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# Commentary

## Thyroid bone disease

In this issue Jyotsna *et al*[1] report the changes in bone mineral density (BMD) in predominantly 25(OH) D deficient patients with Graves disease. They have studied the thyroid functions, bone mineral parameters in serum and BMD before and after the achievement of euthyroid status in study group and related the hormonal changes to BMD. The study mentions that patients with Graves disease had lower BMD compared with controls (euthyroid) for comparable levels of 25(OH) D levels. Body mass Index (BMI) increased with euthyroid status. Though euthyroid state was achieved in four months, the BMI adjusted BMD declined after a year of achieving euthyroid status. The authors also discuss the changes in biochemical parameters of bone mineral metabolism along with a host of caveats in their study.

The first association between multiple fractures and hyperthyroidism was reported in 1980 by von Recklinghausen based on postmortem findings in young women who died after five years of thyrotoxicosis. The histological changes described were those of increased osteoclastic activity, excess osteoid deposition (osteomalacia) and rarefaction (osteoporosis). Later histomorphometric studies have shown both increased osteoblast activity (increased osteoid surfaces and increased calcification rate) and increased osteoclastic activity (increased resorption surfaces and increased active resorption)[2]. Later research in human subjects has established clear association between thyrotoxicosis and high turnover osteoporosis. There is a study which showed the association of overt hyperthyroidism, including Graves disease with loss of skeletal integrity and high risk of hip fractures[3]. The therapeutic suppression of thyroid stimulating hormone (TSH) to treat thyroid cancer, goiter is associated with risk of bone loss and fractures. This is known to be more pronounced during menopause[4,5].

Biochemical studies have helped us to understand the effect of hyperthyroidism on bone formation and resorption. Though hypercalcemia is rare in uncontrolled thyrotoxicosis, serum calcium and phosphorous concentrations are higher than in normal subjects. This occurs despite increased urinary calcium and phosphorous and raised faecal calcium excretion and reduced absorption of calcium from diet. The serum parathyroid hormone levels are low because of hypercalcemia and correlate with free T4 index[6]. Serum alkaline phosphatase and osteocalcin levels are elevated in untreated thyrotoxicosis. The osteoclast markers namely urinary hydroxyproline, urinary pyridinium and deoxypyrodinoline cross-links are elevated in untreated hyperthyroidism[7,8]. In a longitudinal study of bone markers and bone turnover in Graves disease, the mean BMD rose approximately by 6 per cent compared to base line[9]. Biochemical markers predict changes of bone mineral metabolism much earlier than BMD[9].

Recent understanding of hyperthyroid bone disease has shown a paradigm shift in endocrine physiology and unraveled the novel pituitary-bone axis[10,11].

Thyroid hormones namely T4 and T3 stimulate osteoclastic bone resorption *in vitro* and in organ cultures. Initially the osteoblasts are activated which release receptor activator of nuclear factor-kB ligand (RANK-L) a tumour necrosis factor (TNF) family cytokine. This RANK-L couples the osteoblastic activation with enhanced osteoclastic bone resorption[12,13]. There is considerable evidence that other cytokines such as TNFα and interlukin 6 (IL-6) mediate pro-osteoclastic effects of excess thyroid hormones. This is supported by high TNFα and IL-6 levels found in human hyperthyroidism[14]. Though the thyroid hormones indirectly stimulate bone resorption via the osteoblast, direct effect of thyroid hormones on osteoclast is seen during growth and development[15].

Thyroid hormones are anabolic for optimal skeletal growth and modeling during development but are catabolic to mature skeleton[16]. There are many evidences to these observations: in subclinical hyperthyroidism where the thyroid hormone levels are normal but the TSH is suppressed there is high turnover osteoporosis; mice deficient in both α and β thyroid hormone receptors (TRs) display runting rather than defects in bone remodeling[17]; and lastly, both bone density and fracture risk correlate with serum TSH levels and not with thyroid hormone levels[18,19].

There are reports of α TRs and β TRs actions in bone regulation. TR α null mice with normal thyroid hormone and TSH levels demonstrate high bone mass[17]. It is unclear whether the high bone mass is resulted from enhanced osteoblastic bone formation or reduced osteoclastic bone resorption or both. In TR β deficient mice both the thyroid hormone and TSH levels were elevated because of loss of thyroid hormone feedback[22]. TSH is a bone suppressing hormone. TSH inhibits bone resorption directly. There is evidence that the effect of TSH on skeleton was independent of circulating thyroid hormones[20]. These studies imply that the osteoporosis in hyperthyroidism is due to low TSH rather than solely due to high levels of thyroid hormones. TSH signaling is inhibitory of osteoclast is compelling to believe. The osteoblastic effects of TSH are less clear.

There are evidences to show that intermittently administered TSH may be anabolic[21] despite a possible anti-anabolic action when the same hormone circulates at high level. The skeletal effects of TSH are independent of thyroid hormone levels and are exerted in relatively low concentrations and in some instance occur upon intermittent administration. In post-menopausal women a single subcutaneous injection of recombinant human TSH reduces the serum crosslaps to premenopausal levels within two days and the effect lasts up to seven days[22]. However, the effects on serum RANK-L and osteoprotegerin levels have been controversial[23]. Calcein-labelled studies have shown that the anabolic effects of intermittent TSH is due to increased bone formation rates[24]. These skeletal effects of TSH are independent of thyroid hormones and are exerted in relatively low concentrations of TSH and in some instances on intermittent administration. Recently, there are reports showing a correlation between serum cross-lined teleopeptide of type I collagen and serum TSH levels, while there was no such correlation with thyroid hormones[22]. Thus osteoporosis of hyperthyroidism which was thought to be caused by elevated thyroid hormone levels is now attributed at least in part to lowered TSH levels.

Mouse genetic studies have shown that pituitary-bone axis is more ancient than pituitary-thyroid axis and is evident from the fact that haploinsufficiency of TSHRs affects the bone without affecting the thyroid gland. It would be interesting to study the effect of thyroid hormones and TSH on a vitamin D deficient bone tissue. In a study conducted by us at Tirupati (unpublished observation) on 40 patients with Graves disease with low 25(OH)D levels the BMD and Z-scores improved by 6-10 per cent on achieving euthyroid status. There was a negative correlation between the Wynes' score with lumbar BMD at presentation, which might serve as a marker to identify patients who require to be addressed with regard to thyroid bone disease. This study also has carefully documented the biochemical markers of bone mineral metabolism and renal handling of calcium and phosphorous.

The new questions that emerge are: Can new diagnostic tests be devised to exploit pituitary bone axis? Can biological therapies be devised to prevent bone loss in hyperthyroidism and other medical conditions?

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