Bone mineral density and bone structure in primary hypoparathyroidism

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Summary

Since parathyroid hormone has dual properties on bone, both catabolic and anabolic, it is interesting to review how the bone mineral density and structure change in patients with chronic hypoparathyroidism. Others and we have demonstrated consistently that the state of chronic hypoparathyroidism is associated with increased BMD, most notably at the spine. Those with idiopathic hypoparathyroidism have a similar degree of increase in BMD as those with postthyroidectomy hypoparathyroidism. Both groups also have significantly lower level of biochemical markers such as osteocalcin, bone-specific alkaline phosphatase activity and urinary resorption markers as compared with control. This reflects the low rate of bone remodeling and implies a significant reduction in "birth rate" of bone modeling units and prolongs the "life span" of the basic structural unit. It therefore allows for more complete secondary mineralization. The reduction in bone remodeling is further confirmed by bone histomorphometry. The observed effect on BMD is likely a result of the combined effects of decreased bone resorption due to hypoparathyroidism and the improvement in bone mineralization as a result of continuous treatment with calcitriol and calcium.

KEY WORDS: hypoparathyroidism, bone mineral density, biochemical markers, bone histomorphometry, bone geometry.

Parathyroid hormone plays an important role in the regulation of bone metabolism. It regulates calcium homeostasis by affecting intestinal calcium absorption, renal calcium excretion and the rate of bone resorption. Parathyroid hormone acts directly on the skeleton to promote calcium release from bone and on the kidney to enhance calcium reabsorption. It also acts indirectly on the intestinal tract to increase calcium absorption by facilitating the renal conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D. In the state of primary hypoparathyroidism, defective parathyroid hormone secretion leads to the hallmark of hypocalcaemia and hyperphosphataemia. There are multiple etiologies, the commonest of which is due to surgical removal of the parathyroid glands during parathyroid or thyroid surgery and particularly after radical surgery for carcinoma involving structures in the neck. Other causes can be idiopathic, autoimmune or genetic in origin. In hypoparathyroidism, plasma $1,25(OH)_2$ Vit. D level

is low due to the lack of PTH. Conventional therapy with active vitamin D_3 $(1,25(OH)_2$ Vit. D_3 or $1\alpha OH$-Vit. D3) and calcium supplement are required to maintain the calcium level at the lower range of normal.

Secondary hyperparathyroidism has been implicated in the pathogenesis of age-related cortical bone loss and hip fractures (1). Patients with mild asymptomatic primary hyperparathyroidism have preferential reduction in cortical bone mass, with relative preservation of cancellous bone (2). Randomized double-blind studies have also shown that intermittent injection of aminoterminal fragments of human PTH increased bone mineral density in both males (3) and females (4) and reduced fracture rates in postmenopausal female (4). Since parathyroid hormone has dual properties on bone, both catabolic and anabolic, it is interesting to review how the bone mineral density and structure change in patients with chronic hypoparathyroidism.

Bone Mineral Density (BMD) in hypoparathyroidism

As early as in 1967, Dimich et al. (5) observed an increase in radiographic bone density in some patients with hypoparathyroidism. Hossain et al. (6) attempted to quantify it by measuring metacarpal cortical areas with the use of radiogrammetry in patients with hypo- and hyperparathyroidism. The technique is however not sensitive enough to show difference in premenopausal women but in postmenopausal women with hypoparathyroidism, no postmenopausal bone loss was demonstrable. In early 1980's, Seeman et al. (7) measured bone mineral density at the midradius and distal radius by single photon absorptiometry and at the lumbar spine by dual photon absorptiometry in 100 patients with various types of endocrine disorders. Twenty of them (16 female and 4 male) had hypoparathyroidism occurring as a complication of surgery for Ca thyroid or non-toxic goiter. In patients with postsurgical hypoparathyroidism, the mean standard deviation from the age- and sex-specific normal mean was positive and significantly greater than zero at all three scanning sites. A greater increase of BMD was also noted at the lumbar spine than the radius. A decade later, Abugassa et al. (8) also used photon absorptiometry to measure the skeletal mass in 13 females with hypoparathyroidism secondary to thyroid surgery for thyroid carcinoma at 10-13 years after surgery. Bone mass in this cohort was 21-28% above that of a control group of 13 patients who had normal parathyroid function after thyroid surgery. Two years later, another study showed that hypoparathyroidism retarded the rate of postmenopausal bone loss as measured by dual-energy X-ray absorptiometry (DXA) in 33 postmenopausal females with post-thyroidectomy hypoparathyroidism (9). By use of lateral scanning of the third lumbar vertebra with DXA, Duan et al. (10) demonstrated that BMD Z score was higher at the trabecular-rich vertebral body ($1.02 \pm 0.47SD$) as well as predominantly cortical posterior process (0.98 ± 0.66 SD) in 10 postmenopausal women with postsurgical hypoparathyroidism. In the cross-sectional analysis, BMD in patients with hypoparathyroidism was higher compared with age predicted mean at the lumbar spine, proximal femur but not at the distal radius. Moreover, the BMD Z scores correlated with duration of hypoparathyroidism. During longitudinal follow-up over a period of 5 years, BMD remained un-

changed in the patients with hypoparathyroidism but decreased at the femoral neck in controls. Most of these studies were confined to postmenopausal females and postsurgical hypoparathyroidism. Questions arise as to whether the same change in bone mineral density occurs in patients with idiopathic hypoparathyroidism in whom there is no prior history of thyroid function abnormalities and in whom the onset of hypoparathyroidism may be more insidious.

We measured the BMD of lumbar spine and proximal femur in 14 patients, 8 with idiopathic hypoparathyroidism and 6 with postthyroidectomy hypoparathyroidism, using DXA (11). Their age ranged from 23-57 years old, with a mean of 42.5 yr. The age of our patients was younger than that of previous studies. Eight of them were female and five were pre-menopausal. While previous studies attributed the increase in BMD to attenuation of postmenopausal bone loss by hypoparathyroidism, we could show that even in male and younger population before menopause, patients with hypoparathyroidism has a higher BMD than the normal sex- and age-matched controls. This was particularly evident at the lumbar spine, with positive Z score of 1.93±1.03 SD, whereas Z score at the femoral neck was 1.14±0.62 SD (see fig. 1). Six of the eight patients with idiopathic hypoparathyroidism were male. Subgroup analysis showed that those with postthyroidectomy hypoparathyroidism had a mean lumbar spine BMD of 1.434 g/cm^2 (mean Z score 2.26) and femoral neck BMD of 1.026 g/cm^2 (mean Z score 1.31), compared with a mean BMD of 1.364 g/cm^2 (mean Z score 1.68) and 1.022 g/cm^2 (mean Z score 1.02) at spine and hip, respectively, for those with idiopathic hypoparathyroidism (see fig. 2). Although there was a trend towards higher lumbar spine and femoral neck Z score in patients with postthyroidectomy hypoparathyroidism, statistical analysis did not reveal any significant difference in BMD, T scores, and Z scores of the lumbar spine and proximal femur between the two groups. Possible caveats are the small sample size and the difference in sex distribution between the two groups. The latter is unlikely to be significant, because areal BMD of the male skeleton is higher than that of the female because of the greater size of bones in men; yet, this study showed a trend towards higher BMD in the female-predominant postthyroidectomy hypoparathyroidism. Apparently, the transient period of high bone turnover caused by thyrotoxicosis before surgery does not jeopardize bone mass. Indeed, it may even expand the remodeling space for osteoblastic bone formation after surgery.

In conclusion, others and we have demonstrated consistently that the state of chronic hypoparathyroidism is associated with increased BMD, most notably at the spine. Those with idiopathic hypoparathyroidism have a similar degree of increase in BMD as those with postthyroidecto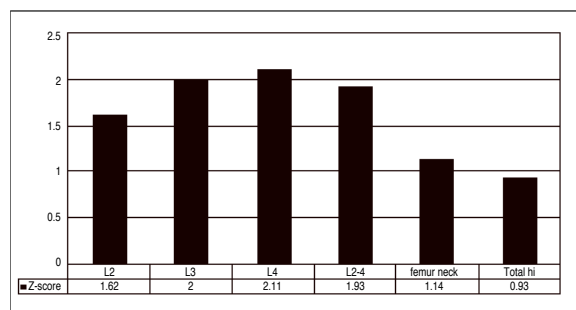my hypoparathyroidism. Whether or not it can be translated to a reduction in fracture risk is still not known. We shall explore the underlying mechanism of the increased BMD from the perspectives of biochemical markers and bone histomorphometry. Recently, data are also present on the bone geometry of patients with hypoparathyroidism.

Bone markers in hypoparathyroidism

Bone remodeling begins with resorption of old bone by osteoclasts, followed by the formation of new bone by osteoblasts. The cycle begins with recruitment from bone marrow monocyte precursors of multinucleated bone-resorbing osteoclasts, which excavate a lacuna space on the surface of bone. Into this lacuna, the osteoclast generates hydrogen ions, lactate, and proteolytic enzymes, which cause a breakdown of the protein matrix of bone and release of calcium and other bone mineral constituents. It is then replaced by bone-forming osteoblasts, derived from connective-tissue precursors and begin the process of filling in the lacuna with a protein matrix, called osteoid, which subsequently becomes fully mineralized new bone. Remodeling is regulated by both local and systemic factors, including electrical and mechanical forces, hormones (e.g. parathyroid hormone, thyroid hormone, vitamin D and its metabolites, estrogen, androgen, cortisol, calcitonin and growth hormone), growth factors (e.g. Insulin-like growth factor 1 and transforming growth factor β) and cytokines (e.g. Interleukins 1 and 6). Biochemical markers that reflect the remodeling process and can be measured in blood or urine are classified as enzymes or proteins that are secreted by cells involved in the remodeling process (e.g. bone specific alkaline phosphatase and osteocalcin) and breakdown products generated in the resorption of old bone (e.g. hydroxyproline, Pyridinolin

Figure 1. Mean Z-scores for the BMD of lumbar vertebra, femur neck, and total hip in patients with hypoparathyroidism (P < 0.001). Reproduced with permission from Ref. 11: Chan FK et al. Increased bone mineral density in patients with chronic hypoparathyroidism. J Clin Endocrinol Metab 2003,88(7): 3155-3159.
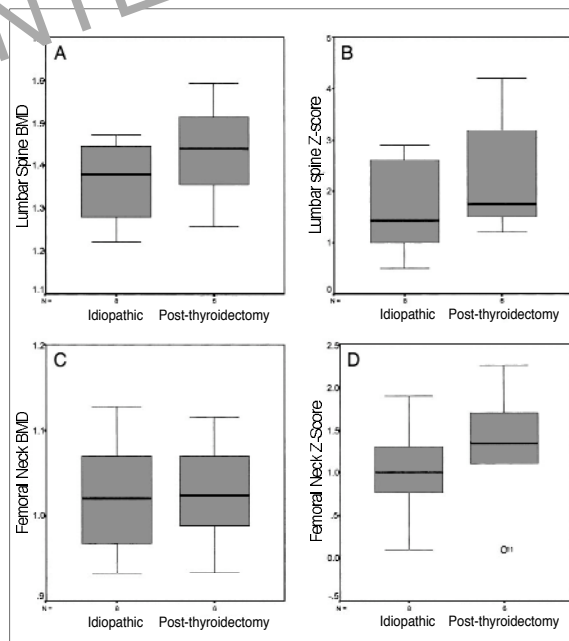

Figure 2. Stem-and-leaf plots showing the distribution of (A) lumbar spine BMD, (B) lumbar spine Z-score, (C) femoral neck BMD, and (D) femoral neck Z-score for the two groups of patients (group 1, idiopathic hypoparathyroidism; group 2, post-thyroidectomy hypoparathyroidism) Reproduced with permission from Ref. 11: Chan FK et al. Increased bone mineral density in patients with chronic hypoparathyroidism. J Clin Endocrinol Metab 2003,88(7): 3155-3159.

cross-links and N-telopeptides). The cells involved in a particular remodeling event are referred to as a basic multicellular unit (BMU). As bone remodeling is coupled, i.e. bone formation is linked to bone resorption, these markers reflect the general process of bone turnover when bone is in steady state.

To evaluate the effect of hypoparathyroidism on the biochemical markers of bone turnover, we measured the serum bone-specific alkaline phosphatase (BAP) level in our patients with hypoparathyroidism by one-step immunoenzymatic assay. The level was then compared to the mean of sex and age-matched controls. We found that serum BAP level of the patients with hypoparathyroidism was significantly lower at 9.35 µg/L as compared to a mean of 12.46 µg/L for the control subjects (10). This reflected the low rate of bone remodeling in patients with hypoparathyroidism and the level was not significantly different between the groups with idiopathic hypoparathyroidism and post-thyroidectomy hypoparathyroidism (12). The result is concordant with other published study on the reduced levels of osteocalin and BAP in patients with hypoparathyroidism (13). In addition, bone resorption markers, urinary hydroxyproline/creatinine ratio was also found to be decreased in patients with hypoparathyroidism . Reduced bone remodeling implies a significant reduction in "birth rate" of BMU and prolongs the "life span" of the basic structural unit, which is either the osteon in cortical bone or the cancellous bone packet in spongy bone (14). It therefore allows for more complete secondary mineralization. This should finally results in an increase in degree of mineralization of bone.

Bone histomorphometry in hypoparathyroidism

The reduction in bone remodeling rate in patients with hypoparathyroidism was further confirmed by bone histomorphometry. Langdahl et al. (15) obtained bone biopsies from 12 patients with vitamin D-treated hypoparathyroidism (8 women and 4 men; 9 post-operative hypoparathyroidism and 3 idiopathic hypoparathyroidism) and 12 age- and sex-matched control controls. The mean total bone resorption rate was significantly reduced by 74% from 3.6 to 0.9 mm/day in hypoparathyroid subjects. The resorption period was prolonged from 25.7 days to 80.0 days and resorption depth was reduced from 55.3 to 41.7 mm. Bone formation was also changed in patients with vitamin D-treated hypoparathyroidism compared to normal individuals. The fractional formation surface was reduced from 12.5% to 5.2%. The balance between resorption and formation was slightly positive in the vitamin D-treated hypoparathyroid patient (+0.96 µm), while it was negative in normal individuals (-4.4 mm); but the difference was not significant (see Fig. 3). The incidence of new resorption lacunae was significantly reduced. In the vitamin D-treated hypoparathyroid patients, the activation frequency was decreased (0.13 per year vs 0.60 per year in the normal individuals). The quiescent period i.e. the period between end of one remodeling sequence and beginning of the next, in the same place on the trabecular surface, was significantly prolonged from 1.66 years in the normal individual to 7.56 years in the vitamin D-treated hypoparathyroid patients. So treatment with vitamin D was not able to restore normal bone turnover even though it normalized serum calcium level in absence of PTH. However, no significant change in bone structural parameters like trabecular bone volume, trabecular thickness, marrow space star volume, and trabecular star volume were observed.

Bone geometry in hypoparathyroidism

Peripheral quantitative computed tomography (pQCT) is not only useful for measuring volumetric bone mineral density (vBMD) of cortical and trabecular bones but can also be used to quantify
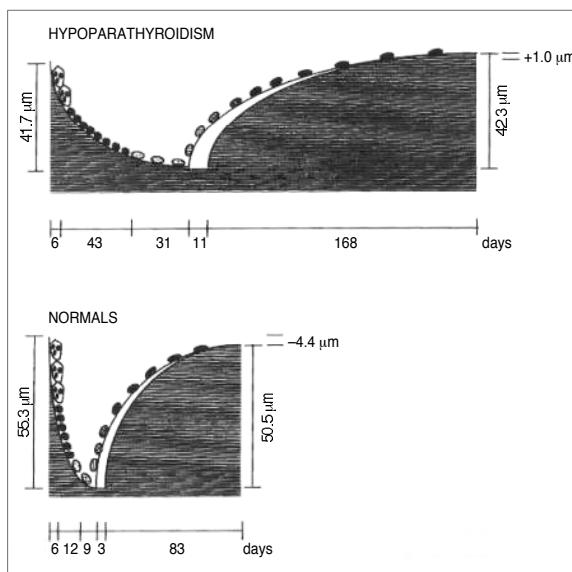

Figure 3. Construction of the remodeling sequence in vitamin D-treated hypoparathyroid patients and normal. Reproduced with permission from Ref. 15: Langdahl BL et al. Bone histomorphometry in hypoparathyroid patients treated with vitamin D. Bone 1996, 18(2): 103-108.

geometric properties of long bone because it can estimate area and circumferences of total bone as well as cortical area and thickness. Trabecular vBMD, but not cortical vBMD was found to be significantly higher in patients with hypoparathyroidism than in controls (16). Total bone area and endosteal and periosteal circumferences were significantly higher in hyperparathyroidism than in controls and hypoparathyroidism (16). It indicated that an excess of endogenous PTH was anabolic for periosteal bone formation. On the other hand, it increased endosteal bone resorption and led to lower cortical area and thickness. In contrary, cortical area and thickness were significantly higher in patients with hypoparathyroidism than controls. Bone strength indices were not significantly different among the three groups.

Treatment effects on BMD

The observed effects on BMD may either be attributable to hypoparathyroidism itself or to continuous treatment with calcitriol and calcium. Hypoparathyroidism *per se* seems to be the most important factor that contributes to a markedly increased BMD. A 70 year-old woman with untreated hypoparathyroidism from the time of thyroid surgery at the age of 29 years has been reported to have increase in bone mineral content at the non-dominant distal forearm and vertebral bone mineral density at the lumbar spine (17). The long duration of no treatment with vitamin D and calcium made this case a golden opportunity to show the impact of hypoparathyroidism alone on bone mineral density. As this patient spent 30 years after menopause, the increase in BMD was again attributed to attenuation of postmenopausal bone loss in the state of hypoparathyroidism. Yet our study has shown that the increased BMD holds true in young pre-menopausal women as well as men with confirmed hypoparathyroidism. Although the biochemical markers and histomorphometry showed both reduction in osteoclastic bone resorption and osteoblastic bone formation, the presence of augmented trabecular bone volume indicated that on balance, formation exceeds resorption. Goltzman's

group has shown that PTHrP haploinsufficiency reduced trabecular bone of PTH-null mice to levels below wild-type by decreasing osteoprogenitor cell recruitment, enhancing osteoblast apoptosis and diminishing bone formation (18). The results reflected the importance of PTHrP for the maintenance of the high bone mass phenotype in the PTH-null mice. Whether PTHrP contributes similarly to the anabolic effect of hypoparathyroidism on human trabecular bone still awaits further evidence.

The effects of calcitriol and calcium on bone mass are controversial. Some researchers reported positive results (19,20), whereas other studies showed decreased bone mass and even increased fracture incidences (21). It has been postulated that the protective effects of vitamin D in osteoporosis can be explained by the suppression of PTH secretion, leading to reduced bone turnover. However, in patients with idiopathic or postthyroidectomy hypoparathyroidism, PTH secretion is already defective, and now data just emerged recently on the effect of treatment on bone mass in these circumstances.

Winer et al. (22) randomized 27 patients with confirmed hypoparathyroidism to either twice-daily subcutaneous injection of PTH or oral calcitriol and calcium, and followed them up longitudinally over a period of three years. Although the PTH group maintained stable whole body and antero-posterior (AP) spine BMD and bone mineral content (BMC) throughout the 3 years, the calcitriol group did show a significant rise in whole body BMD and AP spine BMC respectively. The density results from the femoral neck also showed a rise in BMD and BMC values for both treatment groups. The BMD and BMC values of distal one third of radius remained unchanged for the calcitriol group but showed a non-significant downward trend in the PTH-treated group. It is the first longitudinal study to show increasing BMD in the calcitriol-treated patients with hypoparathyroidism. The rise in bone density is likely a result of the combined effect of decreased bone resorption due to hypoparathyroidism and the improvement in bone mineralization as a result of treatment with calcitriol and calcium.

Conclusions

Bone mineral density was increased in patients with idiopathic as well as post-surgical hypoparathyroidism. The increase in BMD was greater at the spine, a site rich in trabecular bone than at the femoral neck. Peripheral quantitative computed tomography also showed increase in cortical surface area and thickness of the radius bone in patients with hypoparathyroidism. The increase in BMD is attributable to an increase in bone mineralization secondary to suppressed bone turnover, as supported by the low bone turnover markers in patients with hypoparathyroidism. It is also consistent with the bone histomorphometry, which showed virtual absence of detectable cell-based remodeling in patients with hypoparathyroidism. Long-term treatment with calcitriol and calcium may also contribute to part of the increase in BMD. Since intermittent injection of PTH is anabolic on bone and increases the bone mass, a state of hypoparathyroidism after hyperparathyroidism may optimize the bone mineralization and further increase the BMD. Nowadays, drugs such as vitamin D analog and calcimimetic compounds have been developed and are able to suppress endogenous parathyroid hormone secretion. Cyclic administration with these agents following a course of teriparatide treatment may promote the therapeutic effects in patients with osteoporosis.

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