

Review Article

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Bone disease in thyrotoxicosis

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Thyrotoxicosis, a clinical syndrome characterized by manifestations of excess thyroid hormone, is one of the commonly-recognised conditions of the thyroid gland. Thyrotoxicosis causes acceleration of bone remodelling and though it is one of the known risk factors for osteoporosis, the metabolic effects of thyroxine on bone are not well discussed. Studies show that thyroid hormones have effects on bone, both *in vitro* and *in vivo*. Treatment of thyrotoxicosis leads to reversal of bone loss and metabolic alterations, and decreases the fracture risk. There are limited studies in India as to whether these changes are fully reversible. In this review we discuss about the effects of thyrotoxicosis (endogenous and exogenous) on bone and mineral metabolism, effects of subclinical thyrotoxicosis on bone and mineral metabolism and effects of various forms of treatment in improving the bone mineral density in thyrotoxicosis.

Key words Bone formation and resorption - thyroid - vitamin D

Introduction

Thyrotoxicosis is the hypermetabolic condition associated with elevated levels of thyroxine (T4) and/or triiodothyronine (T3). Hyperthyroidism includes diseases that are a subset of thyrotoxicosis, caused by excess synthesis and secretion of thyroid hormone. Usual causes of hyperthyroidism are Graves' disease in the young and the middle aged, and multinodular goiter in the elderly. Thyrotoxicosis can exist without hyperthyroidism, *e.g.* exogenous thyroid hormone intake and thyroiditis.

The hypermetabolic effect of thyrotoxicosis affects every organ system. Thyroid hormone is necessary for normal growth and development, and it regulates cellular metabolism. Excess thyroid hormone causes an increase in the metabolic rate that is associated with increased total body heat production and cardiovascular

activity, manifesting as increased heart contractility, tachycardia and vasodilation.

The presentation of thyrotoxicosis is variable among patients. Thyrotoxicosis leads to an apparent increase in sympathetic nervous system symptoms. Younger patients tend to exhibit symptoms of more sympathetic activation, such as anxiety, hyperactivity, palpitations, sweating and tremor, while older patients have more cardiovascular symptoms, including dyspnoea, atrial fibrillation and unexplained weight loss. The adverse effects of hyperthyroidism on the skeleton were known before the advent of satisfactory treatment for hyperthyroidism. One of the first reports of hyperthyroid bone disease was in 1891 when von Recklinghausen described the "worm eaten" appearance of the long bones of a young woman who died from hyperthyroidism¹. With the introduction of antithyroid drugs and radioiodine in the 1940s, clinically apparent

hyperthyroid bone disease became less common². However, bone density measurements during the last decade have demonstrated that bone loss is common in patients with overt hyperthyroidism and to a lesser extent in those with subclinical hyperthyroidism, whether caused by nodular goiter or excessive doses of thyroid hormone³⁻⁵. Data from India is sparse regarding the effects of thyrotoxicosis on bone and mineral metabolism⁶.

Mechanism: Thyroid hormone directly stimulates bone resorption in organ culture⁷. This action may be mediated by a nuclear triiodothyronine (T3) receptor which has been found in rat and human osteoblast cell lines⁸⁻¹⁰ and in osteoclasts derived from an osteoclastoma¹⁰. Thus, thyroid hormone may affect bone calcium metabolism either by a direct action on osteoclasts, or by acting on osteoblasts which in turn mediate osteoclastic bone resorption¹¹. Experimental studies in mice lacking either the thyroid receptor- α or β , suggest that bone loss is mediated by thyroid receptor¹². Thyroid stimulating hormone (TSH) may also have a direct effect on bone formation and bone resorption, mediated via the TSH receptor on osteoblast and osteoclast precursors¹³. However, bone loss appeared independent of TSH levels in the experiments with mice lacking specific TR isoforms¹².

Increased serum interleukin-6 (IL-6) concentrations in hyperthyroid patients may also play a role in thyroid hormone-stimulated bone loss¹⁴. Interleukin-6 stimulates osteoclast production and may be an effector of the action of parathyroid hormone (PTH) on bone.

Hyperthyroidism

Overt hyperthyroidism is associated with accelerated bone remodelling, reduced bone density, osteoporosis, and an increase in fracture rate^{2,15}. Studies show variable results about the reversibility of bone density changes with therapy. These changes in bone metabolism are associated with negative calcium balance, hypercalciuria, and, rarely, hypercalcaemia^{16,17}.

Bone density: Bone loss is a uniform feature of overt hyperthyroidism. Studies of iliac crest bone biopsies reveal important differences in the effects of thyroid hormone on trabecular and cortical bone². Three-dimensional reconstructions of the remodelling sequence have shown how these changes occur. In the normal remodelling sequence, osteoclastic resorption and osteoblastic bone formation are synchronized. In overt hyperthyroidism, osteoclastic resorption is stimulated

out of proportion to osteoblastic remineralization¹⁸. As a result, the normal cycle duration of approximately 200 days is halved, and each cycle is associated with a 9.6 per cent loss of mineralized bone. In contrast, cycle length approximates 700 days in hypothyroid patients and is associated with a 17 per cent increase in mineralized bone.

The extent of reduction in bone density in hyperthyroid patients ranges from 10 to 20 per cent^{4,19-21}. The extent of the reversibility of bone loss with therapy, however, is unclear. Studies that have looked at changes in bone density after treatment of hyperthyroidism have yielded variable results. Two studies using single photon absorptiometry reported a reduction in bone density of 12 to 28 per cent in hyperthyroid patients which normalized after treatment^{19,20}. Two retrospective Danish studies assessed bone mineral content and regional bone density using dual photon absorptiometry. No differences were found in 55 patients whose hyperthyroidism had been treated surgically and who had been euthyroid for at least six years (mean 12.5 yr)³, or in 39 patients whose hyperthyroidism had been treated medically and who had been euthyroid for at least four years (mean 9.8 yr), compared to age- and sex-matched normal subjects²². A cross-sectional study of 164 women with treated overt hyperthyroidism found reductions in bone density during the first three years after diagnosis and treatment. Three or more years after diagnosis, bone density (spine and femoral neck) was no different from controls, suggesting that the decrease in bone density is reversible²³.

One study found bone density to be the same in 25 thyroxine (T4)-treated women who had received radioiodine therapy for hyperthyroidism and 25 similar women with primary hypothyroidism receiving T4 treatment²⁴. Other studies using dual photon absorptiometry reported reductions in bone density of 12 to 13 per cent in the lumbar spine in patients with hyperthyroidism. However, recovery was incomplete, with increases in bone density of only 3.7 to 6.6 per cent after one year of treatment^{4,21}. Several other²⁵⁻²⁷, but not all²³ reports have also shown incomplete recovery. Greater improvement in bone density has been reported after resolution of hyperthyroidism when hyperthyroid women were treated with both alendronate and methimazole versus methimazole alone²⁸.

As hyperthyroidism is associated with weight loss which in turn, is associated with loss of bone mass, it is reasonable to assume that low bone density seen in cases with hyperthyroidism is due to weight loss

and not due to any direct effect of thyroid function on bone. The Rotterdam study in a large sample of elderly caucasian population suggested that a direct effect of thyroid functions on bone density also exists apart from the effect of weight on bone density²⁹.

Fracture risk: Despite the variable bone density findings, a history of overt hyperthyroidism is a risk factor for hip fracture later in life^{15,30}, which is one of the causes of excess late mortality in previously hyperthyroid patients³¹. It is, therefore, reasonable to assume that in some hyperthyroid patients bone density does not return to normal after antithyroid treatment. In a study of 621 patients treated for hyperthyroidism with radioiodine, the risk of spine and forearm fractures was increased. Curiously, the risk was not increased in patients co-treated with methimazole³². The impact of low serum TSH concentrations on fracture risk was investigated in a prospective cohort study of 686 white women over age 65 yr followed for a mean of 3.7 yr³³. Women with serum TSH concentrations of 0.1 mU/l or less at baseline were at increased risk for both hip and vertebral fracture (relative risk 3.6 and 4.5, respectively). Exogenous thyroid hormone therapy was not a risk factor for fracture in women with normal serum TSH concentrations, but a history of hyperthyroidism was a risk factor for hip fracture, even after adjustment for serum TSH concentration and bone mineral density³³. Serum thyroxine was not measured, so the proportion of women with overt and subclinical hyperthyroidism is not known.

Symptomatic bone disease: Earlier studies documented the potential for symptomatic bone disease in association with reduced bone density. In a study on 187 patients with hyperthyroidism, 15 (8%) had symptoms². These symptomatic patients were all women (80% >50 yr), three-quarters had been hyperthyroid for less than a year, and two-thirds had a fracture or severe bone pain.

Osteomalacia is known to be associated with thyrotoxicosis. In hyperthyroidism, subclinical vitamin D deficiency may get precipitated into an overt form. Osteomalacia may co-exist with thyrotoxicosis, but may remain undiagnosed, unless clinically suspected and biochemically confirmed³⁴.

The most prominent manifestations of Graves' disease in the prepubertal children was accelerated growth and bone maturation³⁵. All the prepubertal children had tall stature at diagnosis, with a height SD score significantly greater than that of their parents.

Increase in height SD score and bone age may be explained by the fact that maturation is affected by GH and thyroid hormone before puberty, whereas at puberty it is mainly influenced by sex hormones. Accelerated growth in the prepubertal children occurred despite accompanying weight loss³⁵.

Mineral metabolism: The increased calcium release into the circulation due to the increased bone resorption affects mineral metabolism which leads to negative calcium balance in hyperthyroid patients¹⁶. Hypercalcaemia occurs in up to 8 per cent of patients¹⁶. Increases in the serum ionized calcium concentration are more common than increase in total calcium¹⁷. The hypercalcaemia suppresses the secretion of PTH, leading to hypercalciuria, which protects against hypercalcaemia but leads to a negative calcium balance.

There is increased skeletal hyper-responsiveness to catecholamines in thyrotoxicosis which contributes for hypercalcaemia and hypercalciuria. This can be reversed at least partially by high dose beta-blocker therapy³⁶. Low serum PTH concentrations reduce the conversion of 25-hydroxyvitamin D (calcidiol) to calcitriol³⁷. The decline in calcitriol production is compounded by an increase in calcitriol metabolism induced by hyperthyroidism³⁸. Low serum calcitriol concentrations diminish intestinal calcium (and phosphorus) absorption, resulting in faecal calcium loss. Malabsorption of calcium may be aggravated by steatorrhoea and increased gut motility³⁹. In one study, plasma-calcitonin and bone density were measured in patients with untreated and treated thyrotoxicosis and treated primary hypothyroidism³⁸. The mean plasma-calcitonin levels in each of these groups did not differ significantly from that found in healthy subjects. No correlation was found between the plasma-calcitonin concentration and the bone density⁴⁰.

It has been shown in dogs that increased calcium mobilization from bone in the hypoadrenal state is thyroxine dependent; thus, adrenalectomized dogs develop hypercalcaemia only in the presence of the thyroid gland. It may be possible that thyroxine is the factor causing increased calcium mobilization, with glucocorticoids in physiological concentrations inhibiting this action. Conversely, it has been suggested that glucocorticoid deficiency leads to release of calcium from bone either by direct action on bone cells or mediated by a decrease in pH in the presence of thyroxine which is necessary for maintenance of

normal bone cell activity. Vasikaran *et al*⁴¹ reported two patients with lymphocytic hypophysitis who had isolated corticotroph failure and secondary hypoadrenalism together with hyperthyroidism due to thyroiditis, and presented with hypercalcaemia. These clinical observations support the theory that thyroid hormone action is important in the aetiology of the hypercalcaemia of hypoadrenalism⁴¹.

Cases of renal tubular acidosis associated with thyrotoxicosis have been reported previously. The mechanism underlying this association is unclear. Various presentations are diabetes insipidus⁴², hypokalaemic paralysis⁴³ or nephrolithiasis⁴⁴, but worsening of bone mineral loss is also expected as calcium is released from bones for buffering of systemic acidosis and results in hypercalciuria.

Biochemical markers: Biochemical markers of bone and mineral metabolism are also affected. The serum concentrations of alkaline phosphatase, osteocalcin, and osteoprotegerin⁴⁵, and fibroblast growth factor-23 (FGF-23)⁴⁶ are increased in overt hyperthyroidism and may remain high for months after treatment, presumably due to a persistent increase in osteoblastic activity^{47,48}. Urinary excretion of bone collagen-derived pyridinium cross-links is increased, and falls to normal shortly after treatment⁴⁹.

Nodular goiter and Graves' disease with subclinical hyperthyroidism

Patients with subclinical hyperthyroidism have normal serum concentrations of free T4 and T3, but subnormal concentrations of thyrotropin (TSH). Any form of hyperthyroidism can be subclinical, but this disorder most commonly occurs in elderly patients with a multinodular goiter or, less often, mild Graves' disease.

Symptomatic bone disease is not a feature of subclinical hyperthyroidism. However, the following observations, strongly suggest otherwise: (i) Decreased forearm bone density, though still in normal range, correlating inversely with serum free T4 values has been documented in women with nodular goiter and subclinical hyperthyroidism⁵⁰. Post-menopausal women (but not pre-menopausal women) with nodular goiter and subclinical hyperthyroidism have also been reported to have reduced bone density in the radius and femoral neck, but not lumbar spine⁵¹, (ii) Post-menopausal women with subclinical hyperthyroidism treated with methimazole had higher distal forearm

bone density as compared with untreated women⁵², (iii) Post-menopausal women with subclinical hyperthyroidism treated with radioiodine and followed for two years did not lose bone from the spine or the hip, whereas untreated women lost bone at both sites⁵³, and (iv) Among patients with Graves' hyperthyroidism taking an anti-thyroid drug, those with subclinical hyperthyroidism had higher serum bone alkaline phosphatase concentrations and urinary pyridinoline excretion than those who were euthyroid⁵⁴.

Subclinical hyperthyroidism due to exogenous thyroid hormone therapy

Many patients treated with T4 have subclinical hyperthyroidism and some have increased bone resorption and reduced bone density. However, evidence for an increased rate of fractures in these patients is less convincing. Many cross-sectional studies^{5,55,56}, a few longitudinal studies^{57,58}, and two meta-analyses have found that patients with exogenous subclinical hyperthyroidism can have the same reduction in bone density as occurs in patients with endogenous subclinical hyperthyroidism, and that careful adjustment of the dose of T4 can minimize this risk.

Two early cross-sectional studies^{5,59} in pre-menopausal women demonstrated that suppressive doses of T4 resulted in reduced density of cortical-rich bone. In another study of 31 pre-menopausal women taking an average dose of 0.175 mg of T4⁶⁰, bone density of the femoral neck and trochanter, but not the lumbar spine, was reduced. However, with one exception⁶¹, other cross-sectional studies have failed to confirm reduced bone density in T4-treated pre-menopausal women^{55,62-67} or in men⁵⁶. The dose in most of these studies was lower than in the initial reports, and the annualized loss of femoral neck density in pre-menopausal women taking T4 significantly correlated with the dose⁶⁶. In another study, 41 women aged >65 yr who were taking T4 and had a serum TSH concentration of 0.1 mU/l lost no more bone over 5.7 yr than did those who were taking T4 but had a serum TSH concentration of 0.1 to 5.5 mU/l⁶⁸. In contrast, most studies have demonstrated that even moderate suppressive doses of T4 can cause bone loss in postmenopausal women^{55,61-64,69,70}. However, the clinical importance of minor reductions in bone density has been questioned⁷¹.

Longitudinal studies in patients receiving thyroid hormone replacement have also demonstrated variable bone loss^{57,58}. Two meta-analyses of the studies on bone density in patients with subclinical hyperthyroidism due

to T4 therapy have been performed^{72,73}. A significant reduction in bone density was found only in post-menopausal women, consistent with the findings in cross-sectional studies⁷¹, and another study also found a reduction in bone density in pre-menopausal women receiving replacement therapy⁷³.

There is a lack of information on the role of calcitonin deficiency^{63,74}. This is a potentially important factor, because surgery, radioiodine therapy, and chronic thyroiditis (which necessitate thyroid hormone replacement) reduce C-cell function. No study has satisfactorily separated the effect of calcitonin deficiency from that of concurrent T4 therapy.

Changes in several other measures of bone and mineral metabolism are also consistent with increased bone resorption in subclinical hyperthyroidism. For example, (i) Urinary excretion of bone collagen-derived pyridinium cross-links is increased in post-menopausal women⁷⁵, (ii) A negative correlation has been demonstrated between the serum osteocalcin and TSH concentrations⁷⁶, (iii) Serum carboxy-terminal-I-telopeptide (ICTP) concentrations are high more often than are serum osteocalcin concentrations in post-menopausal women taking suppressive doses of T4⁷⁷, (iv) Serum ICTP, urine N-terminal telopeptide of type I collagen, and serum osteocalcin were elevated in estrogen deficient post-menopausal women, but not in pre-menopausal women, when T4 dose was carefully titrated to prevent overzealous TSH suppression in patients with thyroid cancer⁷⁸, and (v) Whether patients taking T4 have an increased rate of fractures is uncertain. One study found an increased risk of hip and vertebral fractures in women with low serum TSH concentrations³². A population-based, case-control analysis of the risk of hip fractures in patients taking T4 found an increased fracture risk in men but not in women; serum TSH was not measured⁷⁹. However, in a study of 1180 patients taking T4, 59 per cent had a low serum TSH concentration⁸⁰. An interview study of 330 women taking T4 found no increase in fracture rate⁸¹.

Prevention and treatment of reduced bone density:

There are several measures that may prevent loss of bone density, such as titration of suppressive therapy to maintain a slightly low serum TSH concentration (e.g. between 0.1-0.5 mU/l), calcium supplementation, estrogen replacement therapy while keeping an eye on the adverse effects (Women's Health Initiative study)⁸², and inhibitors of bone resorption (bisphosphonates or calcitonin). Guo *et al*⁸³ demonstrated the benefit

of titrating T4 dose in patients on replacement/suppressive dose of T4. Both lumbar and femoral bone density increased, and serum osteocalcin and urinary excretion of bone collagen-derived pyridinium cross-links decreased when the T4 dose was reduced in post-menopausal women whose initial serum TSH concentration was low.

Many groups have recommended that patients with thyroid cancer maintain very low serum TSH concentrations (less than 0.01 mU/l). However, in one report serum thyroglobulin concentrations did not fall further when serum TSH was suppressed below 0.1 mU/l⁸⁴. The serum osteocalcin concentration is inversely proportional to the serum TSH concentration⁷⁶, and to bone density⁸⁵ in overt hyperthyroidism.

Adequate dietary calcium intake is essential to ameliorate the adverse effects of thyroid hormone on bone. In a study of 46 post-menopausal women taking suppressive doses of T4, those taking placebo had 5 to 8 per cent reductions in bone density over a two-year period, while those given 1000 mg of calcium daily had no measurable bone loss⁸⁶.

Estrogen replacement therapy is protective when co-administered with thyroid hormone. In one study, significant reductions in bone density were found in women taking thyroid hormone, if the T4-equivalent dose was greater than 1.6 µg/kg, but not at lower doses⁸⁷. However, post-menopausal women who also were taking estrogen replacement therapy had no bone loss.

Treatment with inhibitors of bone resorption may be useful in patients with continuing bone loss. In short-term studies pamidronate reduced thyroid hormone-mediated increase in measures of bone turnover^{88,89}. Calcitonin reduced urinary hydroxyproline excretion and serum calcium in patients with overt hyperthyroidism⁹⁰. However, intranasal calcitonin with calcium supplements was no more effective than calcium supplements alone in preventing loss of bone density⁸⁶, and the improvement in bone density during treatment of overt hyperthyroidism was not augmented by administering intranasal calcitonin⁹¹.

T4 replacement therapy

Bone loss would not be expected to occur when hypothyroidism is treated with oral T4 and the serum TSH concentration does not go below the reference range (i.e. if subclinical hyperthyroidism is avoided). In a cross-sectional study, 50 women with primary or

radioiodine-induced hypothyroidism receiving long-term T4 therapy had no change in femoral neck or spine bone density²⁴. In a longitudinal study, 44 children with congenital hypothyroidism treated and followed for an average of 8.5 yr had no change in their bone mineral density and did not differ compared to that of age-matched normal subjects⁹².

Overtly hypothyroid women^{4,93} treated with T4 for six to 12 months showed a decrease in bone density, although this was not observed in men^{94,95}. Hypothyroidism, however, is associated with an increase in bone density. A cross-sectional histomorphometric study using iliac crest biopsies compared 10 untreated hypothyroid patients with 15 patients receiving thyroid hormone for six months; bone density was lower in the treated patients⁹⁶. The untreated hypothyroid patients had a mean cortical width that was higher than that of euthyroid subjects. During this period of increased resorption (continuing for two years after initiating T4 therapy) fracture risk may be increased⁹⁷.

Treatment of subclinical hypothyroidism

If the loss in bone density during the early treatment of hypothyroidism is due to an increase in remodelling and osteoclast resorption followed by an eventual return to steady-state conditions, one would not expect a similar reduction in bone density when T4 was administered to patients with subclinical hypothyroidism. Normalization of serum TSH concentrations in post-menopausal women with subclinical hypothyroidism was not found to be associated with a reduction in bone density⁹⁸; however, another study documented increased parameters of bone turnover and a 1.3 per cent reduction in bone density after 48 wk of thyroxine treatment⁹⁹.

In one cross-sectional study pre-menopausal hypothyroid women with Hashimoto's thyroiditis were treated with an average dose of 0.111 mg per day of T4 for an average of 7.5 yr¹⁰⁰. Serum TSH concentrations were normal throughout the study. The density of the femoral trochanter was reduced by 7 per cent, but there was no change in the density of the lumbar spine. This study suggested that T4 replacement therapy might be sufficiently nonphysiologic and could be associated with increased bone turnover.

There is currently little information regarding deiodination of T4 to T3 within bone. It is possible that bone could be responding to the higher serum T4 concentrations achieved with T4 replacement. In support of this hypothesis, a meta-analysis

demonstrated reduced bone density in pre-menopausal women receiving replacement T4 therapy but not in post-menopausal women⁷³.

Euthyroid patients

Bone density may be sensitive to thyroid hormone concentrations within the normal range. As an example, in a cross-sectional study of 959 post-menopausal women, bone density in the lumbar spine and femoral neck was 3 to 4 per cent lower in patients with TSH 0.5 to 1.1 mU/l compared to patients with TSH 2.8 to 5.0 mU/l¹⁰¹.

Indian data

There is a paucity of data from Indian subcontinent regarding the effect of thyrotoxicosis on bone. Udayakumar and colleagues¹⁰¹ found that 46 of 50 patients had low BMD. Based on the World Health Organization classification¹⁰², 16 patients had osteopenia and 30 had osteoporosis. After control of thyrotoxicosis, the mean bone mass increased from 0.729 to 0.773 g/cm² in one year, compared to age- and sex-matched controls. The drawback of this study was young age of the participants (29.4 yr, 14-38 yr, range) and hence majority were yet to achieve peak bone mass before getting a label of osteoporosis. Also, the vitamin D level was not available. In the context of vitamin D deficiency prevalent in Indian subcontinent¹⁰³⁻¹⁰⁶, this could have a deleterious effect on bone mineral homeostasis. Peak bone mass in Indians is low, reflecting low bone mineral density¹⁰⁷. Dhanwal *et al*¹⁰⁸ compared the effect of vitamin D deficiency on BMD in thyrotoxicosis patients. They showed that hyperthyroid patients with concomitant vitamin D deficiency had lower BMD compared with vitamin D-sufficient patients.

Conclusions

Loss of bone density and elevation of markers of bone resorption is common in thyrotoxicosis. After control of thyrotoxicosis partial recovery takes place. Treatment with anti-resorptive agents results in a better recovery. Similar phenomenon is seen during replacement therapy of patients with overt and subclinical hypothyroidism. Even euthyroid patients with lower TSH values have been shown to have a lower bone density than those with high normal TSH.

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