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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. Subclinical hyperthyroidism exerts many relevant effects on the cardiovascular and skeletal systems with possible effects on quality of life. In part two of this two-part series, Dr Nabil Aly reviews the impact on skeletal systems and treatment options.

Subclinical hyperthyroidism is defined as a normal serum free thyroxin and free triiodothyronine levels with a thyroid-stimulating hormone (TSH) level suppressed below the normal range, which is 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. 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.

Effects on bone metabolism

Overt hyperthyroidism is an important risk factor for osteoporosis and fractures. Thyroid hormones accelerate the rate of bone remodelling, leading to a negative calcium balance and a net bone loss that accelerates the development of osteoporosis, and hence increases bone vulnerability to trauma.

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 (Table 1). Whether it significantly affects bone metabolism and increases the risk of fractures remains a controversial issue. In several cross-sectional studies, bone mineral density was decreased at multiple sites in pre- and postmenopausal women with exogenous or endogenous subclinical hyperthyroidism. This finding, however, was not confirmed in other cross-sectional observations in pre- and postmenopausal conditions, and in exogenous and endogenous conditions.

In a prospective cohort study with case-cohort sampling on 686 women older than 65 years of age with low serum TSH, the risk of fractures was studied after adjusting for age, history of previous hyperthyroidism, and use of oestrogen and thyroid hormone treatment; women with TSH levels <0.1mU/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.
Diagnosis

The development of sensitive assays for TSH has led to the discovery that many older patients have abnormal levels without other alterations in serum thyroid hormone levels, conditions termed subclinical hypothyroidism (isolated elevation of TSH levels) and subclinical hyperthyroidism (isolated suppression of TSH levels).

While the diagnostic criteria and treatment modalities for overt hyperthyroidism are well known, those for subclinical hyperthyroidism are markedly less extensive. It is assumed that most elderly patients with subclinical hyperthyroidism have a multinodular goitre, but several other conditions should be considered in the differential diagnosis. Transient suppression of a TSH level that returns to the normal range within several months is thought to be caused by silent thyroiditis. A suppressed serum TSH level may be related to nonthyroidal illness, steroid or dopamine administration, or pituitary dysfunction; therefore, it is important to exclude these conditions.

Abnormalities in the TSH level may presage the development of overt hyperthyroidism (Graves' disease, multinodular goitre, or Hashimoto's disease/Hashitoxicosis), in which case the free T3 and T4 levels will gradually rise outside of the normal range, resulting in the development of the classic symptoms and signs of hyperthyroidism.

The aetiology of subclinical hyperthyroidism further includes partially or insufficiently treated overt hyperthyroidism, multinodular goitre, Graves' disease (early in its course), iodine-associated hyperthyroidism, solitary autonomous adenoma and thyroiditis (subacute, silent, or postpartum). It is important to exclude the recent administration of radiocontrast material or exogenous iodine exposure, and to consider other causes of hyperthyroidism (eg, trophoblastic tumours, exogenous thyroid hormone ingestion).

In subclinical hyperthyroidism, a 24-hour radioactive iodine uptake (RAIU) will generally be elevated in patients with Graves' disease, multinodular goitre, and solitary autonomous nodule; whereas, the RAIU will be less than five per cent at 24 hours (normal range, five to 30 per cent at 24 hours) in patients in the hyperthyroid phase of subacute, silent or postpartum thyroiditis and in patients taking excess exogenous thyroid hormone.

Natural history

Subclinical hyperthyroidism affects less than two per cent of the elderly population. The potential risks of subclinical hyperthyroidism in the elderly include progression to overt hyperthyroidism, cardiovascular effects (especially atrial fibrillation), and osteoporosis. In patients with toxic adenoma or multinodular goitre, 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 goitre, and administration of an iodide-containing contrast agent. Prospective studies of patients with endogenous subclinical hyperthyroidism show that TSH normalises in almost 50 per cent of cases, whereas overt hyperthyroidism develops at a rate of five per cent per year.

In patients with multinodular goitre, the estimated rate of progression from subclinical to overt hyperthyroidism is also five per cent each year, and it may be significantly higher with the administration of iodine as a dietary supplement in areas where goitre is endemic, or with the use of the antiarrhythmic drug amiodarone, which contains iodine. Progression to prolonged overt hyperthyroidism in patients with underlying Graves' disease is probably less common, given the relapsing and remitting nature of Graves' disease and the eventual development of hypothyroidism in some patients. Although studies have shown that subclinical hyperthyroidism affects clinical parameters, there is no convincing evidence that outcomes are affected. Therefore, treatment decisions should be individualised.

Screening

There is no consensus on screening for thyroid disease. Routine screening of asymptomatic, healthy adults is not recommended; however, physicians should maintain a high index of suspicion and have a low threshold for testing thyroid function in the at-risk population. This approach seems the most prudent choice, given the lack of data that treatment of early asymptomatic disease affects outcome and considering the potential adverse effects of therapy.

Management

General illness

Subclinical hyperthyroidism and its related clinical
manifestations are reversible or may be prevented by timely treatment. However, in up to 50 per cent of affected patients, serum TSH levels return to normal without intervention and in the absence of a toxic nodule (where spontaneous normalisation is unlikely), treatment is not warranted in most patients. Decisions to treat elderly patients with subclinical thyroid disease should be based on a careful assessment of the individual patient. A reasonable treatment option for many is a therapeutic trial of low-dose antithyroid agents for approximately six to 12 months in an effort to induce a remission. In older patients, the symptoms and signs of hyperthyroidism may be unnoticed even in the presence of overt disease and atrial fibrillation is the usual clinical presentation. 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 beta-blocking drug.

**Exogenous subclinical hyperthyroidism**

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. The dose of thyroxin should normally be reduced in patients with exogenous subclinical hyperthyroidism, excluding those with prior thyroid cancer, in whom thyrotropin suppression may be desired. The dose can usually be reduced abruptly to a more appropriate level. For example, in a symptomatic patient who has a markedly elevated serum free thyroxin concentration and a triiodothyronine concentration at the high end of the normal range while taking 250 μg of levothyroxine daily, it would be appropriate to reduce the dose to 150 μg daily and to retest thyroid function at a follow-up visit. The thyrotropin concentration may remain suppressed for six to eight weeks or more in patients with previous over-replacement of levothyroxine. Those on treatment for benign thyroid nodular disease, the dose of L-T4 should be carefully customised, keeping serum TSH near, but not below the lower limit of the normal reference range. In patients with differentiated thyroid cancer with a high risk of recurrence or with known metastatic disease, in whom long-term sustained TSH suppression is warranted, beta-blockade and bone-sparing drugs may be considered.

**Endogenous subclinical hyperthyroidism**

In this group of patients, especially in older patients, the treatment strategy should be the same as that for overt disease, i.e., antithyroid therapy for a rapid control of thyroid hormone excess and radioiodine or surgery for a definitive cure) both eventually associated with a beta-blocking drug. However, in many patients with endogenous subclinical hyperthyroidism who do not have nodular thyroid disease or complications of excess thyroid hormone, treatment is unnecessary, but thyroid-function tests should be performed every six months, with the recognition that the serum triiodothyronine concentration may become elevated before the serum thyroxin concentration does. 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. The routine treatment is not recommended for all patients whose TSH is mildly decreased.

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. 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. In older patients with atrial fibrillation or osteoporosis that could have been caused or exacerbated by the mild excess of thyroid hormone, ablative therapy with iodine-131 is the best initial option.
Key points

- Subclinical hyperthyroidism is characterised by low serum concentration of TSH and the absence of obvious symptoms of hyperthyroidism.
- Potential risks of subclinical hyperthyroidism in the elderly include progression to overt hyperthyroidism, cardiovascular effects (especially atrial fibrillation) and osteoporosis.
- Subclinical hyperthyroidism and its related clinical manifestations are reversible or may be prevented by timely treatment.

Symptom control

Administration of the cardioselective beta-blocker bisoprolol for six 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. Similar results were obtained with individual tailoring of the TSH-suppressive dose of levothyroxin, although the mean score remained significantly higher than that of euthyroid healthy controls.

Bone and mineral metabolism effects

Women affected by endogenous subclinical hyperthyroidism who were treated with antithyroid drugs for two years or with radioiodine significantly increased bone mineral density when compared with untreated women, in whom a progressive bone loss frequently occurs. In exogenous subclinical hyperthyroidism, the use of carefully tailored TSH-suppressive doses of L-T4 did not contribute to osteopenia. Several studies have shown that the negative effects of thyroid hormone on bone can be obviated by adequate dietary calcium intake, bisphosphonates, or by oestrogen replacement therapy in postmenopausal women.

Conclusion

Subclinical hyperthyroidism is a fairly common disorder. 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. It 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.

Conflict of interest: none declared.