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Musculosekeletal Disorders & Aging

Short communication

Thyroid and bone fragility

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Abstract

Introduction

This short communcation seeks to highlight the link between thyroid disease and bone fragility.

Short Communication

Bone remodelling/metabolism involve a homeostatic balance between formation (osteoblastic) and resorption (osteoclastic). This balance is regulated by bone regulatory molecules, including receptor activator of nu-

Elevated thyroid hormone may lead to increased bone resorp-tion activities, which may lead to an increased risk of osteopenia and oste-porotic fractures.

Introduction

The first clinical account which linked thyroid disease with bone fragility was reported by von Recklinghausen[sic]. The study correlated the hyperthyroid state with an increased risk of bone fracture. Over the subsequent 100 years, it has become apparent that both hypothyroidism and hyperthyroidism are associated with an in-creased risk of fractures.

The prevalence of hypothyroidism and hyperthyroidism in the United Kingdom (UK) are estimated at 1%–2% and 0.5%–2%, respectively. Females are predominantly affected by both of these conditions, with a female:male ratio of 10:1. The incidence increases with age; therefore, in an ageing population, thyroid disease should be considered in all individuals presenting with fractures[3].

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The hypothalamic-pituitary-thyroid axis is a classical negative feedback loop. It is important for the synthesis and secretion of thyroid hormones namely thyrotropin releasing hormone (TRH), thyroid stimulating hormone (TSH), thyroxine (T4) and tri-iodothyronine (T3)[2].

Low detectable levels of serum T3 stimulate the paraventricular nucleus of the hypothalamus to synthesise and secrete the tri-pepetide TRH. TRH in turn stimulates the thyrotroph cells of the anterior pituitary gland to secrete TSH. This glycoprotein acts on the seven transmembrane G-protein coupled to TSH receptors (TSHR) on the thyroid gland to promote the synthesis and secretion of the prohormone T4 and active hormone T3. Peripheral conversion of T4 to T3 is achieved by type 2 iodothyronine deiodinase enzyme (D2). D2 contributes to 85% of T3 synthesis; 95% of T4 and T3 are primarily bound to thyroxine-binding globulin (TBG). Uptake of free circulating T3 and T4 is determined by three specific cell membrane transporters: monocarboxylate transporters 8, 10 and organic acid transporter protein-1c1. Intracellular levels of iodothyronine deiodinase enzymes type 1 and 2 determine the activity and availability of active T3[2].

The prevalence of hyperthyroid disease is estimated at between 0.5%–2% in the UK. Primary causes include Graves' disease (an autoimmune IgG-mediated condition), toxic nodular goitre or a solitary thyroid nodule. Secondary causes include de Quervain thyroiditis, carcinoma of the thyroid gland and over-treatment with thyroid medications. Typical clinical presentations of hyperthyroidism may include anxiety, oligo- or amenorrhoea, diarrhoea, irritability, fatigue, increased appetite, intolerance to heat, restlessness, sweating, tremor and weight loss. The main biochemical feature is a decreased TSH level, usually with a concurrent increase in free serum T4. T3 is raised in 1% of patients with hyperthyroidism[3,4].

The prevalence of spontaneous hypothyroid disease is estimated at between 1% and 2% in the UK. Women are predominantly affected, with a female:male ratio of 10:1. The aetiology of hypothyroidism can be subdivided into primary, secondary and transient. Primary causes include autoimmune disease (Hashimoto's thyroiditis and atrophic thyroiditis), iodine deficiency, iatrogenic causes (post-thyroidectomy or radioiodine treatment), medication induced (antithyroid medications, amiodarone and lithium), congenital absence of the thyroid gland or thyroid gland infiltration by amyloidosis or sarcoidosis. Secondary causes include hypopituitarism or hypothalamic disorder. Transient disease may be secondary to withdrawal of thyroid medications or to post-partum thyroiditis[3,4].

Typical features of hypothyroidism may include constipation, depression, decreased appetite, weight gain, dry skin, hoarse voice, reduced libido, thinning and loss of hair, intolerance to cold, lethargy and menorrhagia. Symptoms tend to be insidious in nature, hence patients often present late to healthcare services. In the post-partum woman and the elderly, hypothyroidism can be commonly misdiagnosed and the symptoms attributed to other illnesses. Treatment of hypothyroidism is with levothyroxine, starting at 25 μg/24 h and subsequently increasing according to the response. Close monitoring is recommended, initially at 12-weekly and then at 6-weekly intervals, to ensure TSH > 0.5 mU/L. Thus strict surveillance is recommended as early

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Short communication

Table 1 The reference ranges for the thyroid hormones outside pregnancy. Free tri-iodothyronine (FT3), free thyroxine (FT4), thyroid stimulating hormone (TSH), total tri-iodothyronine (TT3), total thyroxine (TT4). Free T3 and T4 tests are preferred

Serum reference ranges for thyroid hormones	
TSH	0.4–4.5 mU/L
FT4	9.0–25 pmol/L
FT3	3.5–7.8 nmol/L
TT4	60–160 nmol/L
TT3	1.2–2.6 nmol/L

treatment regimens were often too aggressive, leading to suppressed TSH levels and hyperthyroid symptoms[4,5].

The biochemical indicator of subclinical hypothyroid disease is an increase in the serum TSH levels to above 4 mU/L. In overt hypothyroidism, serum free T4 is concurrently reduced. Decreased levels of TSH and serum free T4 may indicate hypothyroidism secondary to pituitary dysfunction. Raised TSH, free serum T3 and free serum T4 indicate resistance to the thyroid hormones[4].

The serum reference ranges for the thyroid hormones are displayed in Table 1. Measurement of free serum levels of T3 and T4 are recommended as they are independent of changes in binding proteins[4].

At present, there is no national screening programme for thyroid disease. Blood tests are performed where there is a clinical suspicion after a thorough evaluation of case history and examination.

***The remodelling of bone has two primary functions in humans: firstly to regulate serum calcium levels and secondarily to maintain skeletal in-tegrity and repair damaged bone[6]. It is a combined effect of two separate processes: bone formation (osteo-blastic activity) and bone resorption (osteoclastic activity). Synchronous activity of the osteoblasts and osteoclasts is mediated by receptor activator of nuclear factor-κ B (RANK). Osteoprotegerin is synthesised by the osteoblasts and acts as a non-competitive inhibitor of the RANK receptor[7,8]. Whilst the RANK ligand (RANKL) stimulates osteoclast recruitment, formation and activity, osteoprotegerin inhibits these actions. Free serum T3 stimulates the synthesis of osteoprotegerin by the osteoblasts, thereby inhibiting the osteoclasts and directly affecting bone remodelling[9]. The balance of all of these processes ultimately determines the bone quality and bone mass.

However, the role of RANK, RANKL and osteoproteregin is widely debated. In pure mice cell culture, T3 was found to have a direct stimulatory effect on osteoclast precursor cells, which was independent of the presence or absence of osteoblasts and osteoprotegerin. Additionally, the nuclear receptor protein TRa1, which binds T3 and DNA, were present directly on the surface of the osteoclast precursor cells. These cells were also stimulated by low levels of TSH, which points towards a direct role for T3 in the activation[6–9].

Hypothyroidism is characterised by decreased bone resorption, decreased bone formation and increased bone mineral density in both trabecular and cortical bone. Levels of the three bone resorption markers namely pyridinoline, deoxypyridinoline and ß-crosslaps are reduced when compared with euthyroid controls[6]. In extreme cases, increased bone mineralisation may result in osteosclerosis of the bone, which would be apparent on a plain X-ray. It was postulated by Korsic *et al.*[10] that high levels of TSH in a hypothyroid patient directly inhibits bone resorption, thereby contributing to bone microdamage and tendency to fracture. The tendency to fracture persisted for up to 10 years after an initial diagnosis of thyroid disease, with regard to hip fractures, and for 5 years, with regard to forearm and spinal fractures[6]. The risk was significantly decreased through adequate treatment with levothyroxine[11].

Hyperthyroidism is characterised by a significantly shortened phase of bone remodelling (reduced by 50%) and accelerated bone turnover. Increased activity of the osteoblasts, and to a greater extent, the osteoclasts, contributes to a 10% reduction in overall bone mass with each cycle of bone remodelling, which may lead to significant osteoporosis[6]. The bone resorption activity of the osteoclasts can be indirectly measured by checking the levels of the bone resorption markers: pyridinoline, deoxypyridinoline and ß-crosslaps. These markers are raised in patients with hyperthyroid disease and directly correlate with free serum T3 levels[11,12]. Altabas *et al.*[6] proposed that disproportionate activation of the osteoclasts in hyperthyroidism is secondary to osteoblast-secreted RANKL and interleukin-6 paracrine factors.

In hyperthyroidism, the histological appearance of the bone differs from normal bone; it appears less dense and with a greater degree of porosity. Irrespective of gender or age[11], all patients with hyperthyroidism are at an increased risk of fracture and this risk remains for up to 5 years after the initial diagnosis[11,13]. Effective surgical or medical treatment is associated with a reduced incidence of fractures in this patient group[6].

As per the population-based studies of euthyroid patients, bone mineral density of the femoral neck was inversely correlated to the serum levels

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Short communication

of free serum T4 and positively correlated with levels of TSH. Despite this, there was no association found between these parameters and fracture risk[14].

To investigate the relationship between thyroid hormone level and bone integrity, a large study of euthyroid patients (n = 1151) was performed by Van de Deure *et al.*[14] The conclusion was that TSH and free serum T4 levels were correlated with bone mineral density of the femoral neck and degree of cortical thickness. Free serum T4 levels were more closely correlated with these bone parameters, so it was postulated that the influence of free serum T4 was greater than that of TSH.

Kim *et al.*[15] performed a large (n = 959) study of the link between TSH levels and bone mineral density in the lumbar spine and femoral neck of healthy post-menopausal women. Increased TSH levels correlated with increased bone mineral density. TSH levels of 0.5–1.1 mU/L, which represent a low to normal level, correlated with significantly lower bone mineral density of the lumbar spine ($p = 0.004$) and femoral neck ($p = 0.006$) than matched euthyroid controls with a TSH level of 2.8–5.0 mU/L. This study suggests that the normal ranges of the thyroid hormones, which are applicable to the general adult population, may not be relevant for post-menopausal women. Therefore, in this patient group, physicians should treat at a low–normal TSH level.

Murphy *et al.*[16] evaluated the association between the levels of T3, T4 and TSH with bone mineral density and fracture risk. In a large study (n = 1278) comprising healthy euthyroid females, levels of T3 ($p = 0.005$) and T4 ($p = 0.004$) were inversely correlated with bone mineral density at the hip. Elevated levels of T3 and T4 were directly correlated with an increased fracture risk of 20% ($p = 0.002$) and 33% ($p = 0.006$), respectively, whilst elevated TSH levels were protective in nature, reducing the risk of fracture by 35% ($p = 0.028$).

There is good evidence that adult patients with established thyrotoxicosis are at a risk of accelerated bone turnover, reduction in the bone remodelling cycle[17], and hence, reduction in bone mineral density[11] and overall bone mass. Previous or current history of hyperthyroidism has been shown to be associated with these problems in both—case controlled[18,19] and population-based studies[20–22].

In summary, thyroid disease has a significant clinical association with bone fragility. It should be considered in all patients presenting with fracture, especially the elderly. For post-menopausal women, the clinician should have a low threshold for instigating blood checks, as normal–high levels of T3 and T4 would seem to predispose to fracture. The UK is an ageing society, so problems relating to poor bone mineral density will become ever more common. Pre-emptive care could improve outcomes in a cost-effective manner.

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