INVITED REVIEW

Subclinical hyperthyroidism: clinical features and treatment options

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Abstract

Subclinical hyperthyroidism appears to be a common disorder. It may be caused by exogenous or endogenous factors: excessive TSH suppressive therapy with L-thyroxine (L-T4) for benign thyroid nodular disease, differentiated thyroid cancer, or hormone over-replacement in patients with hypothyroidism are the most frequent causes. Consistent evidence indicates that 'subclinical' hyperthyroidism reduces the quality of life, affecting both the psycho and somatic components of well-being, and produces relevant signs and symptoms of excessive thyroid hormone action, often mimicking adrenergic overactivity. Subclinical hyperthyroidism exerts many significant effects on the cardiovascular system; it is usually associated with a higher heart rate and a higher risk of supra-ventricular arrhythmias, and with an increased left ventricular mass, often accompanied by an impaired diastolic function and sometimes by a reduced systolic performance on effort and decreased exercise tolerance. It is well known that these abnormalities usually precede the onset of a more severe cardiovascular disease, thus potentially contributing to the increased cardiovascular morbidity and mortality observed in these patients. In addition, it is becoming increasingly apparent that sub-clinical hyperthyroidism may accelerate the development of osteoporosis and hence increased bone vulnerability to trauma, particularly in postmenopausal women with a pre-existing predisposition. Subclinical hyperthyroidism and its related clinical manifestations are reversible and may be prevented by timely treatment.

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Introduction

Subclinical hyperthyroidism is characterized by a low or undetectable concentration of serum thyrotropin (TSH) with free tri-iodothyronine (FT3) and free thyroxine (FT4) levels within laboratory reference ranges. Although there is evidence that subclinical hyperthyroidism may have adverse tissue effects, the level of TSH suppression that determines these negative effects, and the management and treatment of this condition remain controversial issues (1, 2).

The definition of subclinical hyperthyroidism is based only on laboratory, not clinical, criteria and the term probably represents a misnomer (3). In fact, although in the normal reference range, serum thyroid hormones would be increased for the individual with low or undetectable serum TSH levels, thus determining a mild tissue hyperthyroidism. Indeed, the reference ranges for individual test results over a period of 12 months were more narrow than the group reference

ranges on which laboratory reference ranges are based (4). Accordingly, conventional population-based reference intervals for thyroid function tests may not identify values that are outside the normal range for the individual being tested. The pituitary gland is sensitive to minor changes in serum thyroid hormone levels (5), and serum TSH responds with logarithmically amplified variations to such changes (6, 7). Therefore, the distinction between subclinical and overt hyperthyroidism, which is based on the population-based reference range for thyroid hormone levels, is somewhat arbitrary and diagnosis depends on the position of the patient's set point for thyroid hormones within the laboratory reference range.

The view that individuals with an undetectable serum TSH level suffer from a mild form of tissue hyperthyroidism *sensu strictu* is supported by the finding of relevant changes in several cardiovascular measures and in bone structure and metabolism in these individuals. Importantly, these changes

significantly impair quality of life and, especially in the elderly, greatly increase the risk of cardiovascular morbidity and mortality, and of bone fractures.

In this article we have reviewed the literature on subclinical hyperthyroidism, particularly as regards to its clinical features and treatment options. Our intention is to provide physicians with a tool to manage this condition according to the principles of evidence-based medicine.

Etiology and differential diagnosis

Subclinical hyperthyroidism may be caused by exogenous or endogenous factors (8), and may be transient or persistent (Table 1). Adverse tissue effects are similar, whatever the cause of subclinical hyperthyroidism and mainly depend on the duration of the disease. The exogenous form of subclinical hyperthyroidism is usually related to TSH-suppressive therapy with L-thyroxine (L-T4) for a single thyroid nodule, multinodular goiter, or differentiated thyroid carcinoma. In addition, TSH may be unintentionally suppressed during hormone replacement therapy in about 20% of hypothyroid patients (9, 10). The endogenous form is usually related to the same causes as overt thyrotoxicosis, namely Graves' disease, autonomously functioning thyroid adenoma, and multinodular goiter. The two latter causes are particularly frequent in the elderly, especially in areas of iodine deficiency (11–13).

It is important to recognize that subnormal levels of serum TSH do not always reflect the presence of subclinical hyperthyroidism. Subnormal serum TSH may occur in patients with pituitary or hypothalamic insufficiency, or non-thyroid pathological conditions, or consequent to administration of the glucocorticoids, dopamine or amiodarone (14). In addition, TSH concentration may be below the normal range in some elderly patients as a result of decreased age-related thyroid hormone clearance (15). In any case, a careful physical examination, a detailed medical history, and the pattern of thyroid hormones may help to diagnose these conditions.

Epidemiology and natural history

To date, there is no definitive information about the incidence of subclinical hyperthyroidism in the general population. Its prevalence ranges from 0.6 to 16% (10, 16–18) depending on diagnostic criteria, the sensitivity

of the methods used to measure serum TSH concentrations, and iodine intake. Moreover, the reported prevalence of subclinical hyperthyroidism is affected by the investigator's definition of the lower limit of the normal range for TSH being 0.7% when the TSH cut-off point was 0.1 mU/l (19) and 2.1% with a TSH cut-off of 0.3 mU/l (10). In any event, subclinical hyperthyroidism appears to be a frequent disorder; TSH suppressive or unintentional over-replacement L-T4 therapy being the most common causes.

In patients with toxic adenoma or multinodular goiter, subclinical hyperthyroidism is usually a slowly progressive disorder and may last several years before being diagnosed. Factors that may precipitate overt hyperthyroidism are age, iodine prophylaxis in areas of endemic goiter (11), and administration of an iodide-containing contrast agent. Prospective studies of patients with endogenous subclinical hyperthyroidism show that TSH normalizes in almost 50% of cases, whereas overt hyperthyroidism develops at a rate of 5% per year (20). A recent panel of experts (1) classified patients with subclinical hyperthyroidism into two categories: those with mildly low but still detectable serum TSH (0.1–0.4 mU/l) and those with an undetectable serum TSH level (<0.1 mU/l) (1). The progression to overt hyperthyroidism was less common in patients with low TSH than in patients with undetectable TSH (21).

Clinical features

Signs, symptoms and quality of life

With the exception of one study (22), subclinical hyperthyroidism is associated with relevant signs and symptoms of thyroid hormone excess, and with impaired quality of life (12, 22–29). With different kinds of questionnaires formulated to investigate the psychophysical effects of thyroid hormone, patients with subclinical hyperthyroidism, whether exogenous (23–25) or endogenous (26, 27), were found to have a higher prevalence of palpitations, tremor, heat intolerance, sweating, nervousness, anxiety, reduced feeling of well-being, fear, hostility, and inability to concentrate. Noteworthy, in a retrospective study a near threefold increased risk of dementia and Alzheimer's disease was found in patients with subclinical hyperthyroidism (29).

Cardiovascular system

Thyroid hormone excess causes a wide spectrum of cardiovascular changes, which arise from both direct and indirect effects on the cardiovascular system, and effects mediated by neurohormonal activation (30–32). The cardiovascular risk of subclinical hyperthyroidism is related to short-term effects due to the electrophysiological effects of thyroid hormones, and to long-term

Table 1 Causes of persistent subclinical hyperthyroidism.

Endogenous causes

Graves' disease
Autonomously functioning thyroid adenoma
Multinodular goiter

Exogenous causes

Excessive thyroid hormone replacement therapy
Intentional thyroid hormone suppressive therapy

effects resulting from increased left ventricular mass and increased cardiac workload (Table 2). In most studies, patients with subclinical hyperthyroidism, whether exogenous (23–25, 33–36) or endogenous (26, 27, 37), have a higher heart rate and increased prevalence of supraventricular arrhythmias, as assessed by 24-h Holter electrocardiographic monitoring. In individuals with a shorter P–R interval on standard electrocardiogram, due to the presence of two functionally distinct atrio-ventricular nodal pathways, subclinical hyperthyroidism may precipitate re-entrant atrio-ventricular nodal tachycardia (38).

In a longitudinal study over 2 years of atrial fibrillation conducted in 40 patients with subclinical hyperthyroidism (mean age 65 years), the total rate of atrial fibrillation was 28% in patients with endogenous subclinical hyperthyroidism (serum TSH <0.1 mU/l), compared with 10% in age-matched euthyroid controls (39).

Importantly, data from a 10-year follow-up study of elderly patients with endogenous or exogenous subclinical hyperthyroidism (serum TSH ≤ 0.1 mU/l) indicate that this disorder is associated with a threefold higher incidence of atrial fibrillation compared with euthyroid healthy subjects (40).

Similarly, in a retrospective study of 1338 consecutive subjects with endogenous subclinical hyperthyroidism, the prevalence of atrial fibrillation was increased to a similar degree in older people with overt and subclinical hyperthyroidism (41): 2.3% in euthyroid subjects (TSH >0.4 –5 mU/l), 13.8% in patients with overt hyperthyroidism (TSH ≤ 0.03 mU/l with elevated FT3 and FT4), and 12.7% in patients with subclinical hyperthyroidism (TSH <0.4 –0.03 mU/l). The relative risk of atrial fibrillation was 5.8 and 5.2 respectively compared with euthyroid subjects ($P < 0.01$) (41).

Moreover, subclinical hyperthyroidism was found to be an independent risk factor for atrial fibrillation in patients with other pre-existing cardiac risk factors (e.g. coronary heart disease, valvular defects, hypertension) (42).

In this context, the adverse arrhythmogenic effects associated with subclinical hyperthyroidism, most probably triggered by the enhancement of atrial excitability and the shortening of the refractory period of

the conducting tissue, may be particularly hazardous in the elderly, whose cardiovascular function is often borderline. Indeed, atrial fibrillation by itself is an independent risk factor for stroke, angina pectoris, and congestive heart failure, and is associated with a twofold higher risk of death (43, 44).

The most consistent cardiac abnormality reported in patients with exogenous (23–25, 35, 36, 45–48) and endogenous (26, 27) subclinical hyperthyroidism, regardless of the underlying etiology, is a significant increase in left ventricular mass (23–27, 35, 36, 45), with unchanged or increased at-rest systolic function (23–27, 35–36, 46–48), and usually impaired diastolic function that is mainly due to slowed ventricular relaxation (25–27, 36, 45, 49). Using Doppler echocardiography in 60 patients with exogenous subclinical hyperthyroidism, it was found that the left ventricular mass index and various indices of resting left ventricular systolic function were significantly increased compared with euthyroid healthy controls, whereas diastolic function was impaired as documented by the reduced ratio between early and late diastolic peak flow velocities and the prolonged isovolumic relaxation time (36).

The cardiovascular abnormalities were similar in patients with either stable endogenous subclinical hyperthyroidism or exogenous hyperthyroidism (26, 27). Indeed, only one study did not find cardiac abnormalities in patients with endogenous subclinical hyperthyroidism (50).

The mechanism responsible for the increased left ventricular mass and diastolic dysfunction in both exogenous and endogenous subclinical hyperthyroidism is unclear. Cardiac hypertrophy and diastolic dysfunction are hallmarks of chronic hemodynamic overload, arising from relevant molecular rearrangements within the heart, including increased synthesis of contractile proteins and decreased activity of the sarcoplasmic reticulum calcium ATPase. This latter mechanism, in particular, plays a key role in impairing the efficiency of calcium reuptake by the sarcoplasmic reticulum during diastole, and hence in slowing the rate of relaxation of hypertrophied myocardium. However, the operation of these mechanisms in subclinical hyperthyroidism conflicts with the well-known favorable effects promoted by thyroid hormone on intracellular calcium handling, mostly due to the increased activity of the sarcoplasmic reticulum calcium ATPase (31). It may be speculated that, in the long-term, the negative effects promoted by the chronically increased cardiac workload on sarcoplasmic reticulum calcium ATPase overwhelm the positive effects promoted by thyroid hormone, thus leading to impaired myocardial relaxation and diastolic dysfunction (49, 51, 52).

Functional implications of these cardiac abnormalities were shown in patients with exogenous subclinical hyperthyroidism. Using the bicycle ergometer test, significant reductions in the peak workload and exercise

Table 2 Cardiovascular risk in patients with subclinical hyperthyroidism.

Short-term effects due to the electrophysiological action of thyroid hormone

Sinus tachycardia
Atrial premature beats
Atrial fibrillation

Long-term effects prevalently due to increased cardiac workload with enhancement of left ventricular mass

Impaired diastolic function
Systolic dysfunction during effort

duration were found, and were associated with left ventricular systolic dysfunction on effort, as indicated by the poor increase ($\leq 5\%$) or even a decreased ejection fraction during exercise (53). Similarly, using cardiopulmonary exercise testing, exercise tolerance and oxygen uptake at peak exercise and at the anaerobic threshold were significantly decreased (25).

Unfortunately a stratified analyses of TSH value (low or undetectable) was not performed in the studies evaluating the cardiovascular effects of exogenous or endogenous subclinical hyperthyroidism, with the exception of the above-mentioned studies on atrial fibrillation (39–41). However, cardiovascular mortality was found to be increased in a community-based review of subjects aged 60 years or older with endogenous subclinical hyperthyroidism (with TSH values <0.5 mU/l) monitored for 10 years (54). All the above-mentioned cardiac abnormalities might play a role in determining the increased cardiovascular mortality and morbidity in elderly patients with subclinical hyperthyroidism (55).

Bone structure and metabolism

Overt hyperthyroidism is an important risk factor for osteoporosis and fractures (56–59). Thyroid hormones accelerate the rate of bone remodeling, leading to a negative calcium balance and a net bone loss that accelerates the development of osteoporosis, and hence increases bone vulnerability to trauma (58–60). Whether subclinical hyperthyroidism significantly affects bone metabolism and increases the risk of fractures remains a controversial issue. Serum concentrations of several markers of bone synthesis and reabsorption, i.e. osteocalcin and telopeptide type I, and urinary pyridinoline crosslinks and hydroxyproline, are increased in patients with subclinical hyperthyroidism (61–65) and negatively correlated to serum TSH concentrations (62). In several cross-sectional studies, bone mineral density was decreased at multiple sites in pre- (66–69) and postmenopausal women (69–74) with exogenous (66–69, 72) or endogenous (68, 73–74) subclinical hyperthyroidism. This finding, however, was not confirmed in other cross-sectional observations in pre- (70, 75–86) and postmenopausal conditions (76, 79–82, 84, 87–91), and in exogenous (76, 77–83, 85–90) and endogenous conditions (75, 84). Similar results were found in longitudinal studies with decreased or normal bone mineral density in pre- (92–94) or postmenopausal women (72, 91, 92–95) with exogenous subclinical hyperthyroidism. Indeed, in two meta-analyses, exogenous subclinical hyperthyroidism was associated with a significant bone loss in post- but not in premenopausal women (96, 97).

There are at least five explanations for these discrepancies between studies. First, during the last two decades the doses of L-T4 used to suppress TSH in patients

with benign thyroid disease have been progressively reduced. This observation may account for the conflicting results among the early and the more recent studies; it also suggests that careful adjustment of L-T4 therapy can minimize the risk of bone loss, providing *de facto* indirect evidence for the association between subclinical hyperthyroidism and the development and progression of osteoporosis. Secondly, criteria for patient inclusion in these studies have become more restrictive. In fact, many early studies included patients with previous overt hypo- or hyperthyroidism. Thirdly, because the extent of bone loss depends on the magnitude of thyroid hormone excess and its duration, differences in follow-up among longitudinal studies may have contributed to conflicting results. Fourthly, discrepancies among studies exist in the methodology and the protocol used to measure bone mineral density and accurate techniques were applied only recently. Finally, other risk factors for bone loss may have interfered with thyroid hormone excess, accelerating the development of osteoporosis in some cases and attenuating it in others. These include a relative deficiency of calcitonin, insulin-like growth factor type I, dehydroepiandrosterone sulfate, and estrogen (71, 98–100).

In conclusion, subclinical hyperthyroidism predominantly depletes skeletal sites that are rich in cortical bone, depending mainly on disease severity and duration, and the association with other risk factors for bone loss.

The question as to whether subclinical hyperthyroidism increases the risk of fractures also remains controversial. In a study based upon interviews of 300 white postmenopausal women, no increased fracture risk was found in women taking L-T4 (101). In a study of 1180 patients treated with L-T4, the overall fracture rate in women over 65 years after 5 years was 2.5% in those with low TSH, and 0.9% in those with normal TSH values; the difference was not statistically significant (102).

A population-based, case-controlled analysis in a large cohort of patients from the UK found no association between the risk of femur fracture and treatment with L-T4 (103); however, after correction for other confounding risk factors, the risk of femur fracture was significantly associated with L-T4 therapy in males. In a prospective cohort study with case-cohort sampling on 686 women older than 65 years of age with low serum TSH (104), the risk of fractures was studied after adjusting for age, history of previous hyperthyroidism, and use of estrogen and thyroid hormone treatment; women with TSH levels <0.1 mU/l had a threefold increased risk for hip fracture and a fourfold increased risk for vertebral fracture compared with women with a normal TSH concentration. In any event, the use of thyroid hormone by itself does not appear to increase the risk for fracture if TSH levels are maintained within the normal range.

Treatment options

Symptoms, signs and quality of life

Administration of the cardioselective β -blocker bisoprolol for 6 months significantly improves the mean symptom rating scale score in patients with exogenous subclinical hyperthyroidism, mostly because this treatment attenuates many signs and symptoms mimicking adrenergic overactivity (23). Similar results were obtained with individual tailoring of the TSH-suppressive dose of L-T4, although the mean score remained significantly higher than that of euthyroid healthy controls (25). Moreover, treatment for 6 months with methimazole significantly improved symptoms evaluated with the Wayne index in endogenous subclinical hyperthyroid patients, paralleling the normalization of the thyroid status (27).

Cardiovascular system

In patients with exogenous subclinical hyperthyroidism, the addition of the cardioselective β -blocker bisoprolol to L-T4 therapy for 6 months significantly reduced the occurrence of supraventricular arrhythmias, average heart rate, and left ventricular mass, with improvement of diastolic function at rest and systolic performance during exercise (23, 53). Similarly, individual tailoring of the L-T4 dose in patients requiring TSH-suppressive treatment significantly decreased left ventricular mass and increased maximum workload (25). A decrease in the average 24-h heart rate, atrial premature beats, and left ventricular mass has also been reported in patients with endogenous subclinical hyperthyroidism after restoration of euthyroidism by methimazole treatment (27). Moreover, antithyroid therapy was beneficial in restoring a normal sinus rhythm in elderly patients affected by subclinical hyperthyroidism with atrial fibrillation (105). Recently, a study with impedance cardiography found that radioiodine treatment in women with endogenous subclinical hyperthyroidism significantly attenuated the pretreatment cardiac and hemodynamic abnormalities, as indicated by a reduction in heart rate, a normalized cardiac index, and an increased systemic vascular resistance (106). Importantly, patients with new onset of atrial fibrillation may have occult subclinical hyperthyroidism and the treatment with antithyroid drugs may reverse the atrial fibrillation in these cases. This supports the hypothesis that subclinical thyrotoxicosis is among the factors that trigger atrial fibrillation (107, 108).

Bone and mineral metabolism

Women affected by endogenous subclinical hyperthyroidism who were treated with antithyroid drugs for 2 years or with radioiodine significantly increased bone mineral density when compared with untreated

women, in whom a progressive bone loss frequently occurs (73, 109).

In exogenous subclinical hyperthyroidism, the use of carefully tailored TSH-suppressive doses of L-T4 did not contribute to osteopenia (78, 95). Several studies have shown that the negative effects of thyroid hormone on bone can be obviated by adequate dietary calcium intake, bisphosphonates, or by estrogen replacement therapy in postmenopausal women (71, 110–112).

Concluding remarks

Three main conclusions may be drawn from the available data. The first is that subclinical hyperthyroidism is a very common disorder. Excessive TSH-suppressive therapy with L-T4 for benign thyroid nodular disease or differentiated thyroid cancer, or hormone over-replacement in patients with hypothyroidism are the most frequent causes. Nonetheless, endogenous factors are frequent in areas with endemic goiter and iodine prophylaxis, and particularly in elderly subjects. The second conclusion is that the adjective 'subclinical' is a misnomer for this disorder (3). In fact, 'subclinical' hyperthyroidism reduces the quality of life, affecting both the psycho and somatic components of well-being, and produces relevant signs and symptoms of excessive thyroid hormone action, often mimicking adrenergic overdrive. 'Subclinical' hyperthyroidism exerts many relevant effects on the cardiovascular system (113). It is usually associated with a higher heart rate and a higher risk of supraventricular arrhythmias, and with an increased left ventricular mass, often accompanied by impaired diastolic function and, sometimes, by reduced systolic performance on effort and decreased exercise tolerance. Indeed, these abnormalities usually precede the onset of more severe cardiovascular disease, thus potentially contributing to the increased risk for cardiovascular morbidity and mortality observed in these patients. In addition, 'subclinical' hyperthyroidism may accelerate the development of osteoporosis, and hence increase bone vulnerability to trauma, particularly in postmenopausal women with a pre-existing predisposition (Table 3). On this basis, the socio-economic burden of 'subclinical' hyperthyroidism may be greater than

Table 3 Potential skeletal effects of subclinical hyperthyroidism.

Increased markers of bone turnover
Reduced bone density in estrogen-deficient postmenopausal women
Increased risk of fracture in postmenopausal women
Subclinical hyperthyroidism predominantly depletes skeletal sites rich in cortical bone, mainly depending on the severity and duration of TSH suppression, and the association with other well-recognized risk factors for bone loss
The use of thyroid hormone by itself does not increase the risk of fracture if TSH levels are maintained within the normal range

previously thought. The third conclusion is that 'subclinical' hyperthyroidism and its related clinical manifestations are reversible or may be prevented by timely treatment. In patients treated for benign thyroid nodular disease, the dose of L-T4 should be carefully customized, keeping serum TSH near, but not below the lower limit of the normal reference range. In patients on hormone replacement therapy for hypothyroidism, periodic evaluations of serum TSH levels should ensure that replacement therapy is not under- or over-prescribed. In patients with differentiated thyroid cancer with a high risk of recurrences or with known metastatic disease, in whom long-term sustained TSH suppression is warranted, β -blockade and bone-sparing drugs may be considered, in particular in patients above the age of 45 years, since they blunt or even prevent cardiovascular manifestations, and reduce the risk for osteoporosis and bone fractures. This concerns only a small minority of patients. In fact, in low-risk patients with differentiated thyroid cancer, the aim of L-T4 treatment is to maintain serum TSH levels within the normal reference range, once the absence of persistent disease has been documented.

Finally, in patients with endogenous 'subclinical' hyperthyroidism whatever the cause, especially in elderly patients, the treatment strategy should be the same as that for overt disease, i.e. methimazole administration for a rapid control of thyroid hormone excess, and radioiodine or surgery for a definitive cure, both eventually associated with a β -blocking drug.

A recent panel of experts recommends that the treatment of endogenous subclinical hyperthyroidism should be considered in the presence of TSH <0.1 mU/l especially for patients who are older than 60 years and for those with an increased risk for heart disease, osteopenia or osteoporosis, or for those with clinical symptoms suggestive of hyperthyroidism (1). The routine treatment is not recommended for all patients whose TSH is mildly decreased (0.1–0.45 mU/l) (1). In fact, it remains to be established whether a low serum TSH level may be associated with the same adverse effects on bone and heart as an undetectable TSH level (1, 2). In this context, the extent of clinical manifestations of 'subclinical' hyperthyroidism is probably related not only to the magnitude of thyroid hormone excess but also to disease duration, individual sensitivity to thyroid hormone excess, and particularly to the patient's age.

Although almost clinical manifestations of 'subclinical' hyperthyroidism have been described in patients with long-term treatment or persistent disease, transient suppression of serum TSH, as may occur in the course of many thyroid diseases or during L-T4 up-titration, may precipitate such cardiovascular signs and symptoms as palpitations and supraventricular arrhythmias. In the elderly, the symptoms and signs of hyperthyroidism may be unnoticed even in the presence of overt disease (114), with atrial fibrillations

being the usual clinical presentation (115). Therefore, 'subclinical' hyperthyroidism should always be considered as a possible cause of recent onset supraventricular arrhythmias, particularly in the elderly, and thus be treated in a timely fashion with a β -blocking drug.

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