



A case of primary hyperparathyroidism with marked changes in bone mineral density and geometry after parathyroidectomy

Kaji, Hiroshi

Iu, Mei-Fway

Naito, Junko

Sugimoto, Toshitsugu

Chihara, Kazuo

(Citation)

Journal of Bone and Mineral Metabolism, 24(4):349-352

(Issue Date)

2006-07

(Resource Type)

journal article

(Version)

Accepted Manuscript

(URL)

<https://hdl.handle.net/20.500.14094/90000759>



A case of primary hyperparathyroidism with marked changes in bone mineral density and geometry after parathyroidectomy.

¹HIROSHI KAJI, ¹MEI-FWAY IU, ¹JUNKO NAITO, ²TOSHITSUGU SUGIMOTO and ¹KAZUO CHIHARA

¹Division of Endocrinology/Metabolism, Neurology and Hematology/Oncology, Department of Clinical Molecular Medicine, Kobe University Graduate School of Medicine, 7-5-2 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan.

²Division of Endocrinology, Metabolism and Hematological Oncology, Shimane University School of Medicine, 89-1, Enya-cho, Izumo, Shimane, 693-8501, Japan.

Correspondence to: Hiroshi Kaji, M.D.,
Division of Endocrinology/Metabolism, Neurology and Hematology/Oncology,
Department of Clinical Molecular Medicine, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan.
Tel number: +81-78-382-5885, Fax number: +81-78-382-5899
E-mail: E-mail: hiroshik@med.kobe-u.ac.jp

Running title: Bone Geometry Change after Parathyroidectomy

Key words: Primary hyperparathyroidism; Bone mineral density, Bone geometry; Brown tumor; Parathyroidectomy

Introduction

Primary hyperparathyroidism (pHPT) is an endocrine disorder that causes secondary osteoporosis and various bone lesions, such as brown tumor and osteitis fibrosa. Patients with pHPT have reduced bone mineral density (BMD) especially at the cortical bone, whereas bone mass is relatively well preserved in cancellous bone [1-4]. Several studies have suggested that pHPT is associated with an increased risk of vertebral and forearm fractures [5-7].

Numerous studies have demonstrated that pHPT patients regained BMD mainly at trabecular sites after parathyroidectomy (PTX) [4, 7-10]. Although parathyroid hormone (PTH) affects bone geometry [11] and our previous study indicated that bone geometry indices by peripheral quantitative computed tomography (pQCT) are markedly changed in female pHPT patients [12], it remains unknown how bone geometry is affected by PTX.

We present a case of pHPT with severe osteoporosis as well as marked bone lesions including brown tumor. Changes in bone geometry as well as marked increases in BMD were observed after PTX in this patient.

Case report

A 39-year-old female was admitted to our hospital for hypercalcemia in October 2002. She had suffered from pain in her lower extremities since October 1998 when she was 34 years old. She had had general fatigue and

polyuria since 1999, and her pain worsened and her walking was disturbed.

Alfacalcidol (1 $\mu\text{g/day}$) was orally administered before she was admitted to our hospital, because she was clinically diagnosed with osteomalacia for her symptoms even though no measurements of serum calcium had been taken in the other hospital. When she was admitted to our hospital, a mass was palpable on her anterior neck. The laboratory findings of blood and urine were as follows: serum; calcium 14.3 mg/dl, phosphorus 2.3 mg/dl, magnesium 1.7 mg/dl, creatinine 0.5 mg/dl, albumin 4.0 g/dl, intact-PTH 1600 pg/ml (normal range: 10-65), 1, 25 dihydroxyvitamin D3 79 pg/ml (normal range: 20-60), bone-type alkaline phosphatase 325 IU/L (normal range :9.6-35.4), urine aminoterminal telopeptided of type I collagen 390.3 nmol•BCE/mmol•Cr (normal range:9.3-54.3), urine deoxypyridinoline 66.5 nmol/mmol•Cr (normal range: 2.8-7.6), urine calcium/day 343 mg/day, Cca/Ccr (calcium clearance creatinine clearance ratio) 0.028, and %TRP (percentage renal tubular phosphorus reabsorption) 75.5%.

Neck ultrasonography, computed tomography, and magnetic resonance imaging examinations revealed an approximately 3-cm mass in the right lobe of the thyroid, and isotope accumulation was observed on technetium sestamibi scintigraphy (Figure A). X-ray examination showed marked bone change with brown tumor in the left tibia (Figure B). BMD determined by dual energy x-ray absorptiometry (DXA) (QDR-2000) was as follows: lumbar spine 0.456 g/cm² (T score -5.00 Z-score -4.55); femoral neck 0.353 g/cm² (T-score -3.98, Z-score

-3.61); distal radius 0.389 g/cm² (T-score -5.35, Z score -5.10). From these findings, she was diagnosed with primary hyperparathyroidism, and PTX was performed. The histological examination showed that the tumor was a parathyroid adenoma. Although a high dose of calcium and activated vitamin D were administered after parathyroidectomy, she had severely hungry bone with tetany and hypocalcemia and extremely low levels of urinary calcium excretion continued. Six months after operation, the brown tumor greatly improved, and areal BMD by DXA disclosed a marked increase (6 months after PTX: lumbar spine 143%; femoral neck 151%; radius 118% each compared with the basal level before PTX, 12 months after PTX: lumbar spine 184%; femoral neck 187%; radius 119% each compared with the basal level before PTX). The changes in radial volumetric (v) BMD and bone geometry at the 20% site from distal determined by pQCT (XCT-960; Stratec. Pforzheim, Germany) are shown in the table. All computed tomography scans had a slice thickness of 2.5 mm and a vortex size of 0.59 mm. The scanner was positioned at a site on the forearm with a distance from the ulnar styloid process that corresponded to 4% and 20% of forearm length, for distal radius and midradius, respectively. To calculate the structural properties of the cortical shell, trabecular and cortical bone had to be separated. To separate the cortical bone, all voxels (0.295 mm x 0.295 mm x 1 mm) of the scanned image with a BMD lower than the threshold (267 mg/cm³) were eliminated. To separate trabecular bone, 55% of the cross-

sectional area of bone was peeled off from the outer area. BMD was calculated for the cortical bone and the trabecular bone separately. Total area (Tt Ar) was the cross-sectional area of the bone after the soft tissue had been peeled off, and the cortical area (Ct Ar) was the region with linear attenuation. Cortical thickness (Ct Th) was defined as the mean distance between the inner and outer edge of the cortical shell. Endocortical and periosteal circumferences were expressed as ENDO and PERI, respectively. SSIp lay within the theory of stability of mechanical structures against bending or torsion. SSIp was calculated by $(r^2 \times A \times CD/1200)/r_{max}$, where A is the area of a voxel (mm^2), r is its distance from the center of gravity, CD is the cortical density (mg/mm^3) and is divided by the normal physiological density of cortical bone ($1,200 \text{ mg}/\text{mm}^3$), and r_{max} is the maximum distance of a voxel from the center of gravity [13]. The coefficient of variation was under 1%. Total, trabecular and cortical vBMD were increased in a similar manner. As for bone geometry, total and cortical bone areas as well as periosteal circumferences were increased, while endosteal circumferences decreased and cortical thickness greatly increased. Moreover, polar strength strain index (SSIp) also improved.

Discussion

Previous studies demonstrated that pHPT patients rapidly and persistently regained BMD predominantly at trabecular sites but gained little increase in

BMD at cortical sites after PTX [4, 7-10]. We previously reported considerable annual increases in BMD at cortical and trabecular sites 1 year after PTX even in asymptomatic pHPT patients [4]. Moreover, our recent study revealed that PTX led to marked and sustained increases in BMD not only at the lumbar spine but also at the radius in Japanese pHPT patients in a six-year longitudinal study [10]. In this case, marked increases in BMD at the lumbar spine and femoral neck were observed, although BMD changes at the radius were relatively less. Kulak et al. [14] previously reported two pHPT cases with marked increase in bone mass after PTX. These findings suggest that marked recovery of BMD is expected in pHPT patients, especially in severe cases.

pQCT has the potential to measure vBMD and the advantage of distinguishing trabecular from cortical bones. It is also useful to quantify geometric properties of long bones because they can be used to estimate area and circumference of total bone as well as cortical area and cortical thickness [15]. Moreover, pQCT helps to estimate bone strength by calculating SSIp, which has recently been determined to predict bone strength noninvasively [13]. In our previous study [12], the total bone area and endosteal bone and periosteal circumferences of the total bone in pHPT patients were significantly higher than those in control subjects, and the cortical area and thickness in pHPT patients were significantly lower than those in controls matched to age, gender, and body size. These data indicated that an excess of endogenous PTH is anabolic for periosteal bone

formation and leads to thin cortical bone. A continuous excess of PTH increases the activation frequency of bone remodeling on both periosteal and endocortical surfaces. The activation magnitude of bone remodeling is increased during the sustained bone balance between periosteal and endocortical surfaces while bone formation and bone resorption are predominant in periosteal and endocortical surfaces, respectively, resulting in increased periosteal bone formation and endosteal bone resorption. Although there are no reports concerning the effects of PTX on bone geometry in pHPT patients, total bone area and periosteal circumferences were increased in the present case; however, endosteal circumference was decreased. Moreover, cortical area and thickness were markedly increased, and bone strength index also increased after PTX. The intermittent administration of PTH increases both periosteal and endosteal bone formation, resulting in increases in bone total area, cortical area, and thickness [11, 16], which correlates with the findings in the present patient. These findings suggest that the withdrawal and intermittent administration of PTH induces bone formation at periosteal and endosteal sites. PTX might induce change in bone geometry as well as BMD change in pHPT patients in a similar manner with PTH intermittent administration. In the present case, both trabecular and cortical vBMD by pQCT increased after PTX, although the increase in radial areal BMD was slight. These findings suggest that bone geometry modifies the change in areal BMD at the radius. Tsurusaki et al.

reported that vBMD measurement by radial pQCT showed a higher odds ratio than radial DXA for predicting the presence of vertebral fractures in Japanese women [17]. Although the relationship between bone geometry parameters and prospective fracture risk remains unknown, the area BMD by DXA is different from true volumetric BMD, and an excess of endogenous PTH causes a change in bone geometry parameters as well as in BMD [12], suggesting the possibility that DXA is not appropriate for evaluating the effects of PTH, at least on radial bone. Moreover, our recent study indicated that thresholds of area BMD for vertebral fractures were lower, especially at the radial bone in female patients with pHPT [18]. Taking into account these findings, the present case suggests that geometric measurement as well as vBMD measurement by pQCT might be superior to DXA measurement in the evaluation of bone quality and the detection of BMD change after PTX in radial bone. Further study is necessary to clarify this issue.

Brown tumors are non-neoplastic lesions, which are associated with hyperparathyroidism. They are a form of fibrous-cystic osteitis, which represents the terminal stage of the bone remodeling process during primary or secondary hyperparathyroidism. Whether brown tumors are improved by PTX is still unknown. However, in the present case, the brown tumor was markedly improved. In several reports, PTX induced regression or complete tumor

disappearance [19, 20]. Taken together, PTX causes improvement of brown tumors.

In summary, changes in bone geometry as well as marked increases in BMD were observed after PTX in a case of pHPT. pQCT was useful in the evaluation of bone quality and the detection of BMD change after PTX in radial bone.

References

1. Silverberg SJ, Shane E, De La Cruz L, Dempster DW, Feldman F, Seldin D, Jacobs TP, Siris ES, Cafferty M, Parisien MV (1989) Skeletal disease in primary hyperparathyroidism. *J Bone Miner Res* 4: 283–291
2. Silverberg SJ, Loker FG, Bilezikian JP (1996) Vertebral osteopenia: a new indication for surgery in primary hyperparathyroidism. *J Clin Endocrinol Metab* 81: 4007-4012
3. Dempster DW, Paristien M, Silverberg SJ, Liang XG, Schenitzer M, Shen V, Shane E, Kimmel DB, Recker R, Lindsay R, Bilezikian JP (1999) On the mechanism of cancellous bone preservation in postmenopausal women with mild primary hyperparathyroidism. *J Clin Endocrinol Metab* 84: 1562-1566.
4. Nakaoka D, Sugimoto T, Kobayashi T, Yamaguchi T, Kobayashi A, Chihara K (2000) Prediction of bone mass change after parathyroidectomy in patients with primary hyperparathyroidism. *J Clin Endocrinol Metab* 85: 1901-1907
5. Kohsla S, Melton III LJ, Wermers RA, Crowson CS, O'Fallon WM, Riggs BL (1999) Primary hyperparathyroidism and risk of fracture: a population-based study. *J Bone Miner Res* 14: 1700-1707
6. Melton III LJ, Atkinson EJ, O'Fallon WM, Heath III H (1992) Risk of age-related fractures in patients with primary hyperparathyroidism. *Arch Intern Med* 152: 2269-2273
7. Kenny AM, MacGillivray DC, Pilbeam CC, Crombie HD, Raisz LG (1995) Fracture incidence in postmenopausal women with primary hyperparathyroidism. *Surgery* 118: 109-114

8. Silverberg SJ, Gartenberg F, Jacobs TP, Shane E, Siris E, Staron RB, McMahon DJ, Bilezikian JP (1995) Increased bone mineral density after parathyroidectomy in primary hyperparathyroidism. *J Clin Endocrinol Metab* 80: 729-734

9. Silverberg SL, Shane E, Jacobs TP, Siris E, Bilezikian JP (1999) A 10-year prospective study of primary hyperparathyroidism with or without parathyroid surgery. *New Engl J Med* 341: 1249-1255

10. Nomura R, Sugimoto T, Tsukamoto T, Yamauchi M, Sowa H, Chen Q, Yamaguchi T, Kobayashi A, Chihara K (2004) Marked and sustained increase in bone mineral density after parathyroidectomy in patients with primary hyperparathyroidism in patients with primary hyperparathyroidism; a six-year longitudinal study with or without parathyroidectomy in a Japanese population. *Clin Endocrinol* 60: 335-342

11. Zanchetta J, Bogado C, Ferretti J, Wang O, Wilson M, Sato M, Gaich G, Dalsky G, Myers S (2003) Effects of teriparatide [recombinant human parathyroid hormone (1-34)] on cortical bone in postmenopausal women with osteoporosis. *J Bone Miner Res* 18:539-543

12. Chen Q, Kaji H, Iu MF, Nomura R, Sowa H, Yamauchi M, Tsukamoto T, Sugimoto T, Chihara K (2003) Effects of an excess and a deficiency of endogenous parathyroid hormone on volumetric bone mineral density and bone geometry determined by peripheral quantitative computed tomography in female subjects. *J Clin Endocrinol Metab* 88: 2655-2658

13. Ashizawa N, Nonaka K, Michikami S, Mizuki T, Amagai H, Tokuyama K, Suzuki M (1999) Tomographical description of tennis-loaded radius: reciprocal relation between bone size and volumetric BMD. *J Appl Physiol* 86: 1347-1351

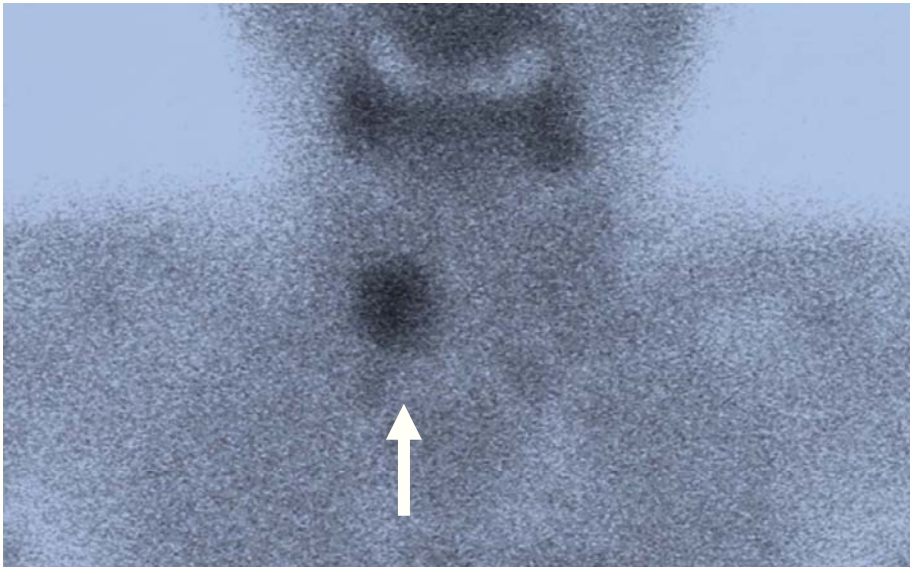
14. Kulak CAM, Bandeira C, Voss D, Sobieszczyk SM, Silverberg SJ, Brandeira F, Bilezikian JP (1998) Marked improvement in bone mass after parathyroidectomy in osteitis fibrosa cystica. *J Clin Endocrinol Metab* 83: 732-735
15. Lehmann R, Wapniarz M, Kvasnicka HM, Baedeker S, Klein K, Allolio B (1992) Reproducibility of bone density measurements of the distal radius using a high resolution special scanner for peripheral quantitative computed tomography (Single Energy pQCT). *Radiology* 32: 177-181
16. Hirano T, Burr DB, Cain RL, Hock JM (2000) Changes in geometry and cortical porosity in adult, ovary-intact rabbits after 5 months treatment with LY333334 (hPTH 1-34). *Calcif Tissue Int* 66:456-460
17. Tsurusaki K, Ito M, Hayashi K (2000) Differential effects of menopause and metabolic disease on trabecular and cortical bone assessed by peripheral quantitative computed tomography (pQCT). *Brit J Radiol* 73: 14-22.]
18. Kaji H, Yamauchi M, Chihara K, Sugimoto T (2005) The threshold of bone mineral density for vertebral fractures in female patients with primary hyperparathyroidism. *Eur J Endocrinol* 153: 373-378.
19. Gurumurthy K, Solomon M, Butt K, Gelfman W, Moel DI (1982) Maxillary brown tumor caused by secondary hyperparathyroidism in an infant. *J Pediatr* 100: 245-247
20. De Pablos PL, Ramos I, De La Calle H (1987) Brown tumor in the palate associated with primary hyperparathyroidism. *J Oral Maxillofac Surg* 45: 719-720

Figure Legends

Figure A. Technetium sestamibi scintigraphy. Isotope accumulation was observed in the right lobe of the thyroid. **B.** X-ray examination at the left tibia. Bone change with brown tumor in the left tibia was observed.

Figure 1

A



B

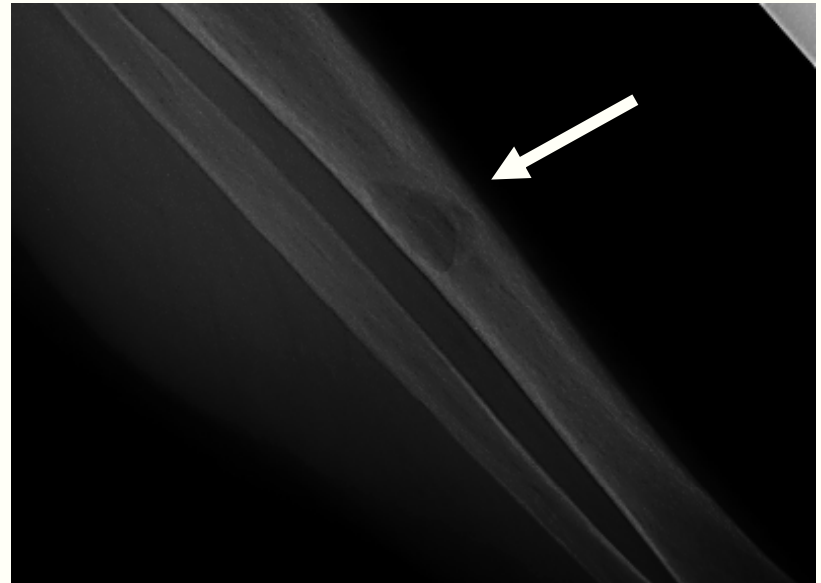


Table. The change in vBMD and bone geometry at the 20 % site by pQCT after PTX

	Basal	1 month after PTX	3 month after PTX	1 year after PTX
Total vBMD (mg/cm ³)	443.9	465.2	493.1	580.6
Trabecular vBMD (mg/cm ³)	233.5	223.5	272.6	308.6
Cortical vBMD (mg/cm ³)	764.6	795.4	814.6	929.0
Tt Ar (mm ³)	97.18	99.55	101.4	104.7
PERI (mm)	34.94	35.37	35.70	36.28
ENDO (mm)	30.87	29.79	28.87	26.28
Ct Ar (mm ²)	21.3	28.92	35.08	49.78
Ct Th (mm)	0.648	0.888	1.086	1.591
SSI _p (mm ³)	97.73	105.4	122.4	143.5