REVIEW

The skeletal consequences of thyrotoxicosis

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Abstract

Euthyroid status is essential for normal skeletal development and the maintenance of adult bone structure and strength. Established thyrotoxicosis has long been recognised as a cause of high bone turnover osteoporosis and fracture but more recent studies have suggested that subclinical hyperthyroidism and long-term suppressive doses of thyroxine (T4) may also result in decreased bone mineral density (BMD) and an increased risk of fragility fracture, particularly in postmenopausal women. Furthermore, large population studies of euthyroid individuals have demonstrated that a hypothalamic–pituitary–thyroid axis set point at the upper end of the normal reference range is associated with reduced BMD and increased fracture susceptibility. Despite these findings, the cellular and molecular mechanisms of thyroid hormone action in bone remain controversial and incompletely understood. In this review, we discuss the role of thyroid hormones in bone and the skeletal consequences of hyperthyroidism.

Introduction

Thyroid hormones have a critical role in skeletal development and the maintenance of adult bone structure and strength (Williams & Bassett 2011). Women are ten times more likely to suffer from thyroid disease and its prevalence increases with age. Between 40 and 60 years of age, the prevalence of thyrotoxicosis is 0.45%; however, this increases to 1.4% after the age of 60 years. Consequently, 3% of women over the age of 50 years receive thyroxine (T4) replacement for either primary hypothyroidism, following radioiodine treatment or after surgery for thyrotoxicosis, and at least one-fifth of these women are over-replaced (Parle et al. 1993). Moreover, subclinical hyperthyroidism, defined as a suppressed thyroid-stimulating hormone (TSH) level in the presence of normal thyroid hormone concentrations, affects an additional 1.5% of women over 60 years of age and its prevalence also increases with age. Despite the frequency of thyroid dysfunction, the role of thyroid hormone excess in the pathogenesis of osteoporosis and fracture has been under-recognised and the underlying mechanisms remain uncertain.

Osteoporosis is defined by the World Health Organisation as a bone mineral density (BMD) of 2.5 or more s.d.s below that of a young adult (T-score ≤ −2.5). It is characterised by low bone mass, micro-architectural deterioration and an increased risk of fragility fracture. Osteoporosis is a global health care problem that costs £1.7 billion in the UK, $15 billion in the USA and €32 billion in Europe per annum. A personal and family history of fracture, low BMD, reduced body mass index, glucocorticoid treatment, smoking, alcohol excess and untreated thyrotoxicosis increase susceptibility to osteoporosis and fragility fracture. Furthermore, subclinical hyperthyroidism is associated with an increased risk of fracture and T4 treatment at doses sufficient to suppress TSH, resulting in increased bone turnover and low BMD in postmenopausal women (Murphy & Williams 2004).

In this review, we describe the systemic and local regulation of thyroid hormone action, examine the role of thyroid hormone in adult bone maintenance and skeletal development and discuss the skeletal consequences of thyrotoxicosis, endogenous subclinical hyperthyroidism and prolonged suppressive T4 treatment.

Thyroid hormone physiology

The hypothalamic–pituitary–thyroid axis

Circulating thyroid hormone concentrations are regulated by the hypothalamic–pituitary–thyroid (HPT) axis (Fig. 1). Medial neurons of the paraventricular nucleus (PVN) of the hypothalamus synthesise and secrete thyrotrophin-releasing hormone (TRH), which in turn stimulates the synthesis and secretion of TSH from anterior pituitary thyrotrophs. TSH, acting on the TSH receptor (TSHR), stimulates thyroid...
TRH production and TSH secretion. DIO1 also converts T4 to T3 in the hypothalamus and pituitary, resulting in the feedback inhibition of the liver, contributing to the pool of circulating T3. Thyroid hormone action is mediated by thyroid hormone receptors (TRs), nuclear receptors which act as hormone-inducible transcription factors, in association with co-regulatory proteins (Fig. 1). Unliganded TRs associate with co-repressor proteins and bind thyroid hormone response elements, in the promoter region of target genes, to mediate transcriptional repression. T3 binding results in a conformational change, dissociation of co-repressors and recruitment of co-activators, resulting in chromatin modification and the activation of gene transcription (Yen 2001, Cheng et al. 2010). TRs are encoded by two genes, THRA and THRB, from which multiple TRα and TRβ isoforms are transcribed. TRα1, TRβ1 and TRβ2 contain DNA and ligand-binding domains and are functional receptors, whereas a number of associations with fT4 and TSH (Panicker et al. 2008b, Medici et al. 2011). These studies have demonstrated that systemic thyroid status is inherited as a complex genetic trait and suggested that genetic heterogeneity may influence intracellular TH supply.

**Regulation of local intracellular T3 supply**

T3 action in target tissues depends on the circulating concentrations of T3 and T4, their uptake into target cells, and local activation or inactivation (Fig. 1). The thyroid secretes mainly the pro-hormone T4 and the majority of circulating T3 is generated in the liver and kidneys by the action of type 1 iodothyronine deiodinase enzyme (DIO1), which catalyses 5′-deiodination of T4. Over 95% of thyroid hormones are bound to plasma proteins and concentrations of fT4 in the circulation remain three to four times those of fT3. Cellular uptake of thyroid hormones is mediated by specific membrane transporters, which include monocarboxylate transporters (MCT8 (SLC16A2) and MCT10 (SLC16A10)) and organic acid transporter protein-1C1 (OATP1C1; van der Deure et al. 2010). The intracellular availability of T3 is determined by the relative activities of DIO2 and DIO3 (Bianco & Kim 2006, St Germain et al. 2009). DIO2 converts the pro-hormone T4 to the active hormone T3 by the removal of an outer-ring 5′-iodine atom, whereas DIO3 inactivates T3 and prevents the activation of T4 by the removal of an inner-ring 5′-iodine atom to produce the inactive metabolites 3,3′,5′-triiodothyronine (reverse-T3) and 3,3′,5′-diodothyronine (reverse-T4; Bianco & Kim 2006). DIO2 activity is regulated by a rapid post-translation mechanism involving T4-induced ubiquitin-mediated proteasomal degradation (Gereben et al. 2008). Thus, in hypothyroidism, DIO2 activity is increased, and in thyrotoxicosis, it is reduced. By contrast, D3 expression and activity is increased in thyrotoxicosis and reduced in thyroid hormone deficiency.

**Thyroid hormone action**

Thyroid hormone action is mediated by thyroid hormone receptors (TRs), nuclear receptors which act as hormone-inducible transcription factors, in association with co-regulatory proteins (Fig. 1). Unliganded TRs associate with co-repressor proteins and bind thyroid hormone response elements, in the promoter region of target genes, to mediate transcriptional repression. T3 binding results in a conformational change, dissociation of co-repressors and recruitment of co-activators, resulting in chromatin modification and the activation of gene transcription (Yen 2001, Cheng et al. 2010). TRs are encoded by two genes, THRA and THRB, from which multiple TRα and TRβ isoforms are transcribed. TRα1, TRβ1 and TRβ2 contain DNA and ligand-binding domains and are functional receptors, whereas...
TRα2 lacks hormone-binding activity and acts as a weak antagonist \textit{in vitro}. The truncated isoforms TRΔα1 and TRΔα2 cannot bind DNA but play a developmental role in the gut epithelium (Plateroti et al. 2001). TRα1, TRα2 and TRβ1 are widely expressed in a tissue-specific and temporospatial manner (Forrest et al. 1990). TRβ2 is primarily expressed in the hypothalamus and pituitary, where it mediates the negative feedback regulation of TRH and TSH (Abel et al. 2001). Both TRα1 and TRβ1 are expressed in skeletal cells but TRα1 is expressed at tenfold higher levels than TRβ1 (O’Shea et al. 2003, Bookout et al. 2006). Accordingly, detailed phenotyping of a series of mice with a mutation or deletion of the Thra or Thrb genes demonstrated that TRα1 is the key mediator of T3 action in bone (Gauthier et al. 2001, O’Shea et al. 2003, 2005, Bassett et al. 2007a,b, Bassett & Williams 2009). Thus, despite systemic euthyroidism, Thra (TRα)-mutant mice display features of impaired thyroid hormone action in bone, with delayed skeletal development and increased bone mass together with impaired bone remodelling in adulthood (Gauthier et al. 2001, O’Shea et al. 2003, 2005, Bassett et al. 2007a,b, Bassett & Williams 2009). Furthermore, the elevated circulating T3 and T4 concentrations in Thrb (TRβ)-mutant mice, which are a consequence of the disruption of the HPT axis, result in the supra-physiological stimulation of TRα1 in bone and advanced skeletal development but adult osteoporosis due to increased bone remodelling (Gauthier et al. 2001, O’Shea et al. 2003, 2005, Bassett et al. 2007a,b, Bassett & Williams 2009). Although the study of global mutant mice has advanced the understanding of thyroid hormone action in bone, such approaches cannot identify the \textit{in vivo} cell targets of T3 action and the application of cell-specific gene-targeting strategies is now required.

\textbf{Skeletal development}

During endochondral ossification, mesenchyme-derived chondrocytes synthesize a cartilage model of each skeletal element termed an anlage. Hypertrophic differentiation begins at the centre of the anlage and is followed by apoptosis, initiating the formation of the primary ossification centre. Hypertrophic chondrocytes synthesize type X collagen, which induces cartilage mineralisation, thus generating a template for osteoblastic bone formation. Epiphyseal growth plates form at either end of the anlage and consist of organised columns of proliferating, differentiating and apoptosing chondrocytes. Chondrocyte enlargement during hypertrophic differentiation results in linear growth and the production of a mineralised cartilage template upon which the trabecular bone is formed. At the edges of the growth plate, perichondrial cells of mesenchymal origin differentiate into bone-forming osteoblasts and synthesize a bone collar, which subsequently becomes the cortical bone. T3 is an important regulator of skeletal development and linear growth. Childhood hypothyroidism results in growth arrest, delayed bone age and a severe disruption of the growth plate architecture (Rivkees et al. 1988, Boersma et al. 1996, Huffmeier et al. 2007). By contrast, juvenile thyrotoxicosis accelerates growth and advances bone age.

\textbf{The bone remodelling cycle}

Functional integrity and strength of the adult skeleton is maintained by a continuous process of repair called ‘the bone remodelling cycle’ (Raggatt & Partridge 2010). This highly synchronised process occurs in basic multicellular units, which comprise osteocytes, osteoclasts and osteoblasts localised within the bone remodelling cavity (Fig. 2). The bone remodelling cycle has a duration of 150–200 days and is characterised by sequential periods of activation, bone resorption, reversal, bone formation and quiescence. Activation of the bone remodelling cycle is initiated by local structural damage, altered mechanical loading mediated by osteocytes embedded within the bone, or by changes in systemic or paracrine factors. Osteocytes are embedded within the bone and connected by a complex network of dendritic processes that is thought to act as the primary skeletal mechano-transducer. Under basal conditions, osteocytes secrete transforming growth factor β (TGFβ) and sclerostin, which inhibit osteoclastogenesis and Wnt-activated osteoblastic bone formation respectively. Increased load or local micro-damage results in a fall in local TGFβ levels (Heino et al. 2002) and the activation of bone lining cells leads

![Basic multicellular unit](image)
to the recruitment of osteoclast progenitors. Osteocytes and bone lining cells express monocyte/macrophage colony-stimulating factor (M-CSF) and receptor activator of nuclear factor \( \kappa B \) (NF\( \kappa B \)) ligand (RANKL), the two cytokines required for the formation of mature multi-nucleated bone-resorbing osteoclasts (Raggatt & Partridge 2010, Nakashima et al. 2011). Osteoclasts adhere to the bone surface, creating a sealed micro-environment into which they secrete acid and proteases that demineralise and degrade the bone matrix. Following the resorption phase, which lasts 30–40 days, reversal cells remove undigested matrix fragments from the bone surface, and local paracrine signals derived from the degraded matrix result in osteoblast recruitment and the initiation of the bone formation phase. Over the following 150 days, mature osteoblasts secrete and mineralise the new bone matrix (osteoid) to fill the resorption cavity. When the repair is complete, bone formation ceases and the surface returns to its quiescent state covered with bone lining cells. This continual process of targeted bone remodelling enables the adult skeleton to repair old or damaged bone, react to changes in mechanical stress and respond rapidly to the demands of mineral homeostasis. However, to ensure that skeletal integrity is maintained, the processes of bone resorption and formation must be regulated tightly. Despite this, the nature of the coupling process remains controversial and involves both systemic and local factors (Raggatt & Partridge 2010). In adults, thyroid hormone deficiency results in reduced bone turnover and a prolongation of the bone remodelling cycle (Melsen & Mosekilde 1980, Eriksen et al. 2002). The demonstration of differences in bone phenotype that are independent of reduced bone mass is critical. However, the expression of TSHR in osteoblasts and osteoclasts suggested that TSH might have direct actions in bone (Abe et al. 2003). Studies of juvenile Tshr-knockout mice (Tshr\(^{−/−}\)), with treated congenital hypothyroidism, identified a phenotype of high bone turnover osteoporosis. Furthermore, in vitro analysis indicated that TSH inhibited both osteoclast and osteoblast activity (Abe et al. 2003). These findings led to the proposal that TSH was a key negative regulator of bone turnover and that bone loss associated with thyrotoxicosis was a consequence of TSH deficiency rather than thyroid hormone excess (Abe et al. 2003). Subsequent studies, however, suggested that TSH enhanced (Sampath et al. 2007, Sun et al. 2008) or had no effect (Bassett et al. 2008) on osteoblast differentiation and function while actions in osteoclasts were either absent (Bassett et al. 2008) or inhibitory (Hase et al. 2006, Sampath et al. 2007, Sun et al. 2008).

To determine the relative importance of T3 and TSH in bone, the skeletal phenotypes of two mouse models of congenital hypothyroidism were analysed. Hyt/hty mice have a Tshr loss-of-function mutation resulting in congenital hypothyroidism with a 2000-fold increase in TSH, whereas Pax8\(^{−/−}\) mice have an intact Tshr but have congenital hypothyroidism due to thyroid follicular cell agenesis and a similar 2000-fold increase in TSH (Bassett et al. 2008). Thus, Hyt/hty mice lack all TSHR signalling, whereas in Pax8\(^{−/−}\) mice, it is maximal. The similar skeletal phenotype in Hyt/hty and Pax8\(^{−/−}\) mice thus indicates that the HPT axis regulates skeletal development via the actions of T3 rather than TSH. Furthermore, TSH treatment of osteoblasts and osteoclasts in vitro does not induce the canonical TSHR secondary messenger cAMP (Tsai et al. 2004, Bassett & Williams 2008) and levels of TSHR protein expression were very low relative to thyroid follicular cells (Bassett & Williams 2008). These findings suggest that differences in TNF\( \alpha \), RANKL, OPG and interleukin 1 signalling reported in response to TSH may be mediated via an alternative G-protein (Bassett et al. 2003, Hase et al. 2006, Ma et al. 2011). Indeed, intermittent TSH treatment of rodents, at doses insufficient to affect thyroid status, resulted in anti-resorptive and anabolic responses sufficient to prevent ovariectomy-induced bone loss (Sampath et al. 2007, Sun et al. 2008).

Subsequently, the role of thyroid hormone excess and TSH deficiency have been variously emphasised in clinical studies investigating the relationship between thyroid status, BMD and fracture (Bassett & Williams 2008, Murphy et al. 2010, Roef et al. 2011). However, since there is a physiological reciprocal relationship between thyroid hormones and TSH, studies of individuals with an intact HPT axis cannot discriminate the skeletal effects of thyroid hormone excess and TSH deficiency. To address this issue, the effects of recombinant human TSH (rhTSH) on bone turnover markers have been studied in women with thyroid cancer receiving suppressive doses of T4. As these patients had previously undergone total thyroidectomy, the rhTSH treatment did not affect T4 and T3 concentrations but increased serum TSH concentrations to > 100 mU/l. rhTSH was found to have no effect on bone formation or resorption markers in pre-menopausal women (Mazziotti et al. 2005, Giusti et al. 2007, Martini et al. 2008). Results in postmenopausal women have been contradictory: two of four studies reported increased bone formation markers and reduced bone resorption markers in response to hTSH, whereas two studies showed no effect (Mazziotti et al. 2005, Giusti et al. 2007, Martini et al. 2008, Karga et al. 2010). Finally, a study of two siblings with isolated TSH deficiency, who had received T4 replacement from birth, reported that

**Direct actions of TSH in skeletal cells**

TSHR is expressed predominantly in thyroid follicular cells, where it regulates proliferation and thyroid hormone synthesis and secretion. However, its expression has also been described in other tissues including the brain, heart, kidney, testis, adipose tissue, pituitary and immune and haemopoietic cells (Davies et al. 2002). The demonstration of TSH expression in osteoblasts and osteoclasts suggested that TSH might have direct actions in bone (Abe et al. 2003). Studies of juvenile Tshr-knockout mice (Tshr\(^{−/−}\)), with congenital hypothyroidism, identified a phenotype of high bone turnover osteoporosis. Furthermore, in vitro analysis indicated that TSH inhibited both osteoclast and osteoblast activity (Abe et al. 2003). These findings led to the proposal that TSH was a key negative regulator of bone turnover and that bone loss associated with thyrotoxicosis was a consequence of TSH deficiency rather than thyroid hormone excess (Abe et al. 2003). Subsequent studies, however, suggested that TSH enhanced (Sampath et al. 2007, Sun et al. 2008) or had no effect (Bassett et al. 2008) on osteoblast differentiation and function while actions in osteoclasts were either absent (Bassett et al. 2008) or inhibitory (Hase et al. 2006, Sampath et al. 2007, Sun et al. 2008).

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BMD and bone turnover markers were normal despite the absence of TSH (Papadimitriou et al. 2007).

In summary, TSH has been proposed as a direct negative regulator of bone turnover. Although, osteoblasts and osteoclasts have been shown to express low levels of TSHR protein, TSH does not induce the canonical secondary messenger cAMP. TSH treatment of cultured osteoblasts and osteoclasts has yielded conflicting results but despite this, studies of intermittent low-dose TSH treatment prevented ovariectomy-induced bone loss in mice.

**Skeletal consequences of thyrotoxicosis**

Established thyrotoxicosis has long been recognised to have detrimental consequences for both the developing and adult skeleton, including permanent short stature, osteoporosis and increased fracture risk (von Recklinghausen 1891). More recently, the effects of subclinical hyperthyroidism, suppressive T₄ treatment and thyroid status in the upper normal range on BMD and fracture risk have been investigated (Table 1).

**Thyrotoxicosis in childhood**


**Thyrotoxicosis in adults**

Prompt diagnosis and treatment of thyroid disease means that severe uncontrolled thyrotoxicosis is now rarely encountered but it is an established cause of high bone turnover osteoporosis and fragility fracture (Vestergaard & Mosekilde 2003). Population and case–control studies have demonstrated that a prior history of hyperthyroidism is an independent risk factor for hip and vertebral fracture (Cummings et al. 1995, Wejda et al. 1995, Seeley et al. 1996, Bauer et al. 2001, Vestergaard et al. 2005, Ahmed et al. 2006). A meta-analysis of 25 studies showed that BMD was decreased and fracture risk increased in untreated hyperthyroidism (Vestergaard & Mosekilde 2003). Hyperthyroidism was associated with a relative risk of hip fracture of 1.6, with the risk increasing significantly with age. A prospective cohort study of postmenopausal women demonstrated that hyperthyroidism was associated with a three- to fourfold increase in fracture and this was only in part due to reduced BMD, suggesting that hyperthyroidism may result in both reduced mineralisation and impaired bone quality (Bauer et al. 1997, 2001).

Histomorphometric analysis has shown that thyrotoxicosis results in an increased frequency of bone remodelling cycle initiation and a shortened cycle duration. The bone formation phase is reduced to a greater extent than the resorption phase, leading to a 10% loss of bone per cycle (Mosekilde & Melsen 1978, Eriksen et al. 1986). Furthermore, increases in biochemical markers of bone resorption (urinary cross-linked N-telopeptides pyridinoline of type I collagen, pyridinoline and deoxypyridinoline collagen cross-links and hydroxyproline) and bone formation (carboxyterminal propeptide of type I collagen, serum alkaline phosphatase and osteocalcin) correlate with disease severity (Harvey et al. 1991, Garnero et al. 1994, Guo et al. 1997, Toivonen et al. 1998). By contrast, hypothyroidism results in reduced bone turnover with a prolongation of the bone remodelling cycle (Melsen & Mosekilde 1980, Eriksen et al. 1986) but hypothyroidism is similarly associated with a two– to threefold increase in fracture risk (Vestergaard & Mosekilde 2002, Vestergaard et al. 2005). Despite these observations, understanding of the molecular mechanisms by which thyroid hormones regulate the bone remodelling cycle remains incomplete. Indeed, although osteoclastic bone resorption is increased in individuals with thyrotoxicosis (Mosekilde et al. 1990), in vitro studies of osteoclast and osteoblast osteoclast co-culture have failed to resolve whether T₃ acts directly in osteoclasts or whether its actions are indirect and mediated by the effects in osteoblasts (Mundy et al. 1976, Allain et al. 1992, Britto et al. 1994, Kanatani et al. 2004). Nevertheless, T₃ has been shown to accelerate osteoblast differentiation directly, resulting in increased osteoid matrix synthesis and mineralisation, thus regulating bone mineralisation and strength (Huang et al. 2000, Stevens et al. 2003, Bassett et al. 2010). Accordingly, in osteoblast cultures, T₃ enhances the expression of type I collagen and markers of osteoblast differentiation including osteocalcin, osteopontin and alkaline phosphatase, while also regulating FGF receptor 1 and IGF1 signalling pathways (Huang et al. 2000, Stevens et al. 2003).

**Thyrotoxicosis and mineral homeostasis**

Thyrotoxicosis is associated with a significant negative calcium balance (Mosekilde et al. 1990, Harvey & Williams 2002) but despite this, hypercalcaemia may occur in up to 20% of hyperthyroid patients. The high bone turnover results in increased mobilisation of calcium from the skeleton and
relative hypercalcaemia inhibits PTH secretion and reduces renal 1–α-hydroxylation of 25(OH)–vitamin D. The increased metabolic clearance associated with thyrotoxicosis further reduces circulating 1,25(OH)2–vitamin D levels, which leads to decreased intestinal calcium and phosphate absorption together with increased faecal calcium losses. Furthermore, the reduced PTH results in increased urinary calcium loss and phosphate resorption. Thus, increased skeletal calcium
mobilisation combined with reduced PTH and 1,25(OH)₂-vitamin D levels result in a significant negative calcium balance in hyperthyroidism (Murphy & Williams 2004).

**Treatment of thyrotoxicosis**

The effects of pharmacological, surgical and radioactive iodine treatment of thyrotoxicosis on bone turnover markers, BMD and fracture risk have been investigated. Two prospective studies demonstrated that elevated bone resorption markers normalised within 1 month of commencing treatment (Siddiqi et al. 1997, Al-Shoumer et al. 2006) and a retrospective cohort study of 630 women treated with thyroidectomy and followed up for an average of 20 years showed no independent influence of hyperthyroidism or T₄ replacement on fracture risk (Melton et al. 2000). Furthermore, a meta-analysis of 20 studies demonstrated that although BMD was reduced at diagnosis, it returned to the normal range within 5 years of treatment irrespective of the modality of treatment (Vestergaard & Mosekilde 2003). Two subsequent studies suggested that BMD returns to normal within 3 years of treatment and increases as much as 4% within the first year (Karga et al. 2004, Udayakumar et al. 2006). Despite the reported rapid improvement in bone turnover markers and BMD, very large population studies have indicated that the increased risk of fracture associated with thyrotoxicosis persists for at least 5 years after diagnosis and treatment (Vestergaard et al. 2005) and is associated with increased mortality (Franklyn et al. 1998).

In summary, juvenile hyperthyroidism is associated with accelerated skeletal development but may ultimately lead to short stature due to premature growth plate closure. In adults, thyrotoxicosis leads to high bone turnover, negative calcium balance and an increased risk of fragility fracture. Treatment of thyrotoxicosis results in the normalisation of bone turnover markers and BMD but an increased risk of fracture persists for 5 years following treatment.

**Endogenous subclinical hyperthyroidism**

Subclinical hyperthyroidism is defined as a suppressed TSH in the context of normal thyroid hormone concentrations. Small studies of patients with subclinical hyperthyroidism have reported conflicting results either describing normal (De Menis et al. 1992, Faber et al. 1994, Mudde et al. 1994, Gurlek and Gedik 1999, Lee et al. 2006) or elevated (Campbell et al. 1996, Kumeda et al. 2000, Tauchmanova et al. 2004, Belaya et al. 2007, Rosario 2008) bone turnover makers. Similarly, small studies of have found either no change (Foldes et al. 1993, Gurlek & Gedik 1999, Ugur-Altun et al. 2003, Lee et al. 2006) or a small reduction in BMD (Tauchmanova et al. 2004, Rosario 2008) in pre-menopausal women with subclinical hyperthyroidism. By contrast, the majority of studies in postmenopausal women demonstrated a reduction in BMD (Foldes et al. 1993, Mudde et al. 1994, Tauchmanova et al. 2004, Lee et al. 2006, Belaya et al. 2007, Rosario 2008).

A large study that included 968 males and 993 postmenopausal women showed that a TSH below the 2.5th percentile was associated with reduced BMD, although insufficient data are available to determine whether the individuals had subclinical or overt hyperthyroidism (Grimnes et al. 2008).

Two large population studies recently investigated the risk of fracture in subclinical hyperthyroidism. In a study of 2004 patients, subclinical hyperthyroidism was associated with an increased risk of fracture with a hazard ratio of 1.25. However, when patients who developed overt thyrotoxicosis or reverted to euthyroidism were excluded, this association was lost (Vadiveloo et al. 2011). In a prospective cohort study of adults over 65 years of age, men with endogenous subclinical hyperthyroidism had a hip fracture hazard ratio of 4.9, whereas no clear association between subclinical hyperthyroidism and fracture was observed in postmenopausal women (Lee et al. 2010). Furthermore, studies by Bauer and Jamal have also reported an increased incidence of fracture in individuals with a TSH concentration suppressed below 0.5 mIU/l but insufficient data are available to determine whether the individuals had subclinical or overt hyperthyroidism (Bauer et al. 2001, Jamal et al. 2005). A limited number of small studies have investigated the effects of normalising TSH in individuals with endogenous subclinical hyperthyroidism. In a prospective study of 16 postmenopausal women, treatment with methimazole did not affect bone turnover markers but distal forearm BMD was increased by the second year of treatment (Mudde et al. 1994), and in a second study of 14 patients, skeletal parameters also improved following treatment (Buscemi et al. 2007). In a study of 16 postmenopausal women treated with radioactive iodine, BMD increased compared with untreated controls (Faber et al. 1998).

In summary, endogenous subclinical hyperthyroidism may be associated with an increased bone turnover, reduced BMD and increased fracture risk, although insufficient data are currently available to draw definitive conclusions. Overall, the evidence suggests a small reduction in BMD and an increased risk of fracture in postmenopausal women and in men but not in pre-menopausal women.

**Suppressive doses of T₄ in differentiated thyroid cancer**

Patients with differentiated thyroid carcinoma are frequently treated for prolonged periods with doses of T₄ sufficient to suppress the circulating TSH concentration. The effects of such long-term exogenous subclinical hyperthyroidism on bone turnover markers and BMD, at a number of anatomical locations, have been investigated in many small studies. In pre-menopausal women receiving suppressive doses of T₄, 16 studies have reported bone turnover markers, with eight showing an increase and eight no change, while 29 studies have reported BMD with nine showing a decrease and 20 showing no change. Heemstra et al. (2006) analysed four

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prospective and 12 cross-sectional studies of pre-menopausal women receiving suppressive doses of T₄, and concluded that treatment with suppressive doses of T₄ did not affect BMD, although a full meta-analysis could not be performed due to heterogeneity. This conclusion was consistent with two preceding systematic literature reviews (Faber & Galloe 1994, Uzzan et al. 1996, Quan et al. 2002, Murphy & Williams 2004, Heemstra et al. 2006) and two meta-analyses (Faber & Galloe 1994, Uzzan et al. 1996). Currently, there are no prospective data on fracture risk in pre-menopausal women receiving suppressive doses of T₄. Nineteen studies have reported bone turnover markers in postmenopausal women receiving suppressive doses of T₄, 13 reported an increase and six showed no change. Thirty studies have reported BMD in postmenopausal women receiving suppressive doses of T₄ and 11 showed a decrease in BMD while 19 showed no change. Furthermore, the two most rigorous cross-sectional studies were also conflicting, with Franklyn et al. (1992) reporting no effect in 26 postmenopausal UK women treated for 8 years whereas Kung & Yeung (1996) found reduced, lumbar spine and femoral BMD in 34 postmenopausal Asian women treated with suppressive doses of T₄. Of three systematic literature reviews, two concluded that skeletal effects of suppressive doses of T₄ in postmenopausal women remain uncertain (Quan et al. 2002, Murphy & Williams 2004) and one concluded that postmenopausal women were the subgroup most at risk (Heemstra et al. 2006). Nevertheless, two reported meta-analyses have suggested that suppressive doses of T₄ in postmenopausal women lead to increased bone loss of ~1% per annum (Faber & Galloe 1994, Uzzan et al. 1996). Eight studies have also included male patients, but only one reported a reduction of BMD in men receiving suppressive doses of T₄ (Jodar et al. 1998). Consistent with this, a meta-analysis concluded that suppressive doses of T₄ had no effect on BMD in men (Uzzan et al. 1996). Currently, no studies with sufficient statistical power to establish the effect of prolonged suppressive T₄ treatment on fracture risk have been reported. However, in a cross-sectional thyroid registry study of 1180 individuals on T₄ replacement, 59% were found to have suppressed TSH but no increased risk of fracture risk was identified (Leese et al. 1992).

In summary, treatment with suppressive doses of T₄ does not affect BMD in pre-menopausal women or men but may lead to reduced BMD in postmenopausal women and the majority of recent studies recommend monitoring these patients. The effects on bone turnover markers remain uncertain and fracture risk has not been studied.

Skeletal effects of thyroid hormone concentrations in the upper normal range

Very few studies have investigated the relationship between bone turnover markers and circulating thyroid hormone concentrations within the euthyroid reference range. Zołkova & Hill (2008) performed a small cross-sectional study in 60 postmenopausal women and reported a correlation between high circulating TSH and lower levels of bone resorption markers. By contrast, several larger studies have investigated the relationship between circulating thyroid hormone concentrations and BMD. Kim et al. (2006) studied 959 healthy postmenopausal Korean women and reported that a low normal TSH was associated with reduced lumbar spine and femoral neck BMD. Morris (2007) investigated 581 postmenopausal American women and reported that a low normal TSH was associated with a fivefold higher incidence of osteoporosis than a high normal TSH. In the Tromsø study of 993 postmenopausal women and 968 men, individuals with a TSH above the 97.5th percentile had increased femoral neck BMD, whereas those with a TSH below the 2.5th percentile had reduced forearm BMD but no association was found between BMD and TSH within the normal range (Grimnes et al. 2008). In the Rotterdam study of 1151 euthyroid men and women aged over 55 years, femoral neck BMD correlated positively with TSH and negatively with fT₄ (van der Deure et al. 2008). A recent large Taiwanese study of 2957 euthyroid healthy male and female individuals over 45 years of age again reported a negative correlation between BMD and fT₄ but found no correlation with TSH (Lin et al. 2011). A cross-sectional study of 677 healthy young men studied at the time of peak bone mass (25–45 years) reported that higher concentrations of fT₃ and

![Figure 3 Effect of variation in fT₄ concentration within the normal reference range on bone mineral density (BMD) in healthy euthyroid postmenopausal women from the Osteoporosis and Ultrasound Study (OPUS; Murphy et al. 2010). Graphs showing mean hip BMD ±95% confidence intervals at the time of entry into the study (white bars) and after 6 years prospective follow-up (grey bars) in relation to quintiles of fT₄ concentration. The fT₄ reference range was determined in 1754 healthy postmenopausal women (25–45 years old) (fT₄; 9–15–16–99 pmol/l). Individuals with fT₄ levels in the highest quintile had lower hip BMD than women with fT₄ in the lowest quintile at the time of entry into the study (P=0.02) and after 6 years of follow-up (P=0.04).](http://www.endocrinology-journals.org)
fT4 were correlated with lower BMD (Roef et al. 2011). A limited number of studies have investigated the relationship between incident fracture and circulating thyroid hormone concentrations within the euthyroid reference range. A 10-year prospective study of 367 healthy postmenopausal women found no association between thyroid hormone concentrations and vertebral fracture (Finigan et al. 2008). Nevertheless, in a population of 130 euthyroid postmenopausal women with osteoporosis or osteopenia, Mazziotti et al. (2010) reported that a TSH in the lower third of the reference range was independently associated with an increased risk of vertebral fracture. Furthermore, a recent large 6-year prospective study of 1287 healthy euthyroid postmenopausal European women demonstrated that higher fT4 was associated with lower BMD and increasing bone loss at the hip (Fig. 3; Murphy et al. 2010). In addition, individuals in the highest quintile for fT4 and fT3 had a 20% and 33% increase in incident non-vertebral fracture respectively, whereas those in the highest quintile for TSH had a 35% reduction in fracture risk (Murphy et al. 2010).

In summary, these studies demonstrate that thyroid status at the upper end of the normal reference range is associated with lower BMD and increased fracture risk.

Conclusions

Thyroid hormone is a key regulator of skeletal development and adult bone maintenance, and thyroid hormone excess leads to detrimental effects in both the juvenile and adult skeleton. Detailed studies of a series of genetically modified mice have demonstrated that the actions of T3 in bone are predominantly mediated by TRα1 and that T3 actions are anabolic during development but catabolic in adulthood. Thus, childhood thyrotoxicosis results in accelerated growth and advanced endochondral ossification, whereas in adults, hyperthyroidism leads to reduced BMD and an increased risk of fragility fracture due to accelerated bone remodelling and an excess of bone resorption compared with bone formation. The sensitivity of the adult skeleton to prolonged exposure to even small changes in thyroid status is illustrated by the reduction in BMD and the increase in fracture risk in postmenopausal women and men with subclinical hyperthyroidism and in postmenopausal women treated with suppressive doses of T4. Furthermore, recent studies have suggested that lifelong exposure to thyroid hormone levels in the upper normal reference range is associated with lower BMD and an increased risk of fracture risk when compared with individuals with a HPT axis set point in the lower normal reference range. Despite these important observations, the cellular and molecular mechanisms of thyroid hormone action in bone remain incompletely understood. While there are direct actions of T3 in chondrocytes and osteoblasts, evidence for such effects in osteoclasts remains controversial and it is unclear whether T3 acts directly or whether its actions in osteoclasts are indirect and mediated by osteoblasts. Furthermore, although a number of studies have suggested that TSH may directly inhibit bone turnover, other studies have been conflicting. Ultimately, these important questions will be resolved by conditional gene targeting of the chondrocyte, osteoblast and osteoclast lineages to identify which bone cells are directly responsive in vivo.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review reported.

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