more severe subclinical hyperthyroidism (undetectable serum TSH level <0.1 mU/L)

Inadequate thyroid hormone therapy, drug interactions and poor compliance may all be responsible for SHypo in 17–30% of hypothyroid patients receiving replacement doses of L-thyroxine (L-T4).[9]

Diagnosis

Subclinical hypothyroidism should be diagnosed only after a detailed personal and familial history, pharmacological evaluation and an accurate clinical assessment. Some familial (e.g. family history of autoimmune thyroid disease and/or endocrine or systemic autoimmune disorders) and genetic disorders (Down's syndrome, Turner's syndrome and Klinefelter's syndrome) should be investigated to identify subjects with an increased predisposition of developing autoimmune thyroiditis.[1,2]

A high thyroid autoantibody titer (usually against anti-peroxidase and/or thyroglobulin, or more rarely, TSH receptor) is frequently associated with a persistently elevated serum TSH concentration.[1,2] The thyroid gland is usually goitrous, but it may also be normal or atrophic; its hypoechogenicity at the ultrasound evaluation allows clinicians to identify individuals with SHypo due to autoimmune disease.[1,2]

The evaluation of transient and false causes of mild increases in TSH should be excluded before treating this disorder. The use of age, race and body mass index reference TSH ranges can help clinicians avoid misclassifying patients with increased serum TSH. Interestingly enough, the serum TSH level is higher in white populations than in black ones, which suggests a genetic and ethnic/race influence.[7] Increased serum TSH might not always reflect mild thyroid hormone deficiency in elderly subjects from iodine sufficient areas because the distribution of serum TSH shifts to higher concentrations with age.[7] An increased serum TSH value in older individuals frequently reflects recovery from acute illness or the use of drugs that can interfere with thyroid function.

The level of serum TSH is higher in overweight and obese individuals than in lean subjects, which could falsely suggest SHypo, especially in patients with negative thyroid autoantibodies. However, this altered thyroid hormone pattern is reversible by loosing weight.[10]

Natural history of mild and subclinical hypothyroidism

Subclinical hypothyroidism may be progressive or reversible. High iodine intake is associated with an increased risk of progression to overt hypothyroidism.[11]

Patients with non-autoimmune thyroiditis may frequently have transient TSH elevation. What is more is that TSH values normalize more frequently in subjects with serum TSH values less than 4–8 mU/L, whereas TSH values above 8–15 mU/L are associated with a low normalization rate of thyroid function.[11–14] The annual rate of progression to overt disease is particularly increased (4.3%) in women with elevated serum TSH and anti-thyroid antibodies.[11–14] A transient expression of TSH-receptor blocking antibodies may explain the improvement of the thyroid function and the progressive TSH normalization which may be observed in some patients with autoimmune hypothyroidism.[1]

The annual rate of progression to overt hypothyroidism in patients with SHypo induced by radioiodine or surgery is 2–6%.[14] Pregnant women with Hashimoto thyroiditis have a high-risk of disease progression.[15]

Adverse effects on cardiac hemodynamic and risk of heart failure in patients with mild and subclinical hypothyroidism

Important cardiovascular and metabolic effects may develop in long-term untreated SHypo (Fig. 1).[16–18] Cardiac function is altered in young patients with mild and SHypo due to the reduced expression of sarcoplasmic reticulum calcium ATPase.[19] Systolic and diastolic function at rest and during exercise are reduced, impairing the quality of life.[19–21]

Vascular function may also be deranged by thyroid hormone deficiency as demonstrated by the increase in systemic vascular resistance and central arterial stiffness and the altered endothelial function due to impaired nitric oxide availability.[1,22,23] The risk of diastolic hypertension may be higher in patients with SHypo than in euthyroid controls, particularly in post-menopausal status.[24,25]

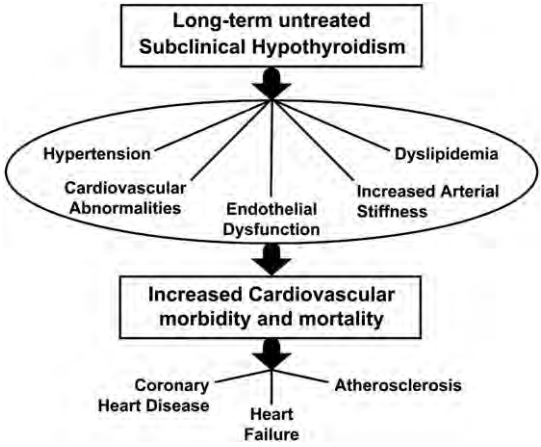

Fig. 1. Cardiovascular risk in patients with long-term untreated subclinical hypothyroidism.

Untreated long-term SHypo may increase the risk of congestive heart failure (CHF),[26] particularly in elderly subjects, starting at a TSH level greater than 7–10 mU/L.[27,28] Subjects with a TSH level of 7 mU/L or greater had a higher risk of heart failure events than euthyroid subjects after 4 years in the population-based Health Aging and Body Composition Study on 2730 subjects aged between 70 and 79 years.[27] Similarly, a higher incidence of CHF events was reported in patients with a TSH level above 10 mU/L, during a 12-year follow-up in the Cardiovascular Health Study of 3065 SHypo subjects with a mean age of 72.6 years.[28]

Further studies are required to assess the risk of CHF in patients with mild SHypo and to evaluate the reversibility of this risk in treated patients.

There are no data on the risk of heart failure in young and middle-aged patients with long-term untreated SHypo.

Subclinical hypothyroidism and the risk of metabolic effects and coronary heart disease

Untreated overt and subclinical hypothyroidism may lead to coronary heart disease (CHD) (Fig. 1).[18,29,30]

Subclinical hypothyroidism is associated with lipid abnormalities, especially increased total and LDL cholesterol, whereas there are conflicting data on HDL cholesterol, triglycerides and Lp(a) among the studies assessing lipid profile in SHypo patients compared to euthyroid controls.[18,29,30] The lipid pattern is particularly altered in SHypo patients with a serum TSH greater than 10 mU/L, in smokers and in insulin-resistant subjects.[18,29,30] Vascular dysfunction and dyslipidemia may increase the risk of atherosclerosis in patients with SHypo. Endothelial dysfunction at the level of coronary circulation may contribute to the increased risk of CHD in patients with mild SHypo.[31]

Data on the link between SHypo and homocysteine, high-sensitive C-reactive protein (hsCRP), coagulation parameters and lipoprotein (a) are conflicting and inconsistent and require additional studies to clarify the potential role of these 'non-traditional' cardiovascular risk factors in increasing the cardiovascular risk in SHypo.[1,30]

The possible link between SHypo and CHD has been assessed in several epidemiological studies. Mild Subclinical hypothyroidism was associated with a twofold increased risk of myocardial infarction and aortic atherosclerosis in the cross-sectional analysis of the Rotterdam study of 1149 women with at least 55 years of age.[32] Similarly, during a follow-up of 8.3 years in the Nord-Trøndelag Health Study (HUNT Study), a Norwegian population-based cohort study of more than 25,000 people with a mean age of 60 years old, TSH levels were positively and linearly associated with CHD mortality in women, but not in men.[33]

On the contrary, an increased risk of CHD was reported in middle-aged men in the cross-sectional evaluation of the Nagasaki Adult Health Study of 2856 subjects from a cohort of atomic bomb

survivors.[34] However, the longitudinal analyses of the Rotterdam and Nagasaki studies did not confirm the association of SHypo with CHD.[32,34]

The recent re-analysis of the Whickham survey of 97 individuals (mean age 49 years) showed that women with subclinical hypothyroidism (defined by TSH between 6.0 and 15 mU/L) had significantly higher baseline levels of blood pressure, cholesterol, LDL cholesterol and homocysteine than women with normal thyroid function.[24] Furthermore, this study reported a positive connection between SHypo and the risk of incident ischemic heart disease during a 20-year follow-up.[24]

The Busselton Study of 3447 Australian subjects was the first study in which the analysis was stratified according to TSH values.[35] In this study, middle-aged subjects (mean age 49.8 years) with SHypo had an increased risk of CHD in the cross-sectional and longitudinal analysis during a 20-year follow-up.[35] The increased risk for CHD was evident in patients with mild and SHypo and did not differ significantly between subjects with and without thyroid autoimmunity.[35]

In the European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk prospective population Study from the United Kingdom, patients with subclinical hypothyroidism did not have an increased risk of CHD, although the authors found an altered baseline cardiovascular risk profile.[25]

The incidence of CHD did not increase in other studies.[27,36–38]

The discrepancies in epidemiological data with reference to the risk of coronary heart disease in subclinical hypothyroidism are probably related to differences in the populations studied (in terms of age, sex, race/ethnicity, life style), the TSH range used to define subclinical hypothyroidism, methods of evaluating cardiovascular disease, differences in adjustments for known risk factors for cardiovascular disease, and the duration of follow-up. Few studies have stratified the analysis by TSH levels. Furthermore, not all of the epidemiological studies have included follow-up data on thyroid function, and in other studies some patients have been treated with thyroid hormone during follow-up.

Two meta-analyses have stratified the evaluation according to the quality criteria and the age of participants.[39,40] The results show that the risk of CHD was significantly increased in subjects below 65 years of age, but not in those aged 65 years or older.[39] In addition, the risk of CHD increased with the severity of thyroid hormone deficiency and was even higher with TSH above 10 mU/L.[40] Interestingly, although the prevalence of CHD was higher in both men and women with SHypo, it was statistically significant only in women.[39]

A recent meta-analysis has analyzed the individual data of 55,287 participants from 11 prospective cohorts.[41] This analysis confirms that the risk of both CHD and mortality due to CHD were significantly increased in participants with TSH levels of 10 mU/L or greater. However, the individual participant data analysis found that the CHD outcomes in adults with SHypo did not differ significantly across sex groups.[41]

All of these results strongly support the association between CHD and SHypo in patients with TSH above 10 mU/L.[39–41] Further prospective studies are required to assess the risk of CHD in patients with mild SHypo. Moreover, it remains to be clarified whether this risk is prevalent in men or women and the age at which this risk can start or disappear.

Subclinical hypothyroidism and the risks of cardiovascular and total mortality

There are conflicting results on the risks of cardiovascular and total mortality in SHypo patients.[27,33–38,42–45]

Three meta-analyses have assessed the risk of cardiovascular and all-cause mortality in patients with SHypo.[39–41] In the meta-analysis by Razvi, the cardiovascular mortality was increased in patients with SHypo younger than 65 years of age, but not in older people.[39]

The meta-analysis of high quality studies by Ochs confirmed a modestly increased cardiovascular risk of CHD and total mortality in subjects with SHypo, with an increased risk in subjects less than 65 years of age.[40]

A pattern of decreased mortality in SHypo was observed in the Leiden 85-Plus Study of 558 individuals aged 85 years and monitored for 4 years.[42] This study suggested that suboptimal replacement therapy, resulting in high levels of TSH and low FT_4 plasma values, was associated with decreasing total mortality in very elderly subjects.[42] Similarly, SHypo was not associated to

increased overall mortality risk in the elderly in the population-based, prospective cohort of the Amsterdam Longitudinal Aging Study.[45] These results could suggest that the traditional cardiovascular risk factors identified in middle-aged populations (increased cholesterol, diastolic hypertension, endothelial dysfunction, obesity and insulin-resistance, etc.) may be less relevant in the elderly or that thyroid hormone deficiency may have a protective effect in very old patients. However, the last meta-analysis by Rotondi showed that there was no significant increased risk of total mortality, CHD mortality or CHD events for the specific age group of 80 years or older.[41] This study confirmed that the risk of CHD mortality, but not of total mortality, was increased in SHypo patients with higher concentrations of TSH[41]; however the effect of increasing TSH levels did not differ according to age.

Large randomized controlled studies are necessary to assess the importance of replacement therapy in elderly patients, especially in presence of minimal TSH elevation.

Subclinical hypothyroidism in patients with co-morbidities

Untreated SHypo is associated with an increased cardiovascular mortality in cardiac patients.[44] A meta-analysis of 7 cohort studies have shown that all-cause mortality is increased in patients with subclinical hypothyroidism and co-morbidity conditions compared to euthyroid controls.[46]In contrast to this report, the outcomes in SHypo patients were not significantly affected in presence of baseline pre-existing cardiovascular disease in the meta-analysis by Rodondi et al.[41]

Therefore, the cardiovascular mortality in patients with SHypo remains controversial in patients with co-morbidities.

Subclinical hypothyroidism, fertility and pregnancy

Thyroid dysfunction and thyroid autoimmunity are prevalent among women in their reproductive age (0.5–5%) and are associated with adverse pregnancy outcomes.[1,2,15] Untreated or inadequately treated chronic autoimmune thyroiditis is the most common cause of thyroid hormone deficiency in pregnancy.[1,15,47]

A recent meta-analysis has selected 38 appropriate studies to evaluate the clinical significance of thyroid dysfunction and thyroid autoimmunity before conception and in early pregnancy.[48] This meta-analysis shows that subclinical hypothyroidism in early pregnancy is associated with the occurrence of pre-eclampsia and an increased risk of perinatal mortality compared to normal thyroid function.[49] Moreover, the presence of thyroid antibodies is associated with an increased risk of unexplained subfertility, miscarriage, recurrent miscarriage, preterm birth and maternal post-partum thyroiditis when compared to the absence of thyroid antibodies.[48]

Another meta-analysis has shown that SHypo pregnant women had more than tripling in the odds of miscarriage and a doubling in the odds of preterm birth in presence of thyroid autoantibodies.[49]

An inverse correlation between maternal thyroid hormone deficiency and the intelligent quotient (IQ) of the offspring has been reported.[1,2,47] Mean intelligence and motor scores may be lower in children born from women with SHypo, hypothyroxinemia and elevated TPO antibodies than in children born from women adequately treated and control subjects.[47,50]

All these adverse effects may be prevented by replacement treatment with L-thyroxine.[1,2,15,47]

Clinical management of patients with subclinical hypothyroidism

The knowledge of the adverse effects of SHypo has improved in the last years and this disorder is more frequently diagnosed in clinical practice. Therefore, it is important to establish the best treatment for mild and SHypo.

Recent data have shown that a single set of thyroid-function tests and biologic variation in thyroid testing may severely limit the diagnosis of true persistent SHypo,[51] supporting the need for a periodic follow-up without therapy before treating this disorder.

Only persistent subclinical hypothyroidism should be treated, and L-thyroxine is the drug of choice for the treatment of SHypo.[1]

Treatment of subclinical hypothyroidism with TSH ≥ 10 mU/L

Treatment of SHypo is recommended for all patients with serum TSH levels ≥10 mU/L.[1,2,4] These patients may have a significantly increased risk of progression to overt hypothyroidism,[11–14] are more frequently symptomatic[52] and may have a higher chance of dyslipidemia[53] and cardiovascular dysfunction with an increased risk of CHD events, CHD mortality[39–41] and CHF.[27,28] Treatment with L-thyroxine is necessary in these patients, especially if they are young or middle-aged to prevent progression to overt disease, to improve symptoms and quality of life and to protect them from the risk of cardiovascular diseases and mortality.[24,28]

Although large randomized controlled studies are necessary to assess the beneficial effects of replacement therapy, all-cause mortality was significantly lower in was significantly lower in thyroxine-treated patients with SHypo than in untreated individuals in the re-analysis of the Whickham Survey.[24]

Treatment of mild subclinical hypothyroidism (TSH 5–9 mU/L)

No consensus exists on the clinical significance and treatment of the mild form of thyroid failure.[1,2,4,5] The available data suggest that treatment of mild SHypo should be personalized.[1,2] Various factors may influence the decision to treat mild SHypo. Clinicians should consider the patients' age, the risk of progression to overt disease, the quality of life, the cognitive, metabolic and cardiovascular risk factors and the presence of associated co morbidities.[1,2]

Young-middle aged patients are more likely to be treated than older patients, especially patients with goiter, positive thyroid antibody tests and progressive increase in serum TSH.[1,2,54]

Subjects with new specific symptoms and/or depression and those with cardiovascular risk factors (hypertension, hypercholesterolemia, insulin-resistance or diabetes, isolated diastolic dysfunction, evidence of impaired endothelial function) are also more frequently treated by clinicians.[1,2,54] Studies regarding the effect of replacement therapy on lipid profile, specific symptoms of hypothyroidism or cognitive and neuropsychiatric symptoms have yielded conflicting results[52,55–60] in patients with mild SHypo. On the contrary, there is evidence of a potential improvement of cardiovascular hemodynamics and cardiovascular risk factors during L-T4 therapy in some placebo-controlled studies[55,56,60–64]; all of these trials concur that replacement therapy may improve systolic, diastolic and vascular function, and, hence, cardiovascular hemodynamic.

These results should be verified in larger randomized trials and longitudinal studies, assessing cardiac morbidity and mortality; however, the available data suggest that L-thyroxine treatment should be administered in patients with mild SHypo in presence of a high cardiovascular risk. Replacement therapy may improve cardiovascular function and/or the associated cardiovascular risks factors. The aim of treatment with L-thyroxine should be to normalize serum TSH levels in a range between 1 and 2.5 mU/L in young and middle-aged patients.[1,2] This treatment does not have any adverse effect in healthy young subjects, especially when the same L-thyroxine product is used and thyroid function is regularly monitored.[1,2]

Treatment of SHypo in elderly subjects

Although large randomized trials are needed, evidence suggests that treatment of mild SHypo should probably be avoided in patients older than 60 years of age[42,65,66] because there is no evidence that these patients are symptomatic and L-T4 treatment does not improve their quality of life.[67,68] Replacement therapy should be individualized in elderly and very elderly patients with a serum TSH concentration above 10 mU/L. The decision to start treatment depends on the presence of associated co-morbidities and quality of life. Heart failure may develop in these patients, especially in cases with underlying heart diseases.[27,28] The risk of heart failure was significantly lower in thyroxine-treated patients with TSH ≥ 10 mU/L.[28] On the contrary, CHD events and mortality are rare in healthy elderly subjects.[39–41] Low doses of L-T4 are often adequate in elderly patients with TSH levels above 10 mU/L because of their decreased thyroxine metabolism. The target serum TSH should be higher compared to younger patients to mimic physiological values (e.g. 4–6 mU/L in individuals older than 70 years).[1,2]

Over-treatment with L-thyroxine should be avoided because of the important consequences of subclinical hyperthyroidism in the elderly.[37,69,70] Negative cardiac effects are only observed in the elderly and in patients with underlying heart disease in case of involuntary over-treatment and TSH

suppression during L-T4 therapy; this happens frequently when a generic substitution of L-T4 is used, in poorly controlled patients and in older patients with low weight and diabetes.[9]

Treatment of mild and SHypo in pregnant women

The benefit or replacement therapy in pregnancy outweighs the potential risks. This treatment is recommended[15,47] because of the adverse effects in the offspring of pregnant women and the adverse consequences in the outcome of pregnancy.[15,47] Treatment with L-T4 should be promptly started to normalize thyroid-function tests as soon as possible in women with increased serum TSH who are TPO antibody positive.[71]

Subclinical hyperthyroidism

Prevalence and etiology

The most common cause of exogenous SHyper (Exo SHyper) is an excessive L-T4 replacement therapy in hypothyroid patients or an intentional TSH suppression in patients with differentiated thyroid cancer (DTC).[1,2,72] Exogenous SHyper is present in about 20–40% of patients receiving L-thyroxine (L-T4) therapy.[9]

Long-term L-T4 suppression of TSH is the traditional treatment for patients with DTC at high-risk of recurrence and progression.[75,76] Experimental and clinical data have demonstrated that TSH stimulates thyroid cell proliferation and thyroglobulin (Tg) production and that TSH suppression is able to inhibit the growth of residual neoplastic tissue and induce the regression of tumor recurrences.[75,76]

Endogenous SHyper (Endo SHyper) is commonly associated with autonomous thyroid function; Graves' disease (GD), toxic multi nodular goiter (TMNG) and toxic adenoma (TA) represent the most frequent causes of this disorder.[1,2,72,73,77] The prevalence of Endo SHyper is between 0.7% and 9%, reflecting the different iodine intake of the population studied and some differences in the degree of TSH suppression, the cause of the disease, the age of the patients and the sensitivity of the methods used to measure serum TSH concentrations.[1,2,72,77] Graves' disease is an autoimmune cause of Endo SHyper which is prevalent in young, middle-aged patients and in areas of high iodine intake.[77] On the contrary, thyroid autonomy, due to TMNG and TA, is the most frequent cause of Endo SHyper in elderly patients and in areas where iodine intake is low.[1,2,77]

Diagnosis

The diagnosis of SHyper should be performed in presence of persistent low-undetectable serum TSH concentrations; FT_4 levels are at the upper limit of their normal range in patients with Exo SHyper,[1,2,76] whereas FT_3 levels may be at the upper limit of their normal range in patients with Endo SHyper.[1,2,77]

The diagnosis of Endo SHyper should include a careful clinical evaluation of symptoms and signs of thyroid hormone excess and the evaluation of potential associated autoimmune conditions, such as ophthalmopathy and autoimmune cardiac involvement.[77]

Since subclinical hyperthyroidism is only detected as a TSH abnormality, the exclusion of transient causes of TSH suppression should be performed before diagnosing a persistent condition of Endo SHyper. Transient TSH suppression usually occurs during subacute, silent or post-partum thyroiditis.[1,2] Some drugs (e.g. high-dose steroids, dopamine or dobutamine, amiodarone) may cause subclinical and overt hyperthyroidism.[1,2] An isolated reduction in serum TSH is common during the first trimester of pregnancy.[1,2] About 1–3% of elderly people (aged 60–80 years or over) have a serum TSH <0.4 mU/L and a blunted TSH response to TRH because of the reduced TSH secretion by the pituitary gland.[1,2] However, in elderly subjects FT_3 levels are decreased due to the reduced peripheral conversion of T_4 to T_3. Low serum TSH due to non-thyroidal illness or central hypothyroidism should be excluded; the presence of low thyroid hormones and a clinical evaluation can help differentiate these conditions from long-term SHyper.[1,2]

An evaluation of thyroid stimulating immunoglobulin (TSI) is necessary for SHyper patients with GD to predict the potential progression to overt disease.[2]

Radioiodine uptake can confirm the diagnosis of SHyper and can guide clinicians in choosing a definitive treatment.[2]

Computed tomography without contrast agents or magnetic resonance imaging should be used to assess a suspected airway compression before deciding a definitive treatment in patients with large goiter.[2]

Natural history of mild and subclinical hyperthyroidism

Patients with SHyper may have a reversible or persistent disease and/or may progress to overt hyperthyroidism. The risk of progression to overt hyperthyroidism is higher in patients with GD than in patients with TMNG.[2,74,78,79] Conversely, the natural history of TMNG is characterized by persistent SHyper and potential progression to overt disease, which is more frequent after iodine administration and is more common in patients with undetectable serum TSH than in presence of low serum TSH.[2,74,79]

Adverse cardiovascular effects of subclinical hyperthyroidism

An increased cardiovascular risk is associated with long-term untreated SHyper (Fig. 2). Some studies have demonstrated an increased prevalence of symptoms and signs of adrenergic overactivity in young and middle-aged patients with exogenous and endogenous SHyper.[80–83] Sinus tachycardia, atrial and ventricular premature beats and reduced heart rate variability are frequent complications of overt and subclinical hyperthyroidism in patients with undetectable serum TSH.[1,2,80–83] Moreover, long-term untreated SHyper may induce changes in cardiac morphology and function because of the increased cardiac workload (Fig. 2).[80–85] The clinical consequences of untreated SHyper in young-middle aged patients with undetectable serum TSH are characterized by increased left ventricular mass, which may impair diastolic filling and exercise tolerance.[1,2,80–85] All of these adverse cardiac effects induced by SHyper represent a negative prognostic factor for cardiovascular mortality and morbidity in the general population. However, their prognostic significance in SHyper patients is unclear.

Risk of atrial fibrillation in mild and subclinical hyperthyroidism

An increased risk of atrial fibrillation (AF) (two–three fold compared to euthyroid age-matched subjects) was associated with SHyper in elderly subjects 60 years or older with low[37] and undetectable[69]serum TSH in the Cardiovascular Health Study[37] and in the Framingham Study,[69] over 10[69] and 13 years of follow-up,[37] respectively. This arrhythmia may also develop in patients with high FT_4 levels[86] and in presence of associated underlying heart disease.[87] The hypercoagulable state

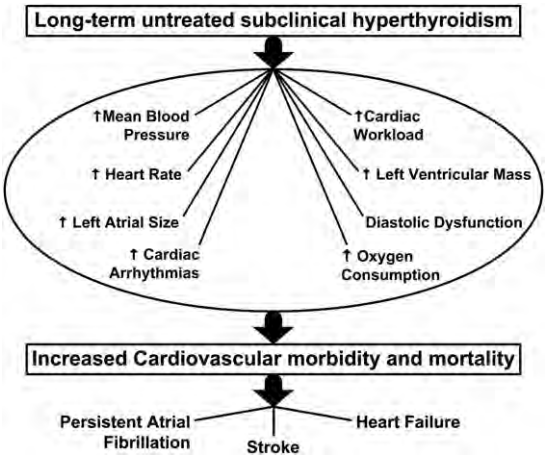

Fig. 2. Cardiovascular risk in patients with long-term untreated subclinical hyperthyroidism.

induced by SHyper may increase the risk of stroke in SHyper patients with AF, especially in presence of underlying cardiac disease.[1,2,77]

Cardiovascular mortality

Studies on the relationship between cardiovascular morbidity and mortality in exogenous SHyper have given conflicting results.[88] An increased risk for cardiovascular morbidity and mortality and dysrhythmias was reported in a recent large population-based study by Flynn among 17,684 patients with Exo SHyper (mean age 61.6 years).[89] These patients had repeated undetectable serum TSH levels ($\leq$0.03 mU/L) during the median follow-up of 4.5 years.[89] The cardiovascular risk increased for all endpoints with older age .In the same population, patients with subnormal serum TSH (0.04–0.4 mU/L) did not have an increased risk of cardiovascular disease or dysrhythmias compared to subjects with normal serum TSH (0.4 mU/L).[89]In the study by Bauer, low serum TSH levels ($\leq$0.5 mU/L) were not significantly linked to excess mortality among older women aged $\geq$65 years after 15.8 years of thyroid hormone use.[90]

Both of these studies suggest an increased cardiovascular mortality only in elderly patients with Exo SHyper and undetectable serum TSH; however, since thyroid hormone levels were not reported, it is uncertain whether the patients of these studies had normal or frankly elevated serum T4 levels.[89,90]

Similar to exogenous disease, the association of endogenous SHyper with cardiovascular mortality is controversial.[35,37,38,42,44,45,88,91–93] An increased circulatory mortality was observed in an English community-dwelling study of people over the age of 60 with mild SHyper (TSH $\leq$0.5 mU/L), during the first five years of follow-up.[38] All-cause and cardiovascular mortality were also significantly higher in individuals with SHyper (TSH $<$0.3) in a prospective observational study from Brazil, during a 7.5-year follow-up.[43] Interestingly, in these two studies the increased mortality emerged during the first years, whereas it was not observed over the full follow-up period of 10 years.[38,43]

Two reports showed that subnormal serum TSH ($<$0.3 mU/L) and high FT_4 values had adverse prognostic effects in very elderly subjects.[42,91] Furthermore, an increased cardiovascular mortality, particularly for cardiac ischemia, was reported in SHyper patients with underlying heart disease and low but persistent detectable serum TSH ($<$0.3 mU/L), during 2.7 years of follow-up.[44]

The conflicting results on the cardiovascular morbidity and mortality in patients with Exo and Endo SHyper reflect the heterogeneity of the different populations studied in terms of causes, sex, age, race, degrees of TSH suppression and duration of the follow-up.

There are some important limits of these epidemiological studies because serum TSH was only evaluated at the beginning of the study in the majority of these reports. Moreover, the studies performed in patients with Endo SHyper did not provide information about the treatment of participants after the baseline diagnosis. Nevertheless, in the recent Thyroid Epidemiology Audit and Research Study (TEARS), Endo SHyper was linked to an increased risk of cardiovascular morbidity and dysrhythmias after the exclusion of treated patients who developed overt hyperthyroidism.[93]

Several meta-analyses have evaluated the cardiovascular and all-cause mortality risks associated with SHyper.[40,46] The meta-analysis by Ochs on five population-based studies showed a modestly increased risk for coronary heart disease, cardiovascular mortality and total mortality in patients with SHyper.[40] According to a recent meta-analysis, elderly patients and patients with co-morbidities can have an increased likelihood of death which may progressively increase during 10 years after the diagnosis of SHyper.[46]

Bone mineral density and risk of bone fracture risk in subclinical hyperthyroidism

A decrease in bone mineral density (BMD) has been reported in post-menopausal women with Exo and Endo SHyper, specifically in cortical bone-rich sites, whereas there is little evidence of an effect on bone in premenopausal women.[93–96]

The effects of Exo and Endo SHyper on the risk of bone fracture are less clear and more debated.

In the prospective cohort study by Bauer of 686 women with Exo Shyper, aged 65 years or older and followed for approximately 4 years, undetectable serum TSH was associated with a four-fold increase risk of vertebral fractures and a three-fold increased risk of hip fracture.[95] Moreover, a suppressed

serum TSH (≤0.03 mU/L) was associated with a doubled risk of osteoporotic fracture in post-menopausal women with ExoSHyper (mean age 60.3 years) in the population-based study by Flynn.[89] Patients with a serum TSH below the reference range, but not fully suppressed (0.04–0.4 mU/L), had no increased risk of fractures.[95] However, data on free T4 levels or T3 levels were not reported in both these studies.[89,95]

A recent prospective US community-dwelling adult study has reported a high incidence of hip fracture in men 65 years or older with Endo SHyper compared to euthyroid controls.[93] Although, the risk of fracture was increased in patients with Endo SHyper in the Thyroid Epidemiology, Audit, and Research Study (TEARS), it was not related to serum TSH concentration.[93]

All of these studies concur that the risk of bone fracture is increased in elderly patients with undetectable serum TSH.

Treatment of subclinical hyperthyroidism

Treatment of exogenous subclinical hyperthyroidism

The concept of TSH-suppression therapy has changed in recent years because of the increased prevalence of small papillary thyroid cancers and the evidence that these low-risk DTC patients generally have an excellent survival rate.[75,76,97] Clinicians must consider the clinical stage of the patients as well as their age and any underlying co-morbidities before starting TSH suppressive therapy.[75,76]

The aim of L-T4 treatment in low-risk patients with cured DTC should be to maintain TSH levels in the normal range to avoid adverse effects because TSH-suppression therapy does not improve the outcome of these patients.[75,76,97]

On the contrary, long-term treatment with TSH suppressive doses of L-T4 should be considered in patients with intermediate and high-risk of differentiated thyroid cancer, before the assessment of the complete remission of the disease; in fact, the outcome of these patients with higher risk of disease progression may be improved by TSH suppression.[97]

In symptomatic young patients with Exo SHyper, the addition of beta-blocking drugs to L-T4 might prevent or counteract the negative cardiac effects of long-term TSH suppression.[80,99] Elderly patients have both a higher risk of disease progression and a higher risk of adverse effects during long-term TSH suppression. The beneficial effects of undetectable TSH suppression on cancer growth should be balanced out with the increased cardiovascular risk in elderly patients with high-risk DTC.[75,76,80]

The adverse effects of L-thyroxine are reversible by decreasing L-thyroxine dosage.[80,81,98] Therefore, when thyroid cancer remission is obtained in patients with DTC, lower doses of L-T4 therapy should be used to obtain a low serum TSH.[75,76]

Treatment of endogenous subclinical hyperthyroidism in patients with undetectable serum TSH

Persistent SHyper should be confirmed before a definitive treatment with radioiodine or surgery in patients with subnormal or undetectable serum TSH.[1,2]

Clinicians are more prone to treat persistent SHyper in advanced age, in patients with undetectable serum TSH and in presence of co-morbidities.[1,2,100,101] However, treatment should also be considered in symptomatic young patients with persistent undetectable serum TSH, especially in presence of underlying heart disease.[1,2]

An increased cardiovascular risk, an amplified risk of osteoporosis and fracture and a greater progression to overt disease are all linked to subclinical hyperthyroidism in elderly patients with undetectable serum TSH and in patients with cardiovascular or bone risk factors.[1,2,37,69,93,96] Both anti-thyroid drugs and radioiodine treatment are able to normalize the cardiovascular and bone parameters in patients with Endo SHyper.[83,84,102–104] In patients with Graves' disease, treatment with either anti-thyroid drugs or radioiodine is appropriate.[1,2,100] RAI therapy is the preferred option, mainly in patients with TMNG and TA, since spontaneous remission is unlikely to occur.[1,2,100] RAI treatment of SHyper should be considered in older patients.[1,2,100] However, elderly subjects with thyroid autonomy are at an increased risk of complications after RAI due to the worsening of hyperthyroidism.[105] These patients, especially those with cardiovascular disease, should be treated with anti-thyroid drugs before RAI therapy to normalize their thyroid function; larger doses of RAI should be administered in these

patients.[1,2,100,106] Anticoagulation should be considered before RAI treatment in patients with atrial fibrillation, particularly in presence of risk factors for stroke.[1,2,100]

Surgery should be considered in all patients with evidence of airway compression.[1,2,100]

Treatment with anti reabsorptive drugs (calcium, vitamin D or bisphosphonates) should be performed in post-menopausal women with Endo SHyper and in patients with osteoporosis or risk factors for bone loss.[1,2,100]

Treatment of endogenous subclinical hyperthyroidism in patients with detectable serum TSH

Young asymptomatic patients with low but detectable serum TSH should be followed without treatment due to the low risk of progression to overt hyperthyroidism and the absence of cardiac and bone risk.[1,2]

Definitive treatment with RAI should be considered in elderly patients for the increased risk of AF 37 and osteoporosis,[95,96], in patients with underlying heart disease and in young symptomatic patients with toxic multi nodular goiter or toxic adenoma with a progressive TSH decrease during the follow-up for the risk of progression to overt disease. Finally, surgery should be performed in patients with large goiter in presence of airway compression.[1,2]

Practice points

- Subclinical thyroid dysfunction is a frequent disorder and may progress to overt disease
- Exo and Endo SHyper may be responsible for an increased cardiovascular risk, especially in presence of undetectable serum TSH
- Elderly patients with SHyper have an increased risk of atrial fibrillation, particularly in presence of an underlying heart disease
- Elderly patients with exogenous and endogenous subclinical hyperthyroidism have an increased risk of bone fracture
- Mild subclinical hypothyroidism may be linked with some important cardiovascular risk factors
- Patients with subclinical hypothyroidism may have an increased risk of CHD in presence of TSH above 10 mU/L
- Elderly patients with subclinical hypothyroidism may have an increased risk of CHF when TSH is above 10 mU/L
- Subclinical hypothyroidism and thyroid autoimmunity are associated with adverse pregnancy outcome

Research agenda

- Further studies are necessary to clarify the potential adverse effects of mild subclinical hypothyroidism and hyperthyroidism and the need to treat these disorders
- Prospective studies are necessary to clarify the risk of CHD in patients with mild SHypo and the age at which this risk may appear or disappear
- Large randomized controlled studies are needed to assess the importance of treating elderly patients with mild subclinical hypothyroidism.
- Prospective studies could explain whether treatment of STD may improve or completely counteract its adverse effects and correlated risks

Disclosure summary

The author has nothing to disclose.

Acknowledgment

Alfonso Gruosso for writing English assistance.

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