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PDF issue: 2025-12-05

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(Citation)
Hormone and Metabolic Research,40(1):60-65

(Issue Date)
2008-01

(Resource Type)
journal article

(Version)
Accepted Manuscript

(URL)
https://hdl.handle.net/20.500.14094/90000755

KOBE UNIVERSITY

Relationship between endogenous parathyroid hormone and bone metabolism/geometry in female patients treated with glucocorticoid

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Running title: Glucocorticoid-induced osteoporosis and parathyroid hormone

Abstract

Although the role of PTH has been debated in glucocorticoid (GC)-induced osteoporosis (GIO), clinical data about the relation of endogenous PTH to bone metabolism in patients treated with GC are still lacking. The present study was performed to examine the relationship of PTH to bone metabolic indices, bone mineral density (BMD) and bone geometry in 174 female patients treated with oral GC for more than 6 months. Dual-energy X-ray absorptiometry and peripheral quantitative computed tomography (pQCT) were employed for the assessment of BMD and bone geometry. No elevation of serum PTH levels was observed in patients treated with GC. Although serum levels of osteocalcin were not related to serum PTH levels, urinary levels of deoxypiridinoline were positively correlated. Serum PTH levels were negatively related to BMD at any site. In pQCT, serum PTH levels were negatively correlated to both trabecular and cortical volumetric BMD. As for bone morphometric indices, serum PTH levels were significantly related to endocortical circumferences, cortical thickness and cortical area. Moreover, serum PTH levels were significantly higher in patients with vertebral fractures, compared with those without vertebral fractures in GC-treated patients. In the present study, serum PTH levels were related to the elevation of bone resorption marker, decreased BMD, cortical thinning and an increase of vertebral fracture risk. The elevation of sensitivity to PTH in bone might play some role in the pathogenesis of GIO.

Introduction

Glucocorticoid (GC) causes bone loss and an increase in bone fragility, resulting in a great increase in fracture risk [1, 2]. Approximately 50 % of patients with Cushing syndrome or patients taking long-term GC have a traumatic fracture due to osteopenia [3, 4]. Although GC-induced osteoporosis (GIO) is frequently seen in patients with GC excess, ambiguous points remain regarding its mechanism.

GC induces osteoporosis by several mechanisms [1, 2]. The negative effect of GC on bone formation is the most crucial in the pathogenesis of GIO, although the mechanism of GC-inhibited bone formation is not fully elucidated. Histomorphometric studies of GIO revealed an increase in the number of osteoclasts and bone-resorbing sites as well as a reduction in bone formation [5]. GC induces accelerated bone resorption in the early phase. Moreover, reduced sex steroid hormones are also related to GIO, although the adverse effects of GC are not mediated exclusively by sex-steroid deficiency. On the other hand, secondary hyperparathyroidism might be induced in GIO by negative calcium balance partly due to reduced calcium absorption in the intestine and renal tubule. The elevation of PTH was classically considered to be important for the pathogenesis of GIO; however, the role of PTH does not seem to be so important in GIO by evidence of bone densitometry, histomorphometry and bone biology [1]. Alternatively, GC may affect bone and induce osteoporosis by increasing the sensitivity of bone cells to PTH, and clinical evidence about PTH sensitivity in GC treatment is lacking. Moreover, the associations between endogenous PTH and bone metabolism remain unknown.

The present study was therefore performed to examine the relationship between endogenous PTH and bone metabolic indices, bone mineral density (BMD) and bone geometry in 174 female patients receiving oral GC treatments.

Participants and Methods

Subjects

One hundred seventy-four female patients who were treated with oral GC (5mg/day and more of predonisolone) for more than 6 months participated in this study. Among these patients, 84 and 90 patients were premonopausal and postmenopausal, respectively. Basal diseases of GC-treated patients are shown in Table 1. We excluded subjects whose activity of daily life was affected. Activity of daily life was assessed by medical review and physical examination. Among 174 patients, 133 patients (75.1 %) had autoimmune diseases. Patients with rheumatoid arthritis were excluded from the study because forearm parameters, such as pQCT parameters, might be influenced by the disease. All subjects were free from other drugs known to influence bone metabolism up to the time of the present study. The study was approved by the ethical review board of Kobe University Hospital. All subjects agreed to participate in the study and gave informed consent.

Biochemical measurements

Blood and urine samples were collected after an overnight fast. Urine samples were obtained from first void urine. Routine serum and urinary chemistry determinations were performed by standard automated techniques. Serum

concentrations of intact PTH were measured by immunoradiometric assay (Allegro Intact PTH IRMA kit; Nichols Institute Diagnostics, San Juan Capistrano, CA), as previously described [6]. Serum levels of osteocalcin (OCN) and urinary levels of deoxypyridinoline (Dpd) were measured, as previously described [7].

Radiography

Lateral radiographs of the thoracic and lumbar spine were taken. The anterior, central and posterior heights of each of the 13 vertebral bodies from T4 to L4 were measured using an electronic caliper. Vertebral fractures were diagnosed to be present if at least one of three height measurements taken from along the length of the same vertebra was decreased by more than 20 % compared with the height of the nearest uncompressed vertebral body. Using this criterion, 40 women were diagnosed as having one or more vertebral fractures. Defining vertebral fracture from radiographs of the lumbar spine is difficult, because there is no gold standard for what types of deformities of vertebral shape are the result of bone breakage. Definitions of vertebral fractures with high true-positive rates and low false-positive rates are clinically useful in identifying women who may have vertebral fractures. The criterion in the present study (>20%) was considered to be good for defining vertebral fractures because it had a relatively high true-positive rate and low false-positive rate based on qualitative classifications from a previous report [8].

BMD measurements by dual energy X-ray absorptiometry (DXA)

BMD values were measured by DXA using QDR-2000 (Hologic Inc., Waltham, MA) at the lumbar spine (L2-4), femoral neck (FN) and distal one third of the radius

(Rad1/3). BMD was automatically calculated from the bone area (cm^2) and bone mineral content (BMC) (g), and expressed absolutely in g/cm^2. The Z-score is the number of SD by which a given measurement differs from the mean for a sex-, age-, and race-matched reference population. The T-score is the number of SD by which a given measurement differs from the mean for a normal young adult reference population. The coefficients of variation (precision) of measurements of the lumbar spine, femoral neck and radius were 0.9, 1.7 and 1.9%, respectively. The coefficient of variation was obtained in vitro using a 'phantom'. Normative data were obtained from a population-based database for Japanese Society of Bone and Mineral Research in 1996.

BMD measurements by pQCT

pQCT analysis was performed at the nondominant forearm using an XCT-960 device (Stratec, Pforzheim, Germany) with a single energy X-ray source, as previously described [9-11]. 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 the site of the forearm whose distance from the ulnar styloid process corresponded to 20% of the forearm length midradius. 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/cm^3) were eliminated [12]. To separate trabecular bone, 55% of the cross-sectional area of bone was peeled off from the outer area. BMD was calculated for cortical bone and trabecular bone separately. The cortical area (Ct. Ar) is a region with linear attenuation. Cortical thickness (Ct. Th) was

defined as the mean distance between the inner and outer edges of the cortical shell. Endocortical and periosteal circumferences were expressed as En. Le and Ex. Le, respectively.

Statistical analysis

All data are expressed as the mean ± SD for each index. Regression analysis was performed using the statistical computer program Abacus Concepts StatView (Abacus Concepts, Inc., Berkley, CA). Simple regression analysis was used to assess the linear relationship between study parameters, and Pearson's correlation coefficients were calculated. Comparisons of each group were made with the nonparametric Mann-Whitney U-test. P values < 0.05 were considered significant.

Results

Background data

Baseline indices of patients treated with oral GC are shown in Table 2. Serum levels of intact PTH of most patients were within the normal range (10-65 pg/ml), although serum PTH levels of 5 patients were more than 65 pg/ml. Baseline indices of BMD and bone morphometric parameters by pQCT of cortical bone are shown in Table 3. Z-scores of BMD were relatively decreased at the lumbar spine and femoral neck, but not at the radius.

Relationship between serum levels of PTH and bone metabolic indices or BMD by DXA

We calculated correlations between bone metabolic indices and serum PTH level. Serum levels of OCN and urinary levels of Dpd were employed as bone formation and resorption indices, respectively. As shown in Table 4, serum levels of OCN were not related to serum levels of PTH. On the other hand, urinary levels of Dpd were positively correlated with serum PTH levels. Serum PTH levels were negatively correlated with BMD at any site, and the correlations were more potent at the radial bone, which is rich in cortical bone, compared with at the lumbar spine and femoral neck. On the other hand, serum levels of calcium, phosphorus and urinary calcium/creatinin ratio were not related to serum PTH levels (r=-0.124, p=0.1092 ; r=-0.123, p=0.1119; r=0.018, p=0.8286, respectively).

Relationship between serum levels of PTH and bone parameters obtained by pQCT

PTH affects bone geometry and our previous study indicated that bone morphometric indices by pQCT are markedly changed in female pHPT patients [6]. Moreover, the change of bone geometry might disturb the exact estimation of BMD by DXA, although the measurement of volumetric BMD is possible in pQCT. We, therefore, examined the relationship between serum levels of PTH and bone parameters obtained by pQCT. As shown in Table 4, serum levels of PTH were negatively correlated to total volumetric BMD as well as both trabecular and cortical volumetric BMD. The correlations were more potent in the relationship between cortical BMD and serum PTH. As for bone morphometric indices, serum PTH levels were positively related to En. Le., but not to Ex. Le. and total bone area (Tt. Ar.) (Table 4). Moreover, serum levels of PTH were negatively correlated to Ct.

Ar and Ct. Th. To determine which variables were independently related to serum PTH levels, stepwise multiple regression analysis describing serum PTH levels was performed including urinary Dpd levels, cortical vBMD and En. Le. as independent variables. Parameters were omitted to exclude variables that were highly interrelated. Urinary Dpd levels and cortical vBMD were selected, although En.Le. was omitted, suggesting that bone resorption indices and BMD parameters were independently related to serum PTH levels.

Relationship between serum levels of PTH and vertebral fractures

We compared serum PTH levels between groups with and without vertebral fractures in patients treated with GC. As shown in Figure 1, serum PTH levels were significantly higher in patients with vertebral fractures, compared with those without vertebral fractures in GC-treated patients. Moreover, similar data were obtained in only postmenopausal patients.

Discussion

The possible role of PTH has been debated in the pathogenesis of GIO [1, 2]. Since predonisolone reduces intestinal and renal calcium absorption at a dose of 20 mg or more, secondary hyperparathyroidism is expected by negative calcium balance due to calcium loss in the intestine and kidney [13-15]. Several earlier studies suggested an elevation of PTH in GC-treated patients [16-18]. Other studies suggested that concomitant vitamin D deficiency and/or resistance might lead to secondary hyperparathyroidism [19]; however, in most studies, an elevation of serum PTH is not observed in patients treated with GC [20-22]. Moreover, the

administration of GC in normal subjects did not induce an elevation of serum PTH concentration [23]. In addition, the reduction of BMD in GIO is trabecular bone dominant (bone loss is especially dominant at the lumbar spine, rather than radial bone) [1, 2, 21, 24]. As for bone metabolism, bone formation is specifically decreased in GIO, which is in contrast with coupling increases in both bone formation and resoption in primary hyperparathyroidism (pHPT) [6, 25, 26]. Namely, bone turnover is reduced and enhanced in GIO and pHPT, respectively. In GIO, there is a decrease in the wall thickness of trabecular packets, trabecular thickness, as well as cancellous bone volume and trabecular connectivity, is typically disrupted, which is in contrast with the findings in pHPT [1]. Our present and previous studies showed that an elevation of PTH was not observed in patients treated with chronic GC treatment [21]. These findings indicate that an elevated PTH is not common in patients with chronic GC treatment, although skeletal responsiveness to PTH may be differently affected by GC without any change in serum PTH level.

The present study revealed that serum levels of PTH were significantly related to urinary levels of Dpd and BMD at any site in patients treated with GC. Moreover, serum levels of PTH were significantly higher in GC-treated patients with vertebral fractures, compared with those without vertebral fractures. The relationship between serum PTH levels and BMD seemed more potent in radial bone, compared with at other sites. Since serum PTH levels were not elevated in patients treated with GC, these data suggested that PTH is partly related to GC-induced bone resorption, BMD reduction, and subsequent increased fracture risk, even if PTH concentration is not elevated and is within the normal range. GC increased

PTH-1 receptor expression in rat osteoblastic ROS17/2 cells [27]. Urena et al. reported that GC induced the availability of PTH-1 receptor in ROS 17/2.8 and opposum renal epithelial OK cells [28]. Majeska et al. reported the potentiation by GC of the inhibitory response of PTH on ALP activity and thus a more marked suppression of bone formation, resulting in a net increase in bone resorption relative to bone formation [29]. Moreover, our previous study revealed that dexamerthasone enhances osteoclast-like cell formation stimulated by PTH [30], and Paz-Pacheco et al. also reported that the addition of GC has a synergistic effect on PTH-mediated bone resorption [31]. Taken together, increased sensitivity to PTH might be partly responsible for GIO even in chronic GC treatment. Alternatively, Bonadonna et al. [32] reported that chronic GC treatment induces the redistribution of spontaneous PTH secretory dynamics by reducing the amount released in tonic fashion and increasing the amount released as pulses, although mean PTH concentration was not changed; therefore, GC might affect PTH secretory dynamics in patients treated with GC.

pQCT has the potential to measure vBMD and the advantage of distinguishing trabecular from cortical bone. It is also useful to quantify geometric properties of long bones because it can be used to estimate the area and circumference of total bone as well as cortical area and cortical thickness [33]. In our previous study [6], the total bone area, and endocortical bone and periosteal circumferences of the total bone in pHPT patients were significantly higher than in control subjects, and the cortical area and thickness in pHPT patients were significantly lower than in controls matched to age, gender, and body size. These data indicated that excess endogenous PTH is anabolic for periosteal bone formation and leads to thin

cortical bone. A continuous excess of PTH increased the activation frequency of bone remodeling on both periosteal and endosteal surfaces. The activation magnitude of bone remodeling is increased during sustained bone balance between periosteal and endosteal surfaces while bone formation and bone resorption are predominant in periosteal and endosteal surfaces, respectively, resulting in increased periosteal bone formation and endosteal bone resorption. On the other hand, the intermittent administration of PTH increases both periosteal and endosteal bone formation, resulting in increases in bone total area, cortical area, and thickness [34, 35]. Although how endogenous PTH affects bone geometry in GIO is unknown in the present study, PTH might affect bone geometry in a similar manner with a continuous excess of PTH. GC may change the rhythm of PTH secretion. Several studies suggested that cortical bone is also affected in patients treated with GC [36, 37]. Tsugeno et al. reported that cortical BMD is useful to predict vertebral fractures in GC-treated postmenopausal patients by using pQCT, suggesting that a change in cortical bone by pQCT is important in the pathogenesis of GIO, followed by subsequent vertebral fractures [38]. The present study revealed that serum levels of PTH were significantly positively correlated to En. Le in patients treated with GC; moreover, serum PTH levels were negatively related to Ct. Th. and Ct. Ar. These findings indicated that PTH is partly responsible for bone morphometric changes in radial bone in GIO. In the present study, radial BMD was most potently correlated to serum PTH levels in patients treated with GC. In volumetric BMD measured by pQCT, serum PTH levels were significantly related to cortical bone, but not to trabecular bone. Radial bone rich in cortical bone is predominantly decreased in patients with pHPT [1]. These findings

suggest that PTH stimulates bone resoption at the endocortical surface, resulting in a decrease in BMD at cortical bone, which might induce a decrease in bone strength due to bone morphometric changes and cortical thinning. These changes by PTH might play some role in the increase of fracture risk in GIO.

The mechanism of GIO mainly includes the suppression of osteoblastic bone formation, and a decrease in serum osteocalcin level is the most sensitve change of bone metabolic indices in patients with GC treatment [1]; however, serum levels of BAP and OCN were not significantly related to serum PTH levels in patients treated with GC in the present study. The present findings suggest that PTH does not seem to be involved in decreased bone formation in GIO, although it may play some role in accerelated bone resorption in GIO. In GIO, there is a rapid, early phase in which BMD falls, possibly by excessive bone resorption, and a slower, more progressive phase in which BMD declines because of impaired bone formation. Thus, PTH may be more important in early phase in patients treated with GC.

The present study has some limitations. First, the sample size was not large enough to make definite conclusions by multiple logistic regression analysis. Multiple logistic analyses might give more useful information to clarify the influence of PTH on vertebral fracture risk and its mechanism in GIO, if the study is extended to a larger scale study. Secondly, since the subjects employed in the present study included many patients with autoimmune diseases, the nature of causal diseases for GC treatment might enhance the increased risk of vertebral fractures in addition to disease-specific influence on BMD and fracture risk. Thirdly, 25-hydroxyvitamin D_3 data were not measured to assess vitamin D status in the present study. Thus,

differences in vitamin D status might affect the relationships between serum PTH levels and bone metabolic parameters.

In conclusion, the present study revealed that serum levels of PTH were not elevated in female patients treated with oral GC treatment. However, serum physiological PTH levels were related to the elevation of bone resorption marker, decreased BMD predominantly at radial bone rich in cortical bone, cortical thinning and an increase of vertebral fracture risk. An elevation of sensitivity to PTH in bone might play some role in the pathogenesis of GIO.

References

1. Rubin MR, Bilezikian JP. The role of parathyroid hormone in the pathogenesis of glucocorticoid-induced osteoporosis: a re-examination of the evidence. J Clin Endocrinol Metab 2002; 87: 4033-4041
2. Mazziotti G, Angeli A, Bilezikian JP, Canalis E. Glucocorticoid-induced osteoporosis: an update. Trends Endocrinol Metab 2006; 17: 144-149
3. Ross EJ, Linch DC. Cushing's syndrome-killing disease: discrimininatory value of signs and symptoms aiding early diagnosis. Lancet 1982; 2: 646-649
4. Adinoff AD, Hollister JR. Steroid-induced fractures and bone loss in patients with asthma. N Engl J Med 1983; 309: 265-268
5. Bressot C, Meunier J, Lejeune E, Edouard C, Darby A. Histomorphometric profile, pathophysiology and reversibility of of glucocorticoid-induced osteoporosis. Metabolic Bone Dis Rel Res 1979; 1: 303-311
6. Chen Q, Kaji H, Iu MF, Nomura R, Sowa H, Yamauchi M, Tsukamoto T, Sugimoto T, Chihara K. 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 2003; 88: 2655-2658
7. Nakaoka D, Sugimoto T, Kaji H, Kanzawa M, Yano S, Yamauchi M, Sugishita T, Chihara K. Determinants of bone mineral density and spinal fracture risk in postmenopausal Japanese women. Osteoporos Int 2001; 12: 548-554
8. Smith-Bindman R, Cummings SR, Steiger P, Genant HK. A comparison of morphometric definitions of vertebral fractures. J Bone Miner Res 1991; 6: 25-34

9. Ruegsegger P, Durand E, Dambacher MA. Localization of regional forearm bone loss from high-resolution computed tomographic images. Osteoporos Int 1991; 1:76-80

10. Kaji H, Kosaka R, Yamauchi M, Kuno K, Chihara K, Sugimoto T. Effects of age, grip strength and smoking on forearm volumetric bone mineral density and bone geometry by peripheral quantitative computed tomography: comparisons between female and male. Endocr J 2005; 52: 659-666

11. Kaji H, Iu MF, Naito J, Sugimoto T, Chihara K. A case of primary hyperparathyroidism with the marked change of bone mimeral density and bone morphometry after parathyroidectomy. J Bone Miner Metab 2006; 24: 349-352

12. Shchiessl H, Ferretti JL, Tysarczyk-Niemeyer G. Noninvasive bone strength index as analysis by peripheral quantitative computed tomography (pQCT). In:Schonau E (eds) Pediatric osteology. New developments in diagnostics and therapy. Elsevier, Amsterdam, p 147-160, 1996

13. Lane NE, Lukert B. The science and therapy of glucocorticoid-induced bone loss. Endoicrinol Metab Clin North Am 1998; 27: 465-483

14. Lund B, Storm TL, Melsen F, Mosekilde L, Andersen RB, Egmose C, Sorensen OH. Bone mineral loss, bone histomorphometry and vitamin D metaboplism in patients with rheumatoid arthritis on long-term glucocorticoid treatment. Clin Rheumatol 1985; 4: 143-149

15. Suzuki Y, Ishikawa Y, Saito E, Homma M. Importance of increased urinary calcium excretion in the development of secondary hyperparathyroidsm of patients under glucocorticoid therapy. Metabolism 1983; 32: 151-156

16. Hahn TJ, Halstead LR, Teitelbaum SL, Hahn BH. Altered mineral metabolism in glucocorticoid-induced osteopenia. Effect of 25-hydroxyvitamin D administration. J Clin Invest 1979; 64: 655-665

17. Gennari C, Imbimbo B, Montagnani M, Bernini M, Nardi P, Avioli LV. Effects of prednisone and defrazacort on mineral metabolism and parathyroid hormone activity in humans. Calcif Tissue Int 1984; 36: 245-252

18. Lukert BP, Adams JS. Calcium and phosphorus homeostasis in man. Effect of glucocorticoids. Arch Intern Med 1976; 136: 1249-1253

19. Cosman F, Nieves J, Herbert J, Shen V, Lidsay R. High-dose glucocorticoids in multiple sclerosis patients exert direct effects on the kidney and skeleton. J Bone Miner Res 1994; 9: 1097-1105

20. Paz-Pacheco E, El-haji Fuleihan G, Leboff MS. Intact parathyroid hormone levels are not elevated in glucocorticoid-treated subjects. J Bone Miner Res 1995; 10: 1713-1718

21. Kaji H, Tobimatsu T, Naito J, Iu MF, Yamauchi M, Sugimoto T, Chihara K. Body composition and vertebral fracture risk in female patients treated with glucocorticoid. Osteoporos Int 2006; 17: 627-633

22. Hattersley AT, Meeran K, Burrin J, Hill P, Shiner R, Ibbertson HK. The effect of long- and shor-term corticosteroids on plasma calcitonin and parathyroid hormone levels. Calcif Tissue Int 1994; 54: 198-202

23. Pearce G, Tabensky DA, Delmas PD, Baker HW, Seeman E. Corticosteroid-induced bone loss in men. J Clin Endocrinol Metab 1998; 83: 801-806

24. Kaji H, Yamauchi M, Chihara K, Sugimoto T. The threshold of bone mineral density for vertebral fracture in female patients with glucocorticoid –induced osteoporosis. Endocr J 2006; 53: 27-34

25. Kaji H, Yamauchi M, Chihara K, Sugimoto T. The threshold of bone mineral density for vertebral fractures in female patients with primary hyperparathyroidism. Eur J Endocrinol 2005; 153 :373-378

26. Kaji H, Nomura R, Yamauchi M, Chihara K, Sugimoto T. The usefulness of bone metabolic indices for the prediction of changes in bone mineral density after parathyroidectomy in patients with primary hyperparathyroidism. Horm Metab Res 2006; 38: 411-416

27. Yamamoto I, Potts Jr JT, Segre GV. Glucocorticoid increase parathyroid hormone receptors in rat osteoblastic osteosarcoma cells (ROS 17/2). J Bone Miner Res 1988; 3: 707-712

28. Urena P, Iida-Klein A, Juppner H, Kronenberg HM, Abou-Smara AB, Segre GV. Regulation of parathyroid hormone (PTH)/PTH-related peptide receptor messenger ribonucleic acid by glucocorticoids and PTH in ROS 17/2.8 and OK cells. Endocrinology 1994; 134: 451-456

29. Majeska RJ, Nair BC, Rodan GA. Glucocorticoid regulation of alkaline phosphatase in the osteoblastic osteosarcoma cell line ROS 17/2.8. Endocrinology 1985; 116: 170-179

30. Kaji H, Sugimoto T, Kanatani M, Nishiyama K, Chihara K. Dexamethasone stimulates osteoclast-like cell formation by directly acting on hemopoietic blast cells and enhances osteoclast-like cell formation stimulated by parathyroid hormone and prostaglandin E2. J Bone Miner Res 1997; 12:734-741

31. Conaway HH, Grigorie D, Lerner UH. Differential effects of glucocorticoids on bone resorption in neonatal mouose calvariae stimulated by peptide and steroid-like hormones. J Endocrinol 1997; 155: 513-521

32. Bonadonna S, Burattin A, Nuzzo M, Bugari G, Rosei EA, Valle D, Iori N, Bilezikian JP, Veldhuis JD, Giustina A. Chronic glucocorticoid treatment alters spontaneous pulsatile parathyroid hormone secretory dynamics in human subjects. Eur J Endocrinol 2005; 152: 199-205

33. Lehman R, Wapniarz M, Kvasnicka HM, Baedeker S, Klein K, Allolio B. Reproducibility of bone density measurements of the distal radius using a high resolution special scanner for peripheral quantitative computed tomography (Single Energy PQCT). Radilogy 1992; 32: 177-181

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

35. Hirano T, Burr DB, Cain RL, Hock JM. Changes in geometry and cortical porosity in adult, ovary-intact rabbits after 5 months treatment with LY333334 (hPTH 1-34). Calcif Tissue Int 2000; 66:456-460

36. Laan RFJM, Buijs WCAM, Erning TJTO, Lemmens JAM, Corstens FHM, Ruijs SHJ, Putte LBA, Riel PLCM. Differential effects of glucocorticoids on cortical appendicular and cortical vertebral bone mineral content. Calcf Tissue Int 1993; 52: 5-9

37. Tsugeno H, Goto B, Fujita T, Okamoto M, Mifune T, Mitsunobu F, Ashida K, Hosaki Y, Tsuji T, Tanizaki Y. Oral glucocorticoid-induced fall in cortical bone

volume and density in postmenopausal athmatic patients. Osteoporos Int 2001; 12: 266-270

38. Tsugeno H, Fujita T, Goto B, Sugishita T, Hosaki Y, Ashida K, Mitsunobu F, Tanizaki Y, Shiratori Y. Vertebral fracture and cortical bone changes in corticosteroid-induced osteoporosis. Osteoporos Int 2002; 13: 650-656

Figure Legend

Figure 1 Comparison of serum PTH levels between patients with or without vertebral fractures in all patients or postmenopausal patients treated with GC Data are expressed as the mean±standard deviations

Table 1. Basal diseases of GC-treated patients

Autoimmune diseaes	**133**
Neurological diseases	**17**
Dermatological diseases	**6**
Respiratory diseases	**4**
Inflamatory bowel diseases	**2**
Hematological diseases	**4**
Granulomatous diseases	**8**
Total	**174**

Table 2. Background data in GC-treated patients

No. of subjects	**174**
No. of subjects with vertebral fractures	**40**
Age (years)	**47.2 ± 16.0**
Body height (cm)	**155.3 ± 6.6**
Body weight (kg)	**52.8 ± 9.1**
BMI (kg/m^2)	**21.9 ± 3.2**
Calcium (mg/dl)	**9.6 ± 0.4**
Phosphorus (mg/dl)	**3.4 ± 0.6**
PTH (pg/ml)	**34.7 ± 14.9 (9-88)**
OCN (ng/ml)	**4.19 ± 2.54**
u-Dpd (nmol/mmol.Cr)	**6.94 ± 3.77**
Current dose of GC (mg/day)	**10.2 ± 6.7**
Maximum dose of GC (mg/day)	**41.3 ± 16.2**
	Mean ± SD

Table 3. Baseline data of BMD and bone morphometric indices in GC-treated patients

DXA		pQCT	
L2-4BMD (g/cm^2)	0.857 ± 0.160	Total vBMD (g/cm^3)	734.8 ± 123.5
L2-4BMD (Z-score)	-0.400 ± 1.268	Trabecular vBMD (g/cm^3)	144.8 ± 53.5
FN BMD (g/cm^2)	0.660 ± 0.124	Cortical vBMD (g/cm^3)	1126.4 ± 65.8
FN BMD (Z score)	-0.387 ± 1.175	Tt. Ar (mm^2)	113.9 ± 15.7
Rad1/3 BMD (g/cm^2)	0.616 ± 0.100	Ex. Le (mm)	37.7 ± 2.6
Rad1/3 BMD (Z score)	0.662 ± 1.415	En. Le (mm)	25.6 ± 3.7
		Ct. Ar (mm^2)	60.7 ± 10.8
		Ct. Th (mm)	1.93 ± 0.39

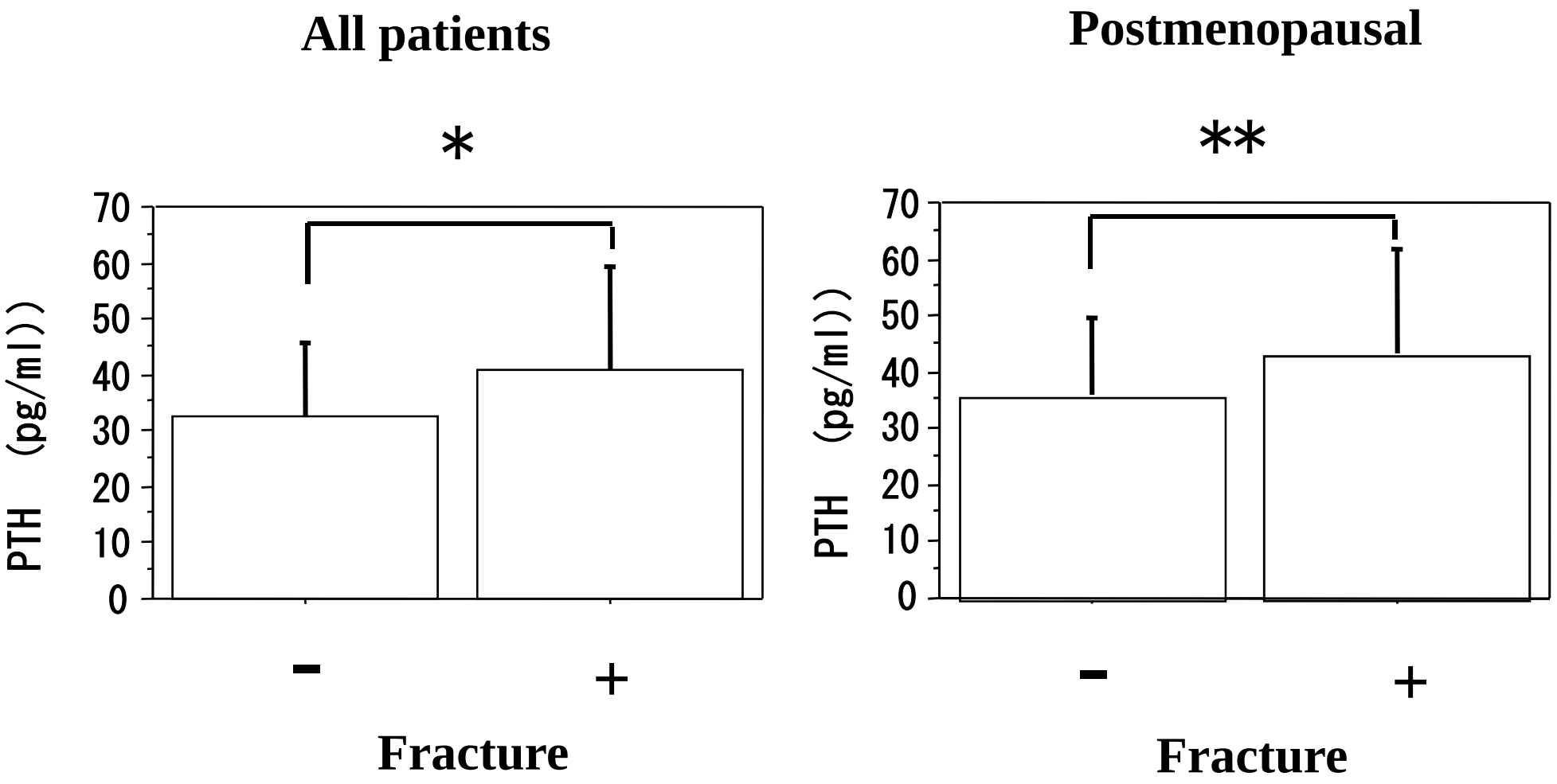
Mean ± SD

Table 4. Correlations between PTH and other indices in GC-treated patients

	PTH
OCN	0.090
u-Dpd	0.201*
L2-4BMD	-0.163**
FN BMD	-0.177**
Rad1/3 BMD	-0.267*
Total vBMD	-0.290*
Trabecular vBMD	-0.163**
Cortical vBMD	-0.294*
Tt. Ar	0.112
Ex. Le	0.107
En. Le	0.260*
Ct Ar	-0.230*
Ct Th	-0.285*

* ; p<0.01: **; p<0.05

Figure 1



*: $P < 0.01$, **: $P < 0.05$