Effect of Thyroid Disorders on Skeletal Health

Tiroid Hastalıklarının İskelet Sağlığına Etkisi

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Abstract

Thyroid physiology is linked to skeletal health. T3 and TSH independently affect bone growth and development, mineralization and remodeling. Thyrotoxicosis, a clinical syndrome characterized by excess thyroid hormone is one of the commonly recognized conditions of the thyroid gland. Thyrotoxicosis causes accelerated bone remodeling and serves as one of the risk factors for osteoporosis. Treatment of thyrotoxicosis leads to reversal of bone loss and decreases fracture risk. Though treatment of thyrotoxicosis leads to improvement of bone mineral density (BMD), it is not necessarily to normal levels. The effects of subclinical hyperthyroidism on the bone are controversial. Thyroidectomy and methimazole may decrease the risk of fractures in these patients compared with treatment with radioiodine. Hypothyroidism may also be risk factor for fractures. Replacement therapy with levothyroxine in hypothyroid patients may temporarily reduce bone density after initiation of therapy. However it is not associated with osteoporosis or increased fracture risk. TSH suppressing doses of levothyroxine may reduce BMD, especially in post menopausal women. Supplementation of calcium and vitamin D in hyperthyroid patients should be considered. There are limited studies in India pertinent to reversibility of these changes. In this review, we have discussed about the effects of various aspects of skeletal health in thyroid disorders *Turk Jem 2012; 16: 19-25*

Key words: Thyroid, skeletal health, levothyroxine, bone mineral density

Özet

Tiroid fizyolojisi, iskelet sağlığı ile ilişkilidir. T3 ve TSH, kemiğin oluşumunu, gelişimini, mineralizasyonunu ve yeniden yapılandırılmasını bağımsız olarak etkilemektedir. Tiroid hormon fazlalığı ile karakterize bir klinik sendrom olan tirotoksikoz, tiroid bezinde sık görülen durumlardan biridir. Tirotoksikoz, kemiğin yeniden yapılanma sürecinde hızlanmaya yol açarak, osteoporoz için bir risk faktörü teşkil etmektedir. Tirotoksikozun tedavisi ile kemik mineral yoğunluğunda (KMY) iyileşme olmakla birlikte, her zaman normal düzeylere dönüş olmamaktadır. Subklinik hipertiroidinin kemik üzerine etkileri ise tartışmalıdır. Bu hastalarda tiroidektomi ve metimazol tedavisi, radyoaktif iyot tedavisine kıyasla, kırık riskinde azalma sağlayabilmektedir. Hipotiroidi de kırıklar için risk faktörü olabilmektedir. Hipotiroidili hastalarda levotiroksin ile replasman tedavisi, tedavi başlangıcından sonra KMY'nda azalmaya yol açabilir. Fakat bu durum, osteoporoz ya da artmış kırık riski ile ilişkili değildir. Levotiroksinin TSH'yı baskılayıcı dozları, başta postmenapozal kadınlarda olmak üzere, KMY'nu azaltabilir. Hipertiroidik hastalarda kalsiyum ve D vitamini desteği göz önüne alınmalıdır. Hindistan'da, bu değişikliklerin geri dönüşümlü olup olmadığına dair sınırlı sayıda çalışma bulunmaktadır. Bu derlemede, tiroid hastalıklarının iskelet sağlığının çeşitli yönlerine etkileri tartışılmıştır. *Türk Jem 2012; 16: 19-25*

Anahtar kelimeler: Tiroid, iskelet sağlığı, levotiroksin, kemik mineral yoğunluğu

Introduction

Thyroid hormone plays a key role in skeletal development, acquisition of peak bone mass and regulation of adult bone turnover. Euthyroid status is essential for maintenance of optimal bone mineralization and strength. The adverse effects of hyperthyroidism on the skeleton were known before the advent of satisfactory treatment of hyperthyroidism. The relationship between thyroid and skeleton was first suggested in 1891 when Von Recklinghausen reported a patient with hyperthyroidism and multiple fractures (1). While the clinical consequences of overt hyperthyroidism on bone have been known for many years, the molecular mechanism of action of thyroid hormone on bone is

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incompletely understood. Early recognition of thyroid diseases and an effective treatment for clinical symptoms have meant that severe bone loss is now not seen commonly. Data from India is sparse regarding the effects of thyroid disorders on bone and mineral metabolism

Bone Effects of Thyroid Hormone

Thyroid hormone directly stimulates bone resorption in organ culture (2). This action is mediated by nuclear triodothyronine (T3) receptor, which is found in osteoblast and osteoclast cell lines (3). The 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 resorption (4). Monocarboxylate Transporter 8 (MCT8) protein is expressed in growth plate chondrocytes, osteoblasts and osteoclasts. Type 1 deiodinase (D1) enzyme is not expressed in bone. D3 is expressed widely with the highest levels occurring in growth plate chondrocytes. D2 mRNA is expressed in embryonic mouse skeleton at embryonic day (E) 14 and increases until E 18 (5). Both thyroid hormone receptor-alpha 1 (TR α1) and thyroid hormone receptor-beta 1 (TR β 1) isoforms are expressed in bone (growth plate chondrocytes, bone marrow stromal cells, osteoblasts and osteoclasts), with TR α 1 levels being 10 fold more than TRβ1 (6). TRα1 is the predominant mediator of T3 actions on bone.

In the skeleton, thyroid-stimulating hormone (TSH) exerts direct action on TSH receptors present on osteoblasts and osteoclasts (7). TSH seems to inhibit bone turnover by suppressing both osteoblast and osteoclast activity. T3 regulates chondrocyte proliferation, promotes terminal differentiation, and induces mineralization and angiogenesis (8).Thyroid hormones stimulate production of type II and X collagen and alkaline phosphatase. T3 seems to induce chondrocyte differentiation, hypertrophy and angiogenesis, but TSH also may play a complementary role in normal mineralization. However, bone loss appeared independent of TSH levels in mice lacking specific TR isoforms (9). Increased serum interleukin-6 (IL-6) concentrations in hyperthyroid patients may also play a role in thyroid hormone stimulated bone loss (10). IL-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 remodeling, reduced bone density, osteoporosis, and an increase in fracture rate. These changes are associated with negative calcium balance, hypercalciuria, and, rarely, hypercalcemia.

1. Bone Density

Bone loss is a uniform feature of overt hyperthyroidism. Studies of iliac crest bone biopsy reveal important differences in the effects of thyroid hormone on trabecular and cortical bone (11). Hyperthyroid patients had only a 2.7% reduction in trabecular bone volume, but there was a 40% increase in osteoclast resorption surfaces in cortical bone and a 32% increase in cortical bone porosity (11). (in the study of Douglas S Ross, MD/IE)There was no change in the osteoid volume in hyperthyroidism. Three-dimensional reconstruction of the remodeling sequence shows that in overt hyperthyroidism, bone resorption and formation are both are accelerated, but osteoclastic resorption is stimulated out of proportion to osteoblastic mineralization (12). The duration of resorption phase is reduced by 60% and the formation phase is shortened by 30%. As a result, the normal cycle duration of approximately 200 days is halved and each cycle is associated with a 9.6% loss of mineralized bone. In contrast, there is 2-fold increase in duration of osteoclastic resorption and 4-fold prolongation of osteoblastic bone formation and secondary bone mineralization in hypothyroidism (13). Cycle length approximates 700 days with 17% increase in mineralized bone.

Most studies on hyperthyroid patients show a reduction in bone density ranging from 10% to 20%. The studies on extent of reversibility of bone loss with therapy have yielded variable results. Two studies using single photon absorptiometry reported a reduction in bone density of 12-28% in hyperthyroid patients which normalized after treatment (14, 15). A cross sectional study (16) of 164 hyperthyroid women found reductions in bone density during the first 3 years after diagnosis and treatment. Three or more years after the diagnosis, bone disease was no different from controls, suggesting that the decrease in bone density was reversible. Two retrospective Danish studies observed no difference in 55 hyperthyroid patients, who were treated surgically and had been euthyroid for at least 6 years (mean-12.5 years) (17) or in 39 hyperthyroid patients who were treated medically and had been euthyroid for at least 4 years (mean-9.8 years), compared to age- and sex-matched normal subjects (18).

A study (19) found that bone density of 25 T4-treated women who had received radioiodine therapy for hyperthyroidism did not differ from 25 comparable women with primary hypothyroidism receiving T4 treatment. Other studies reported a 12-13% reduction in bone density of lumbar spine in hyperthyroid patients, with only 3.7-6.6% increases in bone density after one year of treatment (20,21). Greater improvement in bone mineral density (BMD) was reported when hyperthyroid women were treated with both alendronate and methimazole versus methimazole alone (22).

2. Fracture Risk

It is known that, untreated hyperthyroidism causes severe osteoporosis and pathologic fractures. Hip fracture in later life is a possibility (23) adding to the causes of excess mortality (24). It leads to the assumption that, in some hyperthyroid patients, BMD does not return to normal after antithyroid treatment. There are studies both for and against the idea of fractures in hyperthyroidism. In a retrospective study of 621 patients (25), patients treated with radioiodine had increased risk of spine and forearm fractures, especially in age group 50 years or older. Interestingly, the risk was not increased in patients treated with methimazole. Another study (26) showed that, relative risk of any fractures increased 1.5-fold in thyroidectomized patients versus controls and there was a statistically significant excess of proximal femur fractures in the men with thyroidectomy. A study on thyroidectomized women (27) reported no increase in overall fracture risk relative to incidence rates in the community, though there was a modest but significant increase in hip fracture and 3-fold increase in vertebral fractures.

In another study (28) involving both hyperthyroid and hypothyroid patients, fracture risk in hyperthyroid patients was shown to be increased around the time of diagnosis, which decreased to normal levels after diagnosis. Surgical treatment of hyperthyroidism was associated with decreased fracture risk. However, the hypothyroid patients showed increased fracture risk both before and after diagnosis with a peak around the time of diagnosis. A prospective cohort study (29) investigated the effect of low serum TSH

concentrations on the fracture risk. Women with serum TSH concentrations of 0.1 mU/L or less at baseline were at increased risk for both hip and vertebral fractures. Exogenous thyroid hormone therapy was not a risk factor for fracture in women with normal TSH concentrations but a history of hyperthyroidism was a definite risk factor for hip fracture.

It seems that history of previously treated hyperthyroidism may impose a higher long-term risk for fractures. In hyperthyroid patients, thyroidectomy and the use of antithyroid drug, especially methimazole before definitive treatment, may decrease the risk of fractures in these patients.

3. Symptomatic Bone Disease

Older studies have documented the potential for symptomatic bone disease in association with reduced BMD. In a study of 187 hyperthyroid patients (11), 15 (8%) had symptoms. All patients were women, with 80% > 50 years of age, 75% had hyperthyroid for less than 1 year, and two thirds had a fracture or severe bone pain. Radiographic studies demonstrated generalized osteoporosis with frequent vertebral compression fractures or hypertransluscency of the spine.

In hyperthyroidism, subclinical vitamin D deficiency may get precipitated into an overt form, leading to osteomalacia. Thyrotoxicosis and osteomalacia can independently give rise to proximal myopathy in 61% and 50% cases respectively. Both disorders may coexist demanding clinical suspicion and biochemical confirmation (30).

In prepubertal children, there is accelerated growth and bone maturation leading to advanced bone age, premature fusion of the growth plates, short stature, and craniosynostosis. This may be explained by the fact that prepubertal bone maturation is affected by growth hormone (GH) and thyroid hormone, whereas at puberty it is mainly influenced by sex hormones. In adults, there is high bone turnover osteoporosis and increased fracture risk.

4. Mineral Metabolism

The increased calcium release into circulation resulting from increased bone resorption leads to negative calcium balance in hyperthyroid patients (31) (Figure 1).

• Hypercalcemia with increase in serum ionized calcium concentration occurs in 8% of patients (32). This suppresses PTH secretion leading to hypercalciuria and further negative calcium balance.

• Skeletal hyper responsiveness to catecholamines leads to hypercalcemia and hypercalciuria. This can be reversed partially by high-dose beta blockers (33).

• Low serum PTH concentration reduces the conversion of 25-hydroxyvitamin D (calcidiol) to calcitriol (34). Hyperthyroidism per se induces calcitriol metabolism (35).

• Low serum calcitriol concentrations diminish intestinal calcium and phosphorous metabolism, resulting in fecal calcium loss. Increased gut motility and steatorrhea aggravate malabsorption of calcium (36).

• Thyroxine may be the factor that promotes calcium mobilization from bone, which is inhibited by glucocorticoids in physiological concentration. Conversely, glucocorticoid deficiency leads to release of calcium from bone either by direct action on bone cells or mediated by a pH decrease in the presence of thyroxine which is necessary for maintenance of normal bone cell activity. It explaines the fact that in hypoadrenal dogs, calcium mobilization from bone is thyroxine dependent and adrenalectomized dogs develop hypercalcemia only in the presence of thyroid gland. Previous reports of patients with secondary hypoadrenalism due to lymphocytic hypophysitis and thyrotoxicosis due to thyroiditis demonstrated hypercalcemia (38). These observations suggest that thyroid hormone action is necessary in the etiopathogenesis of hypercalcemia in hyopoadrenalism.

• In a study (37), no correlation was observed between plasma calcitonin concentration and BMD.

• Cases of thyrotoxicosis associated with renal tubular acidosis (RTA) have been reported (39). Three of those had hypokalemic periodic paralysis caused by distal RTA. The mechanism is unclear.

5. Biochemical Markers of Increased Bone Loss

The increased calcium release into circulation resulting from increased bone resorption leads to negative calcium balance in hyperthyroid patients (31) (Figure 1).

Subclinical Hyperthyroiddism

Subclinical hyperthyroidism in most cases is endogenous. It most commonly occurs in elderly patients with a multinodular goiter or less often in those with mild Graves' disease. It can be due to exogenous supply of suppressive doses of thyroid hormone therapy.

1. Endogenous Subclinical hyperthyroidism

Symptomatic bone disease is not a feature of endogenous subclinical hyperthyroidism.

• A prospective cohort study (44)of 458 women over age 65 years demonstrated similar bone loss over 4-6 years in patients with low, normal or high TSH levels However, there were studies negating this view.

• Decreased forearm bone density correlating inversely with serum free T4 values were documented in women with nodular goiter and subclinical hyperthyroidism (45). Postmenopausal women with nodular goiter and subclinical hyperthyroidism had reduced BMD at the radius and femoral neck, but not in the lumbar spine (46).

• Another study (47) compared 30 premenopausal and 30 postmenopausal women with subclinical hyperthyroidism due to multinodular goiter versus 60 healthy women. A significant decrease was found in femoral BMD in pre and post menopausal women compared to controls, with greater decline in

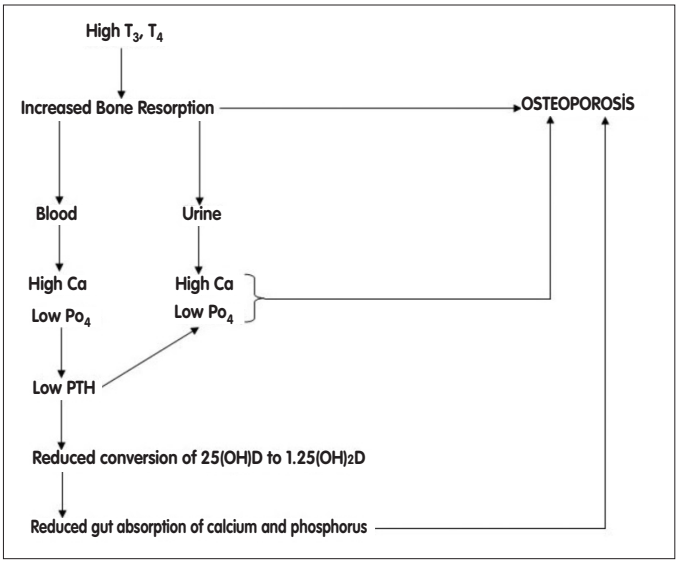

Figure 1. Effect of hyperthyroidism on bone and mineral metabolism

postmenopausal women. Lumbar BMD was decreased only in postmenopausal women.

• Postmenopausal women with subclinical hyperthyroidism treated with methimazole had higher distal forearm BMD compared to untreated women (48). Older age with lower serum TSH values and higher prevalence of osteoporosis was found in 49 women in an observational study involving a total of 130 postmenopausal women (49).

• Postmenopausal women with subclinical hyperthyroidism treated with radioiodine and followed for 2 years did not lose bone from spine or hip, where as untreated women lost bone at both sites (50).

• Among patients with Graves' disease taking an antithyroid drug, those with subclinical hyperthyroidism had higher serum bone ALP and urinary pyridinoline excretion than those who were euthyroid (51).

• In another recent study (52) involving 2374 postmenopausal women, the risk of nonvertebral fracture was increased by 20% and 33% in women with higher fT3 and fT4, respectively, whereas higher TSH was protective and the risk was reduced by 35%.

2. Exogenous Subclinical Hyperthyroidism

Many patients treated with T4 have subclinical hyperthyroidism and some have increased bone resorption and reduced BMD. However, evidence is less convincing. Many studies have found that patients with exogenous subclinical hyperthyroidism can have same reduction in BMD as occurs in patients with endogenous subclinical hyperthyroidism and careful adjustment of T4 dose can minimize this risk.

Two early cross-sectional studies of premenopausal women demonstrated reduced cortical bone density with suppressive doses of T4. In a study (53), 28 premenopausal women taking an average T4 dose of 0.175 mg showed 5% and 9% reduction in wrist BMD at 5 years and 10 years, respectively (53). In other study (54), 31 premenopausal women receiving 0.175mg T4 showed decreased BMD at femoral neck and trochanter, but not at lumbar spine.

In a metaanalysis of 13 cross-sectional studies involving female patients on suppressive doses of T4 (55), no significant bone loss was detected in premenopausal women, but a 0.91% per year excess bone loss was observed in post menopausal group compared with normal individuals. However, with one exception of a cross sectional study (56), another metaanalysis of 41 cross sectional studies (57) concluded that suppressive T4 therapy caused significant bone loss at the lumbar spine and hip in postmenopausal women but had no significant effect on premenopausal women or men. The annualized loss of femoral neck BMD in premenopausal women taking T4 significantly correlated with the dose (58). In another report (59), women over 65 years of age, who were taking T4 and had TSH-0.1 mU/L lost no more bone over 5.7 years than did those who were taking T4 but had a serum TSH- 0.1 -5.5 mU/L.

In contrast, more studies have demonstrated that even moderate suppressive doses of T4 can cause bone loss in postmenopausal women (60, 61). However, this is not a uniform finding (62) and others have questioned clinical importance of minor reductions in bone density (63). Serum carboxyl-terminal-I-telopeptide (ICTP) concentrations are high more often than are serum osteocalcin concentrations in postmenopausal women taking suppressive doses of T4 (64) with a negative correlation between the serum osteocalcin and TSH concentrations (65).

An important caveat affecting the interpretation of these studies is the lack of information on the role of calcitonin deficiency (66). This is a potentially important factor, because surgery, radioiodine therapy and chronic thyroiditis reduce C-cell function. None of the studies have satisfactorily separated the effect of calcitonin deficiency from that of concurrent T4 therapy.

Two retrospective studies opposing the concept of increased fracture risk in women taking T4 were published. A study involved 1180 women over age 65 years, showed insignificant increase in overall fracture risk over 5 years in those with low serum TSH levels (67). Another interview study of 330 women taking T4 found no increase in fracture rate.

Prevention and Treatment of Reduced Bmd

There are several therapeutic measures aimed at prevention of bone loss

• Titration of suppressive therapy to maintain a slightly low serum TSH concentration (0.1-0.5 mU/L)

• Calcium supplementation

• Estrogen replacement therapy (68)

• Inhibitors of bone resorption: bisphosphonates or calcitonin

In a study, (68) when the T4 dose was reduced in postmenopausal women with low initial low serum TSH, BMD increased at the lumbar spine and femur with simultaneous reduction of serum osteocalcin and urinary excretion of bone-collagen derived pyridinium cross-links. More studies are needed to better define the degree of TSH suppression necessary to achieve the desired goal with T4 suppressive therapy. Many authors have recommended that patients with thyroid cancer maintain very low serum TSH concentrations (<0.01 mU/L). However, in a report, serum thyroglobulin concentrations did not fall further when serum TSH was suppressed below 0.1 mU/L (69).

There are studies on calcium supplementation, bisphosphonates, estrogen replacement, and calcitonin to prevent accelerated osteoporosis caused by hyperthyroidism. In a study of 46 postmenopausal women taking suppressive doses of T4 (70), those taking placebo had 5-8% reduction in BMD over a 2-year period, while those taking 1000 mg calcium daily had no measurable bone loss. Women taking >1.6µg/kg T4 had significant reduction in BMD, but not at lower doses (71). However, postmenopausal women receiving estrogen replacement therapy had no bone loss. Adding hormone replacement therapy (HRT) to T4 suppressive therapy resulted in significantly higher BMD at the femur and lumbar spine of postmenopausal women (72).

Studies have elucidated the efficacy of bisphosphonates such as alendronate (73), risendronate (74) and pamidronate (75) in terms of increased BMD, reduced markers of bone turnover when used along with antithyroid medications. Calcitonin was found to increase BMD and reduce urinary hydroxyproline excretion when used along with antithyroid medications (76). However, intranasal calcitonin with calcium supplements was no more effective than calcium supplements alone in preventing loss of bone density (70) and the improvement of BMD was not augmented by administering intranasal calcitonin (77).

Hypothyroidism and Bone Loss

Despite normal bone density, patients who have hypothyroidism may be at a higher risk for fractures. The greater risk does not seem to be related to be a deleterious effect from the use of levothyroxine replacement. The mechanism for possible impaired bone strength in hypothyroid patients is unknown.

In a study involving 408 patients with primary idiopathic levothyroxine substituted hypothyroidism (78), overall fracture risk was increased in patients >50 years compared to controls and was limited to forearms. This increase was temporary and limited to period within first 2 years after the diagnosis of hypothyroidism. Another study involving 413 women (79) demonstrated that femoral neck BMD was significantly reduced both in subclinical hyperthyroid group and in subclinical hypothyroid group compared to euthyroid group. In contrast, lumbar BMD showed no difference between the groups.

1. Replacement Doses of Levothyroxine and BMD

Bone loss would not be expected to occur when hypothyroidism is treated with oral T4 and the serum TSH concentration goes below the reference range. In a cross-sectional study (19), 50 women with primary or radioiodine-induced hypothyroidism receiving long term T4 therapy had no change in femoral neck or spine density. In a longitudinal study (80), 44 children with congenital hypothyroidism treated for 8.5 years had no change in their BMD and BMD did not differ from that of age-matched normal subjects. In a cohort of 124.655 patients (with a fracture) from Denmark, no effect of T4 therapy on fracture risk was observed (81). In another study (67), thyroxine replacement was not associated with an increase in risk for overall fracture. Another study involving primary hypothyroidism patients receiving T4 for more than 5 years (82) showed no difference between controls and patients in regional or total BMD. Longitudinal studies have also demonstrated variable effects of thyroid hormone replacement on bone loss (83, 84) Overtly hypothyroid women treated with T4 for 6-12 months have a decrease in BMD (85), although this seems not to be so for men (86). Hypothyroidism, however, is associated with an increase in BMD. Patients receiving thyroid hormone for 6 months had lower BMD than untreated patients with the mean cortical width being higher in untreated patients than that of euthyroid subjects (87).

2. Treatment of Subclinical Hypothyroidism

If the loss in BMD during the early treatment of hypothyroidism is due to an increase in remodeling and osteoclast resorption followed by an eventual return to steady conditions, then one would not expect a similar reduction in BMD when T4 was administered to patients with subclinical hypothyroidism.

In a study (88), normalization of serum TSH concentrations in postmenopausal women with subclinical hypothyroidism was not associated with a reduction in BMD, however, another study (89) documented increased parameters of bone turnover and 1.3 5(1.3%) reduction in BMD after 48 weeks of T4 therapy. A cross sectional study (90) involving 26 premenopausal hypothyroid women with Hashimoto's thyroiditis, who were treated with an average dose of 0.111 mg/day T4 for an average of 7.5 years, observed that with normal TSH concentrations throughout the study, density of femoral trochanter was reduced by 7% without any change in lumbar spine. This study suggested that T4 replacement therapy may be sufficiently nonphysiologic that it 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 recent meta-analysis demonstrated reduced BMD in premenopausal women receiving T4 therapy but not in postmenopausal women (57).

Thyroid Cancer and Bone Metastasis

In papillary thyroid cancer (PTC), bone metastases occur in fewer than 2% of patients. In follicular thyroid cancer, metastases to bone occur in 7%-20% of cases. These osseous metastases are poorly differentiated resulting in poor prognosis with a mean survival estimated at 4 years (82). Thyroid cancers most commonly metastasize to vertebral bodies resulting in lytic bone lesions. However, long bones, the pelvis and skull can be involved. I-131 scanning has poor sensitivity in detection of distant metastasis. Radiographs and bone scintigraphy often detect the disease only after more than 50% of the bone is destroyed. Bone scintigraphy often detects skeletal metastases earlier if there is a significant osteoblastic component. Computed tomography is valuable in imaging for cortical erosion and subclinical fracture in osseous metastases, where as magnetic resonance imaging is for medullary component of bone and detailing the intraosseous and extraskeleton extent of disease. In a study on 19 patients to compare different imaging modalities (91), positron emission tomography (PET) detected 81.3%, Methoxyisobutyl Isonitrile (MIBI) scan detected 62.5% and I-131 detected 68.8% of total lesions. PET was found to be superior to Tc-MIBI and I-131 scan in detecting distant spread. Lung metastases were detected in 73.3%, 46.7% and 66.7% of cases, respectively. The 3 imaging modalities were comparable in detecting bone metastases, all detecting about 83% of lesions.

In another study involving patients with carcinoma thyroid (92), serum ICTP, urine N-terminal telopeptide of type 1 collagen and serum osteocalcin were elevated in estrogen deficient postmenopausal women, when T4 dose was carefully titrated to prevent overzealous TSH suppression in patients with thyroid cancer.

Indian Data

There is paucity of data in Indian subcontinent. In a study from Chennai involving 50 hyperthyroid patients with a mean age of 29.4 years, 46 had bone involvement (92%)(93). 16 (32%) patients had osteopenia and 30 (60%) had osteoporosis. 30 (60%) had Graves' disease and 20 (40%) had multinodular goiter. Forty-four (88%) were treated with subtotal thyroidectomy and 6 (12%) were treated with radioactive iodine. After control of thyrotoxicosis, the mean BMD increased from 0.729 g/cm^2 to 0.773 g/cm^2. The drawback of this study was that the mean age of the patients was 29.4 years and hence majority was yet to achieve peak bone mass before getting a label of osteoporosis. The vitamin D levels also were unavailable. Because in the background of vitamin D deficiency which is prevalent in Indian subcontinent (94), this could have deleterious effects on bone mineral homeostasis. Vitamin D Deficiency what could have?

Dhanwal et al. (95), compared the effects of vitamin D deficiency on BMD in thyrotoxic patients. They found that in vitamin D-deficient group, the mean BMD T-scores were in the osteoporotic range at hip and forearm (-2.65±1.13 and -3.04±1.3) and in the osteopenia range at lumbar spine (-1.83±1.71). However, in vitamin D-sufficient group, the mean BMD-T-scores were in the osteopenia range (-1.64±1.0, -1.27±1.6, -1.60±0.7) at hip, forearm and lumbar spine, respectively. The mean BMD-Z scores were also significantly lower in vitamin D-deficient group compared with those in vitamin D-sufficient group. Finally, BMD values (g/cm2) at the hip and forearm were significantly lower in vitamin D-deficient group compared with those in vitamin D-sufficient group. This study showed that hyperthyroid patients with concomitant vitamin D deficiency had lower BMD compared with vitamin D-sufficient patients.

Conclusion

T3 and TSH independently affect bone growth and development, mineralization and remodeling. Previously treated hyperthyroidism is likely a long-term risk factor for fractures. Thyroidectomy and methimazole may decrease the risk of fractures in these patients compared with treatment of radioactive iodine. Hyperthyroidism may also be a risk factor for fractures, but the same is not related to thyroxine replacement in hypothyroid patients. TSH suppressing doses of levothyroxine may reduce BMD in postmenopausal women. Supplementation of calcium and vitamin D in hyperthyroid patients should be considered.

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