REVIEW ARTICLE

Bone mineral metabolism in thyrotoxicosis

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ABSTRACT

Thyrotoxicosis is an important reversible cause of osteoporosis. Different studies from west have reported bone loss including osteopenia and osteoporosis in patients with active hyperthyroidism and subclinical hyperthyroidism. In fact osteopenia /osteoporosis is a risk in patients of hypothyroidism on replacement therapy. Metabolic bone homeostasis abnormalities in these patients with hyperthyroidism include hypercalcemia which is due to increased bone resorption, normal to elevated phosphorous and elevated alkaline phosphatase levels. PTH levels are usually depressed due to hypercalcemia. But the situation is different in India due to widespread vitamin D deficiency. There is scarcity of data from India. Only few published reports have shown osteopenia or osteoporosis in these patients which recovers partially after treatment with antithyroid agents, surgery or radioiodine therapy. Recently in a study we have observed that almost 30% patient with hyperthyroidism have concomitant vitamin D deficiency. In this study we have showed that Indian patients with hyperthyroidism do not have hypercalcemia, and bone as represented by bone density is more as compared to western patients. This has been attributed to coexisting vitamin D deficiency in these patients with thyrotoxicosis. But more studies are needed to confirm these findings and also to see the effect of vitamin D supplement in these patients. This article reviews the bone mineral homeostasis and bone mineral density in patients with hyperthyroidism with review of some of the Indian studies.[IJEM 2007;11(1&2):33-36]

Key words: Thyrotoxicosis, osteoporosis, vitamin D deficiency, Metabolic bone disease, bone density.

INTRODUCTION

Graves' disease is a common endocrine disorder. Patients with active Graves' disease have widespread systemic manifestations involving all organ systems such as CNS, respiratory, cardiovascular, reproductive, gastrointestinal and skeletal system. The effects are due to the metabolic actions of excess thyroid hormones. Patients with Graves' disease in India present with severe thyrotoxicosis, late in their clinical course and with unique clinical fetures (1-4). Recently, Goswami and coworkers have reported widespread vitamin D deficiency in healthy individuals residing in Delhi due to skin pigmentation and poor sunlight exposure (5). Patients with Graves' disease in India have marked proximal muscle weakness due to skeletal muscle myopathy. Majority of patients have increased skin pigmentation during thyrotoxic state (6). Thyroid hormones have direct catabolic effect on bone mineral homeostasis leading to increased bone mineral resorption and calcium loss through kidneys (7). Increased skin pigmentation and related vitamin D deficiency coupled with excessive urinary calcium loss, caused by thyrotoxicosis, may well be responsible for causing significant abnormalities in bone mineral homeostasis in thyrotoxic patients in India. Negative calcium balance due to catabolically induced increase in bone resorption may also be operative in Indian thyrotoxic patients. This article is to review the bone mineral homeostasis and bone mineral metabolism in patients with hyperthyroidism with Indian context.

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Regulation of normal bone mineral homeostasis

Bone mineral homeostasis is predominantly controlled by three hormones i.e. PTH, 1,25 (OH)2 D and calcitonin (8). These hormones act on three target tissues i.e. Bone, intestine and kidney. There is a close interaction among PTH, 1,25(OH)2D and calcitonin to regulate serum calcium, phosphorous, and magnesium levels through actions on target tissues. In skin ultraviolet light (wave-length of 290-315 nm) converts 7- dehydrocholestrol, a precursor of cholesterol to vitamin D3 (9). Vitamin D3 is metabolised in the liver to 25(OH) D by 25- hydroxylase enzyme and ?then in kidneys to its active form 1,25 (OH)2 D by 1- hydroxylase enzyme (9). Serum 25(OH) D has longer half life of 21 days and is measure of vitamin D nutritional status. 1,25 (OH)2 D stimulates calcium absorption in gut, and also regulates bone turnover and renal excretion of calcium and phosphorous (9). The net effect of 1,25 (OH)2 D is to raise serum calcium while decreasing PTH. Serum calcium and 1,25 (OH)2 D levels regulate PTH secretion from parathyroid gland. PTH stimulates bone turnover, renal phosphorous excretion by inhibiting phosphorous reabsoption in proximal and distal tubules and renal calcium reabsoprtion at distal tubule. The net effect of PTH is to raise serum Ca and 1, 25 (OH)2 D while decreasing serum phosphorous levels.

Normal bone remodeling

Bone remodelling is a dynamic process and characterized by coupling between resorption and formation. It is initiated by activation of osteoclast precursors that become mature osteoclasts by proliferation and differentiation(10). The osteoclasts cause bone resorption until they have reached a final resorption depth. The osteoblasts then invade the area and begin bone formation. The end product of the remodelling sequence is the bone structural unit which is characterized by a certain structural thickness. The sequence of events in remodeling i.e. activation resorption - formation (ARF sequence) is most easily demonstrated in cortical bone(11). The space corresponding to the amount of bone resorbed by osteoclasts but not formed by osteoblasts is the remodeling space. Activation frequency indicates how often a given site of the bone surface undergoes resorption and subsequent formation. Normal trabecular bone is activated with an interval of 2 to 3 years, whereas the activation frequency in cortical bone is lower(11). Besides paracrine and local factors, the activation frequency is regulated by a variety of hormone; PTH, 1,25 (OH)2D growth hormone and thyroid hormones increase and calcitonin, corticosteroid and estrogen reduce the activation frequency .

Bone mineral metabolism homeostasis in Hyperthyroidism

The first report of hyperthyroid bone disease was in 1891 when von Recklinghausen described the "worm eaten" appearance of long bones of a young women who died due to hyperthyroidism(12) Plummer gave similar description in 1920 and reported "a 53 year old women gave a history of hyperthyroidism. The patient died three hours after operation. The ribs showed multiple fractures, were very friable and could easily be crushed between the fingers. The calvarium was found to be extremely thin, and was almost translucent when held up to the light". In early part of century emphasis of studies in thyrotoxicosis was on calcium - phosphorus metabolism. With the introduction of antithyroid drugs and radioiodine therapy in 1940's, clinically apparent hyperthroid bone disease became less common. In 1970's, with the availability of serum 25(OH) D assay, there was resurgence of interest in vitamin D metabolism in hyperthyroidism. Recently introduced bone density measurements like DEXA, markers of bone and formation has led to further interest in the hyperthyroidism related bone disease(13). These newer techniques have documented skeletal loss in patients with hyperthyroidism and as well as in those on excessive thyroid hormone replacement.

Histomorphometric studies demonstrate that thyroid hormones increase the activation of new remodeling cycles and stimulate osteoclastic and osteoblastic activity in trabecular and cortical bone. In invitro organ culture of fetal rat bone Mundy *et al* has demonstrated a direct stimulation of bone resorption by thyroid hormones(14). Addition of thyroid hormone increased 45Ca release by 10-60% during a six day long culture of bones of fetal rats previously treated with radioisotope. Histologically an increase in number and activity of osteoclasts was detected. These cells appeared similar to those seen in cultured bone treated with PTH(14). The stimulation of bone resorption was inhibited by cortisol, calcitonin and phosphate as well as by propranolol. The mechanisms of thyroid hormone induced bone resorption include cAMP mediated, increased sensitivity of beta adrenergic receptors to catecholamines, increased sensitivity of bone cells to PTH, osteoclast activator factor and interleukin-1 (IL-1) mediated increased bone resorption(15).

Alterations in calcium homeostasis in hyperthyroidism

The majority of patients with hyperthyroidism in the West have normal or increased serum total calcium levels and the mean plasma calcium concentration is higher than control subjects are. Till 1963, only 31 cases of thyrotoxic hypercalcemia were reported in literature(15). In 1966, Baxter and Bondy reported hypercaleamia in 19 of the 77 patients(23%) with hyperthyroidism. In other series percentage of patient with hypercalcemia in thyrotoxic state varies between 5-27%(16). Manicort *et al*, observed an increase in serum free calcium in 50% of subjects with hyperthyroidism(17).

Propranolol therapy also improves hypercalcemia of hyperthyroidism. Hypercalcemia usually resolves after attainment of euthyroid state. Reversibibily of hypercalcemia has been observed with all therapeutic modalities i.e., subtotal thyroid resection, antithyroid drugs and radioiodine therapy. Magnitude of disturbances in serum calcium in hyperthyroidism correlates with serum T3 levels(7,17). Severe (> 15mg/dl) and symptomatic hypercalcemia is rare among patients with hyperthyroidism. Symptomatic hypercalcemia responds to rehydration, use of corticosteroids, calcitonin and phosphate therapy.

Renal calcium excretion is usually increased in hyperthyroidism and correlates positively with excess thyroid hormone levels and cortical osteoclastic activity(7). It is caused by enhanced mobilization of bone mineral in hyperthyroid state, and remains elevated even on calcium deficient diet. In kidney the filtered calcium load is enhanced due to increase in serum ultrafilterable calcium and GFR as well as reduced tubular reabsorption because of suppressed PTH levels.

Alteration in phosphorous homeostasis in hyperthyroidism

There are variable reports on serum phosphorous levels in patients with hyperthyroidism. Most of the studies indicate hyperphosptaemic state. However, a few studies show normal or low levels of serum phosphorous(7). Hyperphosphatemia in hyperthyroidism has been explained on the basis of an enhanced tissue catabolism leading to an excess input of phosphorous to the plasma pool from bone and tissues and lower fractional clearance of phosphorous and increased renal tubular reabsoption of phosphorous(7). The changes in serum phosphorous are due to suppressed PTH levels as well as due to direct effects of thyroid hormones on tissue phosphate metabolism and renal phosphate handling. These effects lead to increased filtered load of phosphorous in patients with hyperthyroidism. Antithyroid treatment normalizes serum phosphorous concentration(18).

Alkaline phosphatase levels in hyperthyroidism

Patients with hyperthyroidism have elevated levels of serum alkaline phosphatase in as many as 50% of cases(19). A direct correlation between serum thyroxine concentration and serum alkaline phosphatase levels has been found by several workers. The raised levels of serum alkaline phosphatase levels could be either of hepatic or bone origin However, Cooper *et al* could not detect parallel increase in 5'-nucleotidase and Sr. alkaline phosphatase in patients with hyperthyroidism(20). This suggests that increased serum alkaline phosphatase is due to increased osteoblastic activity. Following treatment serum alkaline phosphatase levels remains elevated for several months suggesting increased bone turn over continues even after restoration of a normal metabolic rate.

Parathyroid hormone secretion in hyperthyroidism disease

In 1964 Harrison *et al*. described an increased sensitivity to exogenous PTH in patients with hyperthyroidism(15). Bouillon and DeMcor first reported a decrease in serum PTH concentration in patients with hyperthyroidism(21). The above observation has been confirmed by other investigators as well. However, some of researchers could not demonstrate a decline in serum PTH levels among patient with hyperthyroidism possibly due to difficulty in differentiating between normal and decreased concentrations due to less sensitive PTH assays (22). There is inverse relationship between serum calcium and serum PTH levels indicating that increased serum calcium levels inhibit PTH secretion from parathyroid gland. Suppressed PTH levels also explain the raised serum phosphorous and increased maximal tubular absorption rate for phosphorous.

Vitamin D and its metabolites in hyperthyroidism

Serum levels of 25(OH) D, 1, 25 (OH)2D and other metabolites of vitamin D have been studied by various investigators. Most of the studies have documented normal serum levels of 25(OH) D levels in hyperthyroidism(23-25). However, there are a few reports of subnormal 25(OH) D levels in patients with hyperthyroidism (26-28). Ventertazs *et al* & Mosekilde *et al* reported significantly lower plasma 25(OH)D levels in thyrotoxic patients when compared to value observed in controls. However, no correlation was observed between serum 25(OH)D and bone histomorphometry(27). Recently Yamashita *et al* has reported subnormal levels of 25(OH)D levels in 40% of females and 18% of males in a series of 208 patients with Graves' disease. The subnormal levels of mean plasma 25(OH)D levels in the above studies was postulated to be due to reduced intestinal absorption of vitamin D due to steatorrhea or to hepatic enzyme induction, reduced sun exposure or deficient vitamin D intake in diet(26).

In subjects with hyperthyroidism high serum calcium, low PTH and high phosphorous levels suppress renal 25(OH)D 1-? hydroxylase activity leading to decrease in 1, 25(OH)2D levels . Serum 24, 25(OH)2D levels are increased in patients with hypothyroidism and correlates with serum thyroid hormone levels (18).

Hyperthyroidism and Bone density

Hyperthyroidism is an important cause of secondary osteoporosis. Early studies have used conventional radiography to assess bone mineral content(29). During 1970-80s single photon absorptiometery and dual photon absorptiometry were used to quantify bone mineral density at various sites(30). Tsai K S *et al* studied bone mineral density in 24 untreated patients with hyperthyroidism using dual photon absorptiometry and showed significant increase after one year treatment with antithyroid drugs and propranolol. From 1991 onwards dual energy absoptiometry (DEXA) is available for bone mineral density measurements. DEXA allows rapid, accurate and highly reproducible assessment of mineral content with a minimal exposure to radiation (13). Bayley *et al* (1980), studied bone mineral and muscle mass using in vivo neutron activation analysis in patients with hyperthyroidism before and after treatment. In this method stable 48Ca is converted to radioactive 49Ca and radioactivity recorded corresponds to mineral content. The latter is normalized to body size and expressed as calcium bone index (Ca BI). Muscle mass was also measured by counting the radioactive 40K in a whole body counter and then normalized with body size(31). Reversibility of both bone mineral mass and body muscle mass was recorded after one year of treatment with radio-iodine therapy(31).

Krolner *et al*, investigated 25 patients with hyperthyroidism and demonstrated 12.5% lower bone mineral content at lumbar spine when compared to healthy controls. In this study lumbar bone mineral content increased by 3.7% after 1 year of antithyroid therapy. Most of the subsequent studies have shown significant increase in bone mineral density following treatment(20). There are few published studies from India on hyperthyroidism and bone density. Udaykumar and coworkers have reported

32% osteopenia and 60% osteoporosis in a group of 50 hyperthyroid patients. They also demonstrated reversal of bone loss after one year treatment with antithyroid medications(31).

Indian situation is also peculiar that despite adequate sunlight vitamin D deficiency is prevalent in our country. Recently we concluded a study on bone mineral homeeostasis and bone mineral density in patients with thyrotoxicosis (unpublished data). We studied 30 patinets having thyrotoxicosis (majority being Graves'disease) and concluded that in contrast to western data hypercalcemia is not a feature of Indian patients with hyperthyroidism in fact, 26% of these patients showed hypocalcemia and 30% of these patients have concomitant vitamin D deficiency. In this study, BMD expressed as either T or Z score was in the osteoporotic range in 20%, 36%, and 22% and at hip, forearm and lumbar spine respectively. BMD was compared in vitamin D deficient and sufficient patients and it was observed that vitamin D patients have more severe bone loss which is contributed by vitamin D deficiency. Thus Indian patients with thyrotoxicosis are different from the western patients from bone mineral homeostasis point of view. These patients have hypocalcemia rather then hypercalcemia as seen in west and this is due to associated vitamin D deficiency. Future scientific work is needed to study the effect of vitamin D in therapeutic doses in patients with hyperthyroidism with concomitant vitamin D deficiency.

CONCLUSION

In summary patients with hyperthyroidism have significant impact on bone mineral homeostasis. Western data suggests that thes patients have hypercalcemia, hyperphosphatemia raised alkaline phospahtase and reduced bone mineral density. However the available data from India suggests that due to concomitant vitamin D deficiency these patients have normal calcium levels and increased bone loss.

REFERENCES

1. Goswami R, Seth A, Sosnami AK, Kochupillai N: Prevalence of enuresis and other bladder symptoms in patients with active Graves' disease. Br J Urol 1997:80:(4):536-6.
2. Guleria R, Goswami R, Shah P, Pande JN, Kochupillai N: Dyspnoea, lung function and respiratory muscle presence in patients with Graves' diseases. Ind J Med Res 1996:104:299-303
3. Goswami R, Tandon RK, Dndha A, Kochupillai N: Prevalence and significance of steatorrhea in patients with active Graves' disease. Am J Gastroenterol 1998:93:1122-25
4. Goswami R, Kochupillai N: Adrenocortical reserve in patients with Graves' disease. Eur J Endocrinol 2001:144:(1):85.
5. Goswami R, Gupta N, Goswami G, Marwaha RK, Tondon N, Kochupillai N: Prevalence and significance of low 25 hydroxy vitamin D concentrations in healthy subjects in Delhi. Am J Clin Nutr 2000:72:472-5.
6. Michelangeli VP, Pwape G, Sinha A *et al*: Clinical features and pathogenesis of thyrotoxicosis in adult Melanesians in Papua New Guinea. Clinical Endocrinol (oxf) 2000:52:261-266.
7. Mosekilde L, Christensen MS: Decreased parathyroid function in hyperthyroidism: inter relationship between serum parathyroid hormone, calcium phosphorus metabolism and thyroid function. Acta Endocrinol 1977:84:566-575.
8. Bikle DD: Regulation of bone mineral homeostasis : An integrated new in Favus MJ ed. Primer on the metabolic bone disease and disorders of mineral metabolism. New York. Raven Press 1993:76-82, 8
9. Anthony W, Porman and Helen L Heny: Vitamin D: Metabolism and mechanism of action. Primer on the metabolic bone disease and disorders of mineral metabolism. New York. Raven Press 1993:63-69.
10. Eriksen EF: Normal and pathological remodeling of human trabecular bone. Three-dimensional reconstruction of the remodeling sequence in normal and in metabolic bone disease. Endocr Rev 1986:7:379.
11. Eriksen EF, Melsen F, Mosekilde L: Reconstruction of the resorption site and iliac trabecular bone. A kinetic model for bone resorption in 20 normal individuals. Metab Bone Disease. Endoer Rev 1984:5:235.
12. Von Rechklinghausen F in Festschrift R, Virchow edited by G Reimer: P 20, Berlin 1891.12.
13. Wahner HW, Fogelman I: The evaluation of osteoporosis. Dual energy x-ray absoptiometry in clinical practice. London Martin Dunitz: 1994.
14. Mundy GR, Shapiro JL, Bandelin JG, Canalis EM, Raisz LG: Direct stimulation of bone resorption by thyroid hormones. J Clin Invest 1976:58:529-534.
15. Gowen M, Wood DD, Ihrie EF, McGuire MKB, Russel GG: An inteleukin like factor stimulates bone absorption in vitro. Nature 1983: 306: 378-380.
16. Baxter JD, Bondy PK: Hypercalcemia of thyrotoxicosis. Ann Intern Med 1966:65: 429-442.
17. Manicourt D, Detester Mirking N, Brauman H, Corvilain J: Disturbed mineral metabolism in hyperthyroidism good correlation with tri-iodothyronine. Clin Endocrinol 1979:10: 407-412.
18. Mosekilde L, Christensen MS, Melsen F, Sorensen NS: Effect of anti-thyroid treatment on calcium phosphorus metabolism in hyperthyroidism. 1: Chemical quantities in serum and urine. Acta endocrinol 1978: 87: 743-750.
19. Bommer J, Ritz E, Gengenbach E: Parathyroid activity in hyperthyroidism. Calcif Tissue Res (Suppl) 1976:21:288-293.
20. Bouillon R, DeMoor P: Parathyroid function in patients with hyper or hypothyroidism. J Clin Endicornol Metab 1974:38: 999-1004.
21. Krolner B, Jorgensen JV, Nielsen SP: Spinal bone mineral content in myxoedema and thyrotoxicosis. Effect of thyroid hormones and antithyroid treatment. Clin Endocrinol 1983:18:439-446.
22. Bouillon R, Muls E, DeMoor P: Influence of thyroid function on the serum concentration of 1.25-dihydoryvitamin D. J Clin Endocrinol Metab: 1980:51:793-797.
23. Macfarlane A, Mawer EB, Berry J, Hann J: Vitamin D metabolism in hyperthyroidism. Clin Endocrinol 1982:17:51-59.
24. Bijlsma JWJ, Duursma SA, Roelofs JMM, derKinderen PJ: Thyroid function and bone turnover. Acta Endocrinol 1983:104:42-49.
25. Mosekilde L, Lund B, Sorensen OH, *et al*: Serum 25-hydroxycholecalciferol in hyperthyroidism. Lancet 1977:1:806.
26. Velentzas C, Orepoulos DB, From G, *et al*: Vitamin D levels in thyrotoxcosis. Lancet 1977:1:370-371.
27. Yamashita H, Nognchi S, Kakatsh K, *et al*: High prevalence of vitamin D deficiency in Japanese male patients with Graves'. Endocr J 2001:48:(1):63-9.
28. Fraser A, Anderson J, Smith D, Milson G: Osteoporosis and fracture risk following thyrotoxicosis. Lancet 1971 (1): 981-83.
29. Tsai KS, Lai SM, Huang KM, Chang PV, Su CT, Chen FW: Decreased bone mineral density in patients with prolonged thyrotoxicosis before and after treatment. J Formosan Med Arch 1991:90:251-57.
30. Bayley TA, Harrison JE, McMeill KG, Mernagh JR: Effect of thyrotoxicosis and its treatment on bone mineral and muscle mass. J Clin Endocrinal Metab 1980:50:916.
31. Dhanwal Dinesh, Goswami R, Gupat N and Kochupillai: Bone mineral homeostasis and bone mineral densilty in vitamin deficient and sufficient patients with hyperthyroidism. (Unpublished data)