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 (T_4) 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.

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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 (T_4) 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 T_4 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 T_4 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) in 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

Figure 1 Systemic thyroid hormone concentrations are controlled by the negative feedback regulation of the hypothalamic-pituitary-thyroid (HPT) axis. TRH stimulates the release of TSH from the anterior pituitary, which then stimulates the synthesis and secretion of T_4 and T_3 by the thyroid gland. DIO2 converts the pro-hormone T_4 to the active hormone T_3 , which binds and activates TR β 2 in the hypothalamus and pituitary, resulting in the feedback inhibition of TRH production and TSH secretion. DIO1 also converts T_4 to T_3 in the liver, contributing to the pool of circulating T_3 . Thyroid hormones enter target cells via specific cell membrane transporters and intracellular supplies of T_3 to the nucleus of T_3 -target cells are regulated by the relative activities of DIO2 and DIO3. Expression of DIO2 results in the activation of T_4 to T_3 , increased intracellular T_3 concentrations and stimulation of T_3 -target gene transcription. Expression of DIO3 prevents the activation of T_4 and inactivates T_3 , resulting in the repression of T_3 -target gene transcription. PVN, paraventricular nucleus; TRH, thyrotrophin-releasing hormone; TSH, thyroid-stimulating hormone; DIO1, DIO2 and DIO3, type 1, 2 and 3 deiodinases; MCT8 and MCT10, monocarboxylate transporters 8 and 10; OATP1C1, organic acid transporter protein-1C1; TR, thyroid hormone receptor; TR β 2, thyroid hormone receptor β 2; RXR, retinoid X receptor; T_4 , thyroxine; T_3 , 3,5,3',5'-L-triiodothyronine; r T_3 , 3,3',5'-triiodothyronine; T_2 , 3,3'-diiodothyronine.

follicular cell growth and the synthesis and secretion of both the pro-hormone 3,5,3',5'-L-tetraiodothyronine (T_4) and, to a lesser extent, the active hormone 3,5,3'-L-triiodothyronine (T_3). Thyroid hormones exert their effects in a wide range of peripheral tissues but also act in the PVN and pituitary to inhibit the synthesis and secretion of TRH and TSH respectively. These actions complete the physiological negative feedback loop that determines the set point for circulating thyroid hormone concentrations. Thus, the HPT axis maintains a reciprocal relationship between thyroid hormones and TSH (Bassett & Williams 2008). The set point of the HPT axis is at least in part genetically determined with 45–65% of the inter-individual variation in serum TH concentrations due to genetic factors (Hansen *et al.* 2004, Panicker *et al.* 2008a, Medici *et al.* 2011). Accordingly, a recent genome-wide linkage scan, in dizygotic twins, identified eight quantitative trait loci associated with free T_4 (f T_4), free T_3 (f T_3) and TSH concentrations and an association study of 68 candidate genes involved in thyroid hormone synthesis, metabolism or transport identified

a number of associations with f T_4 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 T_3 supply

T_3 action in target tissues depends on the circulating concentrations of T_4 and T_3 , their uptake into target cells, and local activation or inactivation (Fig. 1). The thyroid secretes mainly the pro-hormone T_4 and the majority of circulating T_3 is generated in the liver and kidneys by the action of type 1 iodothyronine deiodinase enzyme (DIO1), which catalyses 5'-deiodination of T_4 . Over 95% of thyroid hormones are bound to plasma proteins and concentrations of f T_4 in the circulation remain three to four times those of f T_3 . 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 (SLCO1C1); van der Deure *et al.* 2010). The intracellular availability of T_3 is determined by the relative activities of DIO2 and DIO3 (Bianco & Kim 2006, St Germain *et al.* 2009). DIO2 converts the pro-hormone T_4 to the active hormone T_3 by the removal of an outer-ring 5'-iodine atom, whereas DIO3 inactivates T_3 and prevents the activation of T_4 by the removal of an inner-ring 5-iodine atom to produce the inactive metabolites 3,3',5'-L-triiodothyronine (reverse- T_3) and 3,3'-diiodotyrosine (T_2 ; Bianco & Kim 2006). DIO2 activity is regulated by a rapid post-translation mechanism involving T_4 -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. Thus, the relative local expression of DIO2 and DIO3 represents a homeostatic mechanism that regulates target tissue responses to thyroid hormone (Gereben *et al.* 2008).

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. T_3 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 TR α and TR β isoforms are transcribed. TR α 1, TR β 1 and TR β 2 contain DNA and ligand-binding domains and are functional receptors, whereas

TR α 2 lacks hormone-binding activity and acts as a weak antagonist *in vitro*. The truncated isoforms TR $\Delta\alpha$ 1 and TR $\Delta\alpha$ 2 cannot bind DNA but play a developmental role in the gut epithelium (Plateroti *et al.* 2001). TR α 1, TR α 2 and TR β 1 are widely expressed in a tissue-specific and temporo-spatial manner (Forrest *et al.* 1990). TR β 2 is primarily expressed in the hypothalamus and pituitary, where it mediates the negative feedback regulation of TRH and TSH (Abel *et al.* 2001). Both TR α 1 and TR β 1 are expressed in skeletal cells but TR α 1 is expressed at tenfold higher levels than TR β 1 (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 TR α 1 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* (TR α)-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* (TR β)-mutant mice, which are a consequence of the disruption of the HPT axis, result in the supra-physiological stimulation of TR α 1 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 *in vivo* cell targets of T₃ action and the application of cell-specific gene-targeting strategies is now required.

Skeletal development

During endochondral ossification, mesenchyme-derived chondrocytes synthesise 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 synthesise 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 synthesise 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.

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 (TGF β) and sclerostin, which inhibit osteoclastogenesis and Wnt-activated osteoblastic bone formation respectively. Increased load or local micro-damage results in a fall in local TGF β levels (Heino *et al.* 2002) and the activation of bone lining cells leads

Figure 2 Schematic representation of the basic multicellular unit of the bone remodelling cycle. The bone remodelling cycle is initiated and orchestrated by osteocytes, which are embedded within mineralised bone and communicate via ramifications of dendritic processes. Bone remodelling may result from changes in mechanical load, structural damage or exposure to systemic or paracrine factors. Haemopoietic cells of the monocyte/macrophage lineage differentiate to mature osteoclasts and resorb bone. During the reversal phase, osteoblastic progenitors are recruited to the site of resorption, differentiate and synthesise osteoid, and mineralise the new bone matrix to repair the defect. Crosstalk between bone-forming osteoblasts and bone-resorbing osteoclasts regulates bone remodelling and maintains skeletal homeostasis. M-CSF, macrophage colony-stimulating factor; OPG, osteoprotegerin; RANK, receptor activator of NF κ B; RANKL, RANK ligand.

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 κ B (NF κ 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.* 1986) and is associated with a two- to threefold increase in fracture risk (Vestergaard & Mosekilde 2002). By contrast, established thyrotoxicosis is a recognised cause of high bone turnover osteoporosis and fragility fracture (Vestergaard & Mosekilde 2003).

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 TSHR 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 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/hyt* 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/hyt* mice lack all TSHR signalling, whereas in *Pax8*^{-/-} mice, it is maximal. The similar skeletal phenotype in *Hyt/hyt* 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 changes in TNF α , RANKL, OPG and interleukin 1 signalling reported in response to TSH may be mediated via an alternative G-protein (Abe *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

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 childhood is rare but most commonly caused by Graves' disease. Juvenile thyrotoxicosis results in accelerated growth and advanced bone age, and in severe early cases it can cause premature fusion of the growth plates and cranial sutures resulting in persistent short stature and craniosynostosis (Segni *et al.* 1999). By contrast, 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). T₃ excess accelerates the pace of growth plate chondrocyte differentiation via actions on the key Indian hedgehog/parathyroid hormone-related peptide, bone morphogenetic protein, fibroblast growth factor (FGF), growth hormone (GH), insulin-like growth factor 1 (IGF1) and canonical Wnt signalling pathways (Robson *et al.* 2000, Stevens *et al.* 2000, Barnard *et al.* 2005, Dentice *et al.* 2005, O'Shea *et al.* 2005, Lasso *et al.* 2009, Wang *et al.* 2010, Xing *et al.* 2012). In addition, T₃ acts to accelerate cartilage matrix synthesis, modification, mineralisation and degradation (Ishikawa *et al.* 1998, Robson *et al.* 2000, Himeno *et al.* 2002, Makihira *et al.* 2003, Bassett *et al.* 2006).

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 the

Table 1 Summary of large studies and meta-analyses

Year	Study type	Population	Numbers	Summary of findings	Reference
Studies of individuals with abnormal thyroid function					
1992	Thyroid registry	T ₄ -treated pre- and post-MW and men	1180 individuals	No increased fracture risk associated with suppressed TSH	Leese <i>et al.</i> (1992)
1994	Meta-analysis	Pre- and post-MW	13 studies of BMD	Reduced BMD in post-MW associated with suppressed TSH	Faber & Galloe (1994)
1995	4-year prospective study	Post-MW > 65 years old	9516 individuals	History of TTX associated with an increased risk of hip fracture	Cummings <i>et al.</i> (1995)
1996	Meta-analysis	T ₄ treatment of pre- and post-MW and men	33 studies of BMD	Suppressive T ₄ treatment associated with reduced BMD in post-MW	Uzzan <i>et al.</i> (1996)
1998	Thyroid registry	Radioiodine-treated TTX in women and men	7209 individuals	Increased risk of fracture and mortality	Franklyn <i>et al.</i> (1998)
2000	Retrospective cohort	Thyroidectomy-treated TTX in women	630 individuals	No increase in overall fracture risk	Melton <i>et al.</i> (2000)
2001	4-year prospective cohort study	Post-MW	686 individuals	Suppressed TSH associated with an increased risk of hip and vertebral fracture	Bauer <i>et al.</i> (2001)
2002	Literature review	Subclinical hyperthyroidism in pre- and post-MW and men	11 studies of BMD	No effect of subclinical hyperthyroidism in pre-MW and men	Quan <i>et al.</i> (2002)
2003	Meta-analysis	Hyperthyroidism in pre- and post-MW and men	20 studies of BMD and five studies of fracture	BMD reduced and fracture risk increased in TTX	Vestergaard & Mosekilde (2003)
2004	Literature review	Thyroid disease in pre- and post-MW and men	24 studies of BMD and 13 studies of fracture	Suppressed TSH associated with an increased risk of fracture	Murphy & Williams (2004)
2005	Cross-sectional study	Post-MW (fracture intervention trial)	15 316 individuals	Osteoporosis and vertebral fracture associated with low TSH	Jamal <i>et al.</i> (2005)
2005	Case-control study	Women and men with fracture	124 655 individuals, 373 962 controls	Increased risk of fracture for 5 years after diagnosis of TTX	Vestergaard <i>et al.</i> (2005)
2006	Literature review	Suppressive T ₄ therapy in pre- and post-MW and men	21 studies of BMD	Post-MW most at risk from T ₄ -suppressive treatment	Heemstra <i>et al.</i> (2006)
2006	Cross-sectional study	Women and men (Tromsø study)	27 159	Increased risk of fracture associated with TTX in men and women	Ahmed <i>et al.</i> (2006)
2011	Retrospective cohort	Subclinical hyperthyroidism in pre- and post-MW and men (TEARS study)	2004	Increased risk of fracture but not correlated with TSH level	Vadiveloo <i>et al.</i> (2011)
Studies of normal euthyroid individuals					
2006	Cross-sectional study	Post-MW	959 individuals	Low normal TSH associated with reduced BMD	Kim <i>et al.</i> (2006)
2007	Cross-sectional study	Post-MW	581 individuals	Low normal TSH associated with an increased risk of osteoporosis	Morris (2007)
2008	Cross-sectional study	Women and men (Tromsø study)	1961 individuals	TSH within the normal range not associated with BMD	Grimnes <i>et al.</i> (2008)
2008	8-year prospective study	Women and men over 55 years old (Rotterdam study)	1151 individuals	FT ₄ and TSH associated with BMD but not fracture	van der Deure <i>et al.</i> (2008)
2010	6-year prospective study	Post-MW (OPUS study)	1278 individuals	High normal fT ₃ and fT ₄ associated with reduced BMD and an increased risk of fracture	Murphy <i>et al.</i> (2010)
2011	Cross-sectional study	Women and men	2957 individuals	High normal fT ₄ associated with reduced BMD	Lin <i>et al.</i> (2011)
2011	Cross-sectional study	Young men	1677 individuals	High normal fT ₃ and fT ₄ associated with reduced BMD	Roef <i>et al.</i> (2011)

Post-MW, postmenopausal women; pre-MW, pre-menopausal women; TTX, thyrotoxicosis; BMD, bone mineral density.

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 $1,25(\text{OH})_2$ -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 T_4 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 markers. 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 T_4 in differentiated thyroid cancer

Patients with differentiated thyroid carcinoma are frequently treated for prolonged periods with doses of T_4 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 T_4 , 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

prospective and 12 cross-sectional studies of pre-menopausal women receiving suppressive doses of T_4 , and concluded that treatment with suppressive doses of T_4 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 & Galloë 1994, Uzzan *et al.* 1996, Quan *et al.* 2002, Murphy & Williams 2004, Heemstra *et al.* 2006) and two meta-analyses (Faber & Galloë 1994, Uzzan *et al.* 1996). Currently, there are no prospective data on fracture risk in pre-menopausal women receiving suppressive doses of T_4 . Nineteen studies have reported bone turnover markers in postmenopausal women receiving suppressive doses of T_4 , 13 reported an increase and six showed no change. Thirty studies have reported BMD in postmenopausal women receiving suppressive doses of T_4 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 T_4 . Of three systematic literature reviews, two concluded that skeletal effects of suppressive doses of T_4 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 T_4 in postmenopausal women lead to increased bone loss of $\sim 1\%$ per annum (Faber & Galloë 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 T_4 (Jodar *et al.* 1998). Consistent with this, a meta-analysis concluded that suppressive doses of T_4 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 T_4 treatment on fracture risk have been reported. However, in a cross-sectional thyroid registry study of 1180 individuals on T_4 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 T_4 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. Zofkova & 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 fT_4 (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 fT_4 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 fT_3 and

Figure 3 Effect of variation in fT_4 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 $\pm$ 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 fT_4 concentration. The fT_4 reference range was determined in 1754 healthy postmenopausal women ≥ 55 years old (fT_4 : 9.15–16.99 pmol/l). Individuals with fT_4 levels in the highest quintile had lower hip BMD than women with fT_4 in the lowest quintile at the time of entry into the study ($P=0.02$) and after 6 years of follow-up ($P=0.04$).

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 1278 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 TR α 1 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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