Subclinical hyperthyroidism: features and treatment

Subclinical hyperthyroidism is an entity that is being increasingly recognised, probably because of the ageing of the population and the development of assays with enhanced thyroid-stimulating hormone sensitivity. It is characterised by a clearly low serum concentration of thyrotropin and the absence of obvious symptoms of overt hyperthyroidism. In this two part article, **Dr Nabil Aly** reviews the clinical features and treatment options in older adults.

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Subclinical hyperthyroidism is defined as a normal serum free thyroxin (T4) and free triiodothyronine (T3) levels with a thyroid-stimulating hormone (TSH) level suppressed below the normal range and usually undetectable. It has many relevant effects on the cardiovascular system and predominantly depletes skeletal sites that are rich in cortical bone. Consistent evidence indicates that 'subclinical' hyperthyroidism reduces the quality of life, affecting both the psychological and somatic components of well-being, and produces relevant signs and symptoms of excessive thyroid hormone action, often mimicking adrenergic overactivity[1]. In addition, it is becoming increasingly apparent that subclinical 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 or may be prevented by timely treatment.

Definition

The definition of subclinical hyperthyroidism is based only on laboratory, not clinical, criteria and the term probably represents a misnomer[2]. Subclinical hyperthyroidism is characterised by a low or undetectable concentration of serum thyrotropin (TSH) with free triiodothyronine (FT3) and free thyroxin (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[3,4]. In fact, although in the normal reference range, serum thyroid hormones (FT3 and FT4) 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 narrower than the group reference ranges on which laboratory reference ranges are based[5].

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[1]. The pituitary gland is sensitive to minor changes in serum thyroid hormone levels, and serum TSH responds with logarithmically amplified variations to such changes[1,6]. 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 is supported by the finding of relevant changes in several cardiovascular measures and in bone structure and metabolism in these individuals[1]. 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

Table 1. Causes of persistent subclinical hyperthyroidism

Endogenous causes	Exogenous causes
• Graves' disease	• Excessive thyroid hormone replacement therapy: Hypothyroidism
• Autonomously functioning thyroid adenoma	• Intentional thyroid hormone suppressive therapy: Benign thyroid nodular disease or differentiated thyroid cancer
• Multi-nodular goitre	

fractures. Recently, a panel of experts classified patients with subclinical hyperthyroidism into two categories[3]:

> Those with mildly low but still detectable serum TSH (0.1–0.4 mU/l)

> Those with an undetectable serum TSH level (<0.1 mU/l).

The progression to overt hyperthyroidism was less common in patients with low TSH than in patients with undetectable TSH[7].

Age-related thyroid change

There are several age-related structural changes of the thyroid gland. Some studies have shown an increase and others a decrease in the size of the gland with ageing. This discrepancy is probably related to dietary iodine intake. At the same time, however, there is a decrease in the number and size of the follicles as well as in colloid content. Histopathologic examination shows lymphocytic infiltration and fibrosis of the connective tissue[8]. The gland also becomes increasingly nodular with age. In spite of these structural changes, results of thyroid function tests are normal in most patients. Serum levels of T4 remain constant with ageing, because a decline in production is offset by slower metabolism. Although initial studies in heterogeneous populations suggested a decline in T3 levels with ageing, later studies in selected healthy persons showed that the levels are unaffected[9]. TSH levels typically remain normal, except for a mild decrease in extreme senescence (ie, octogenarians)[8]. A blunting of diurnal variation in thyrotropin levels and the thyrotropin response to thyrotropin-releasing hormone may occur, especially in elderly men, but this effect is rarely clinically significant[8]. Some studies also have shown an elevation in thyroid auto-antibodies with ageing, but the increase seems to be the effect of age-associated disease rather than ageing per se[10].

Aetiology

Subclinical hyperthyroidism may be caused by exogenous or endogenous factors[11], 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 levothyroxin for a single thyroid nodule, multinodular goitre or differentiated thyroid carcinoma. In addition, TSH may be unintentionally suppressed during hormone replacement therapy in about 20 per cent of hypothyroid patients[12,13]. The endogenous form is usually related to the same causes as overt thyrotoxicosis, namely Graves' disease, autonomously functioning thyroid adenoma and multinodular goitre. The two latter causes are particularly frequent in the elderly, especially in areas of iodine deficiency[1].

It is important to recognise 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 (steroids), dopamine and dopamine-agonists 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. In the elderly, the symptoms and signs of hyperthyroidism may be unnoticed even in the presence of overt disease, with atrial fibrillations being the usual clinical presentation[16,17]. Therefore, subclinical hyperthyroidism should always be considered as a possible cause of recent onset supraventricular arrhythmias.

Table 2. Cardiovascular risk in patients with subclinical hyperthyroidism

Short-term effects due to the electro-physiological action of thyroid hormone	Long-term effects prevalently due to increased cardiac workload with enhancement of left ventricular mass
Sinus tachycardia Atrial premature beats Atrial fibrillation	Increase in left ventricular mass Impaired diastolic function Systolic dysfunction during effort Increased cardiovascular mortality and morbidity in the elderly.

Clinical features

Subclinical hyperthyroidism is associated with relevant signs and symptoms of thyroid hormone excess, and with impaired quality of life[1]. In older people, the symptoms and signs of hyperthyroidism may be unnoticed even in the presence of overt disease. Atrial fibrillation may be the primary manifestation of subclinical hyperthyroidism in them[18]. Studies with questionnaires formulated to investigate the effects of thyroid hormone among patients with subclinical hyperthyroidism, whether exogenous[19-21] or endogenous[22,23], 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. In a retrospective study, almost a threefold increased risk of dementia and Alzheimer's disease was found in patients with subclinical hyperthyroidism[24]. 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[25-27].

Cardiovascular effects

The cardiovascular risk of subclinical hyperthyroidism is related to short-term effects due to the electrophysiological effects of thyroid hormones, and to long-term effects resulting from increased left ventricular mass and increased cardiac workload (*Table 2*). In most studies, patients with subclinical hyperthyroidism, whether exogenous or endogenous, have tachcardia and increased prevalence of supraventricular arrhythmias, as assessed by 24-hour electrocardiographic monitoring[1]. Subclinical hyperthyroidism may precipitate re-entrant atrioventricular nodal tachycardia in individuals with a shorter P–R interval[28]. In addition, data from a 10-year follow-up study of elderly patients with endogenous or exogenous subclinical hyperthyroidism indicate this disorder is associated with a threefold higher incidence of atrial fibrillation compared with euthyroid healthy subjects[29].

Similarly, in a retrospective study of 1,338 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[30]: 2.3 per cent in euthyroid subjects, 13.8 per cent in patients with overt hyperthyroidism and 12.7 per cent in patients with subclinical hyperthyroidism. The relative risk of atrial fibrillation was 5.8 and 5.2 respectively compared with euthyroid subjects[30]. Moreover, subclinical hyperthyroidism was found to be an independent risk factor for atrial fibrillation in patients with other pre-existing cardiac risk factors

Key points

- Subclinical hyperthyroidism is characterised by low serum concentration of TSH and the absence of obvious symptoms of hyperthyroidism.
- Excessive TSH-suppressive therapy with levothyroxin for benign thyroid nodular disease or differentiated thyroid cancer, or hormone over-replacement in patients with hypothyroidism is the most frequent causes.
- It can produce relevant signs and symptoms of excessive thyroid hormone action, often mimicking adrenergic overdrive.

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(eg, coronary heart disease, valvular defects, hypertension)[31].

The most consistent cardiac abnormality reported in patients with exogenous and endogenous subclinical hyperthyroidism, regardless of the underlying aetiology, is a significant increase in left ventricular mass, with unchanged or increased at-rest systolic function, and usually impaired diastolic function that is mainly due to slowed ventricular relaxation[1]. The mechanism responsible for the increased left ventricular mass and diastolic dysfunction in both exogenous and endogenous subclinical hyperthyroidism is unclear[1]. All the cardiac abnormalities mentioned might play a role in determining the increased cardiovascular mortality and morbidity in elderly patients with subclinical hyperthyroidism[1].

Conclusion

Subclinical hyperthyroidism is a fairly common disorder. It may be caused by exogenous or endogenous factors: excessive TSH suppressive therapy with levothyroxin for benign thyroid nodular disease, differentiated thyroid cancer, or hormone over-replacement in patients with hypothyroidism is the most frequent causes. Consistent evidence indicates that subclinical hyperthyroidism reduces the quality of life, affecting both the psychological and somatic components of well-being, and produces relevant signs and symptoms of excessive thyroid hormone action, often mimicking adrenergic over-activity. Subclinical hyperthyroidism exerts many significant effects on the cardiovascular system and the resulting abnormalities are potentially contributing to the increased cardiovascular morbidity and mortality observed in these patients.

The second part of this article in the November edition will look at the effects on osteoporosis and increased bone vulnerability to trauma.

Conflict of interest: none declared.