Glucocorticoid Excess Affects Cortical Bone Geometry in Premenopausal, but not Postmenopausal Women

Hiroshi Kaji*[,1], Mika Yamauchi[2], Kazuo Chihara[1] and Toshitsugu Sugimoto[2]

[1]Division of Diabetes, Metabolism and Endocrinology, Department of Internal Medicine, Kobe University Graduate School of Medicine, 7-5-2 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan.

[2]Internal Medicine 1, Shimane University Faculty of Medicine, 89-1, Enya-cho, Izumo, Shimane, 693-8501, Japan

* To whom correspondence should be addressed: Hiroshi Kaji, Division of Diabetes, Metabolism and Endocrinology, Department of Internal Medicine, Kobe University Graduate School of Medicine. 7-5-2 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan.

Phone#: 81-78-382-5885, Fax#: 81-78-382-5899,

E-mail: hiroshik@med.kobe-u.ac.jp

Running title: Glucocorticoid excess affects bone geometry

Abstract

Glucocorticoid (GC) excess causes a great increase in fracture risk, but the effects of GC excess on cortical bone geometry are unknown. The present study was performed to examine the effects of GC excess on cortical bone geometry in both premenopausal and postmenopausal women. Ninety-six women receiving oral GC treatments and ten women with Cushing's syndrome (CS) were each compared to age-matched control subjects using peripheral quantitative computed tomography. Total area, periosteal circumferences and polar strength strain index (SSIp) were significantly lower in GC-treated patients, compared with control subjects in premenopausal women, but not in postmenopausal women. Moreover, cortical area and thickness as well as periosteal circumferences and SSIp were significantly lower in patients with CS, compared with controls in premenopausal women, but not in postmenopausal women. Total area, cortical area, cortical thickness, periosteal circumferences as well as SSIp were significantly lower in GC-treated patients with vertebral fractures, compared with those without vertebral fractures in premenopausal women, but not in postmenopausal women. In conclusion, endogenous or exogenous GC excess affects bone geometry of forearms of premenopausal, but not postmenopausal women. These effects of GC excess on bone geometry may provide a strength loss mechanism beneath increased vertebral fracture risk.

Key words: glucocorticoid, Cushing's syndrome, fracture, bone geometry

Introduction

Glucocorticoids (GC) are used for the treatment of various serious diseases of autoimmune, neurological, dermatological and respiratory origin. GC-induced osteoporosis (GIO) is a serious problem for patients taking GC therapy and many patients suffer from decreases in quality of life and reduced ability to conduct activities of daily life. GC administration causes bone loss and an increase in bone fragility, resulting in a great increase in fracture risk [1-6]. Approximately 50 % of patients with Cushing's syndrome (CS) or patients taking long-term GC have fragility fractures [3, 4, 7, 8]. Excessive intrinsic GC due to CS is associated with increased bone resorption markers, decreased BMD and increased fracture risk [7-13]. However, a meta-analysis of prior GC use and fracture risk suggested that fracture risk was only partly explained by BMD [4]. Moreover, the thresholds of BMD for vertebral fractures were higher in patients with oral GC treatment [14, 15]. These findings indicate that BMD differences may not adequately explain fracture risk in patients with GC excess.

Bone strength is determined by bone structural dimensions and by the limiting properties of the bone tissue. The latter may be influenced by accumulated micro damage, bone turnover effects, anomalies of bone matrix proteins and degree of mineralization [16]. Peripheral quantitative computed tomography (pQCT) has the potential to measure volumetric BMD and the advantage of distinguishing trabecular from cortical bones. More importantly it can measure geometric properties of long bones, such as area and circumferences of total bone as well as cortical area and cortical thickness [17]. Moreover, pQCT helps to estimate bone strength by calculating polar strength strain index (SSIp), which has recently been

shown to predict bone strength noninvasively [18]. Bone size increases with aging [19]. Increased bone loss after menopause is associated with increased rates of periosteal apposition [20]. Our previous study revealed that both excess and deficiencies of endogenous parathyroid hormone (PTH) affect bone geometry determined by pQCT [21]. Moreover, age, grip strength and smoking affected forearm bone geometry in pQCT [22, 23]. These findings suggest that bone geometric changes are useful in evaluating mechanisms of bone fragility. Although several studies reported that a decrease in cortical BMD is associated with fracture risk in GIO [24, 25], the effects of GC excess on cortical bone geometry remains unclear at the present time.

The present study employed pQCT to examine the effects of GC excess on cortical bone geometry in female patients receiving oral GC treatments or patients with CS. Moreover, the influences of GC excess on bone geometry were analyzed by separating the groups with or without menstration.

Subjects and Methods

Subjects

To assess the effect of exogenous GC excess on bone geometry, ninety-six 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, 48 and 48 patients were premenopausal and postmenopausal, respectively. Premenopausal women had menses with normal cycle at the study point, and had not used hormonal contraceptives. Basal diseases of GC-treated patients are shown in Table 1. We excluded those subjects whose activities of daily life were diminished

by medical review and physical examination. Among 96 patients, 62 patients (64.6 %) had autoimmune diseases. Patients with rheumatoid arthritis or those, which were treated with bisphosphonates, were excluded from the study. Control subjects were Japanese women who visited our outpatient clinic in order to determine whether or not they might suffer from osteoporosis or who were recruited as normal volunteers. They were age- and body size-matched with premenopausal and postmenopausal GC patients, respectively.

To assess the effects of endogenous GC excess on bone geometry, 10 patients (4 premenopausal and 6 postmenopausal women) with CS before treatment participated in this study. CS was diagnosed by clinical features, increased excretion of urinary free cortisol, inappropriate suppression of serum cortisol by low dose dexamethasone suppression test and lack of physiological circadian rhythm of serum cortisol. Control subjects were Japanese women who visited our outpatient clinic in order to determine whether or not they might suffer from osteoporosis or who were recruited as normal volunteers matched by age and body size and menstrual status.

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.

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 considered 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. Defining vertebral fracture from radiographs of the lumbar spine is difficult defining the type of vertebral deformity that corresponds to fractures. 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 [26].

BMD Measurements by pQCT

pQCT analysis was performed at the non-dominant forearm using an XCT-960 device (Stratec, Pforzheim, Germany) with a single energy X-ray source, as previously described [27]. All computed tomography scans were acquired with a slice thickness of 2.5 mm and a pixel size of 0.59 mm. The scanner was positioned at the site of the forearm whose distance from the ulnar styloid process 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 were 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 a threshold of 267 mg/cm^3 were eliminated [28]. 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 and trabecular BMD were measured at distal radius. Cortical BMD and bone geometry indices were measured at midradius. Cortical area is the region with linear attenuation. Cortical thickness was defined as the mean distance between inner

and outer edge of the cortical shell. SSIp is an index of mechanical resistance to bending or torsion. SSIp was calculated by: (r^2 x A x CD/1200)/rmax, 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 mg/mm^3), and rmax is the maximum distance of a voxel from the center of gravity [29]. The coefficient of variation was under 1%.

Statistical Analysis

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

Results

Background Data

Baseline indices are shown in Table 2 in premenopausal and postmenopausal women treated with GC and corresponding age-matched control subjects. Numbers of patients with vertebral fractures were 7 and 18 in premenopausal and postmenopausal women treated with GC, respectively. Body height, body weight and the body mass index (BMI) were similar between controls and GC-treated patients in both premenopausal and postmenopausal women. Baseline indices are

shown in Table 3 in premenopausal or postmenopausal women with CS and each age-matched control subjects. Control subjects were also matched with body height and BMI, and there were no significant differences in body weight between control and CS patients in both premenopausal and postmenopausal women.

Comparisons between Women on GC Treatment and Age-matched Controls

We compared various indices between controls and GC-treated patients in both premenopausal and postmenopausal women (Table 4). Total BMD as well as trabecular and cortical BMD were not different between controls and GC-treated patients in both premenopausal and postmenopausal women. As for bone geometry indices, total area, periosteal circumferences and SSIp were significantly lower in GC-treated patients, compared with control subjects in premenopausal women. In postmenopausal women, cortical area and SSIp were significantly higher in GC-treated patients, compared with control subjects, although its significance is unknown. Grip strength was not significantly related to any pQCT parameters in postmenopausal women treated with GC (data not shown). However, in premenopausal women treated with GC, grip strength was significantly related to total and trabecular BMD, cortical area and thickness ($r= 0.533$, $p=0.0001$; $r=0.489$, $p=0.0005$; $r=0.313$, $p=0.0358$; $r=0.389$, $p=0.0078$, respectively), although it was not significantly related to cortical BMD, total area, periosteal and endocortical circumferences and SSIp (data not shown). These findings suggest that grip strength modulated the effect of GC on pQCT parameters in premenopausal women.

Comparisons of CS and Age-matched Controls

Various indices were compared by pQCT between patients with CS and age-matched control subjects in premenopausal or postmenopausal women (Table 5). Total BMD and cortical BMD were significantly lower in patients with CS, compared with control in premenopausal women, but not in postmenopausal women. As for bone geometry indices, cortical area and thickness as well as periosteal circumferences and SSIp were significantly lower in patients with CS, compared with controls in premenopausal women, but not in postmenopausal women. Endocortical circumferences were similar between controls and CS patients in both premenopausal and postmenopausal women.

Comparison of Various Indices by pQCT between GC-treated Women with or without Vertebral Fractures

Various indices were compared by pQCT between GC-treated women with and without vertebral fractures (Table 6). Total and trabecular BMD were significantly lower in GC-treated patients with vertebral fractures, compared with those without vertebral fractures in premenopausal women, but not in postmenopausal women. Total area, cortical area, cortical thickness, periosteal circumferences as well as SSIp were significantly lower in GC-treated patients with vertebral fractures, compared with those without vertebral fractures in premenopausal women, but not in postmenopausal women. Endocortical circumferences were similar between GC-treated patients with and without vertebral fractures in both premenopausal and postmenopausal women.

Effects of GC treatment Details in Premenopausal Women

GC administration was associated a significant change in bone geometry in premenopausal women. We therefore examined the correlation coefficients between bone geometry indices by pQCT and GC treatment in premenopausal women (Table 7). Only duration of GC treatment, but not the present dose or the maximum dose, were significantly correlated with cortical area, cortical thickness and periosteal circumferences, which were significantly affected by GC excess and related to the presence of vertebral fractures in premenopausal women.

Correlations between BMD and Cortical Thickness or Area in Women with and without GC Treatment

We examined the relationships between BMD and cortical thickness or area in women with and without GC treatment. As shown in Table 8, cortical thickness and area were correlated with BMD parameters with and without GC treatment in both premenopausal and postmenopausal women. However, the relationships between cortical area and trabecular or cortical BMD seemed lower in premenopausal women, compared with those in postmenopausal women.

Discussion

To our knowledge, the relationship between GC administration and bone geometry has not been previously studied in humans. In animal studies, GC administration resulted in a decreased periosteal mineralizing surface in rat [30], and the longitudinal axes of vertebrae and lengths of femurs were smaller in GC-treated

minipigs [31]. These findings raise the possibilities that GC administration might reduce bone size in growing animals and might affect bone geometry. In the present study, total bone area, periosteal circumferences and SSIp were significantly lower in GC-treated patients compared with matched controls in premenopausal women, but not in postmenopausal women. Moreover, total bone area, periosteal circumferences and SSIp were significantly lower in GC-treated patients with vertebral fractures, compared with those without vertebral fractures in premenopausal women. These findings suggest that the strength loss and increased fracture risk in patients with GC treatment is evident in the geometry. Therefore, the disruption of the adapted change of bone geometry by GC might partly augment a decrease in bone strength induced by low BMD.

A long-term and continuous pattern of GC use resulted in an increased risk of hip and vertebral [4, 33, 34]. The number of collapsed vertebral bodies was significantly correlated to age of disease onset, disease duration and urinary free cortisol levels at disease diagnosis in patients long term cured from Cushing disease [35]. In several studies, the daily dose of GC was shown to predict fractures [2, 6]. In the present study, duration of treatment was significantly related to reduced cortical area and thickness as well as to smaller periosteal circumferences in premenopausal women, although these parameters were not significantly correlated current or maximum dose level. These findings suggest that duration of GC use might affect fracture risk by affecting bone geometry in premenopausal women with GC treatment. Subjects in our study predominantly suffered autoimmune diseases with relatively small differences daily doses of GC. This may be why we were unable to detect a dose level effect on geometry.

Endogenous GC excess exerts negative effects on bone in patients with CS. Bone formation and resorption markers were decreased and increased in CS, respectively [11, 12]. As for BMD, lumbar spine BMD, which is rich in trabecular bone, is generally decreased in most patients with CS [9, 10]. Decreased BMD was reported in the studies using peripheral pQCT [36]. Moreover, several studies indicated that the fracture risk is increased in CS [7, 8, 13]. In the present study, total bone area, periosteal circumferences and SSIp were significantly lower in patients with CS, compared with control group in premenopausal women, but not in postmenopausal women. These findings suggest that bone geometry is changed in patients with CS, and that endogenous GC excess affects bone geometry in a manner similar to exogenous GC administration. The negative effect of GC on bone formation may be crucial in the pathogenesis of GIO, although the mechanism of GC-inhibited bone formation is not fully elucidated [37]. GC-inhibited bone formation might result in reduced periosteal circumferences, although how GC excess influences bone formation on endocortical and periosteal surfaces is still unknown. Reduced sex steroid hormones are also related to GIO. However, sex hormone deficiency does not seem to be related to GC-induced change of bone geometry in the present study, since those changes were greater in presumably estrogen replete premenopausal women. On the other hand, secondary hyperparathyroidism might be induced in GIO. However, PTH affects bone geometry by increasing periosteal circumferences [38], which is contrary to the effects of bone geometry by GC excess in the present study [21]. Alternatively, as consequence of the catabolic action of GC on protein metabolism, patients with CS possess myopathy with muscle weakness, which might lead to bone loss by

reducing the mechanical stimulus on bone induced by muscle contraction [8]. It is therefore possible that GC excess decreases periosteal circumferences by reducing muscle mechanical tension.

The resistance to flexion of a cylinder is strengthened by increasing its external diameter. An increase in cortical thickness also reinforces bone strength. The biomechanical failure force of the long bone is correlated with the cortical bone thickness, cross-sectional area, and peripheral area moments of inertia (architectural indices of bone rigidity), but not with bone mineral content [39, 40]. Moreover, architectural properties of cortical bone were effective in predicting vertebral fractures in postmenopausal women [41, 42]. BMD is decreased predominantly at trabecular bone in GIO and CS. However, several studies indicated that cortical factors are also affected and related to vertebral fractures by GC excess [24, 25]. These findings indicate that GC excess affects cortical bone as well as trabecular bone. In the present study, there were no significant differences in any cortical parameters between groups with and without vertebral fractures in postmenopausal GC-treated patients. In contrast, in premenopausal patients, total bone area, periosteal circumferences. cortical area, cortical thickness and SSIp were significantly lower in GC-treated patients with vertebral fractures, compared with those without vertebral fractures. These findings suggest that the altered cortical factors are related to the decreased bone strength in patients with GC treatment at least in premenopausal women.

Estrogen state affects bone metabolism and BMD. There have been several studies, which examined the effects of GC excess on bone metabolism in either premenopausal or postmenopausal population [36, 43-45]. Karavitaki et al [43]

reported that bone loss is less profound in the peripheral skeleton of premenopausal female patients than with newly diagnosed patients with CS, although previous study have shown that young/adolescent patients on GC therapy can lose bone mass more rapidly than older patients [46]. In the present study, the changes of bone geometry by GC excess were observed in premenopausal patients, but not in postmenopausal patients. In adulthood, total cross-sectional area and periosteal circumference increases with aging. Moreover, the apparent rate of endocortical bone resorption is greater than that of periosteal apposition. Consequently, cortical area decreases with aging especially in postmenopausal women [23, 41, 47, 48]. Increased bone loss after menopause is associated with increased periosteal apposition rate [20]. These findings suggest that periosteal bone formation enhanced by estrogen withdrawal reverses the decrease of periosteal circumferences in GC excess. Moreover, estrogen may make GC-induced effects on bone geometry more evident by suppressing the mechanical load response on the periosteal surface of long bones in premenopausal women, since endogenous estrogen inhibits periosteal bone apposition in response to mechanical loading (49, 50). Alternatively, GC excess affects potently higher metabolic bone, such as trabecular bone. Several reports suggest that bone turnover is high in premenopausal women [44, 45], and rapid bone loss is observed after GC treatment in young women [46]. Therefore, bone metabolism might be easily influenced by GC excess in premenopausal women, compared with in postmenopausal women, resulting in significant changes of bone geometry in young women. The relationships between cortical area and trabecular or cortical BMD seemed lower in premenopausal women, compared with those in

postmenopausal women with and without GC treatment in the present study. We can therefore speculate that cortical bone geometry is affected by some factors other than BMD in premenopausal women, which might be easily modulated by GC treatment.

In the present study, vertebral fractures were more frequent in postmenopausal women than in premenopausal women. Although the present study suggested that GC-induced bone geometry change is important for reduced bone strength in premenopausal women, but not in postmenopausal women, GC might potently affect BMD and bone quality of vertebral bone in postmenopausal women. Moreover, bone geometry change might play less important role for the strength of vertebral bone, compared its role in forearm bone.

The present study has some limitations. First, sample size was not large enough to make definitive conclusions. Secondly, since the subjects employed in the present study included many patients with autoimmune diseases, the nature of causal diseases for GC treatment might independently increase risk of vertebral fractures as well as influence on bone geometry and fracture risk.

In conclusion, the present study first showed that endogenous and exogenous GC excess affects forearm bone geometry in premenopausal women, but not postmenopausal women. In GC-treated or CS premenopausal women, cortical area and periosteal circumferences were decreased, which might be related to vertebral fracture risk.

References

1. Sambrook P, Birmingham J, Kempler S, Kelly P, Eberl S, Pecock N, Yeates M, Eisman J (1990) Corticosteroid effects on proximal femur bone loss. J Bone Miner Res 5: 1211-1216
2. Van Staa TP, Laan RF, Barton IP, Cohen S, Reid DM, Cooper C (2003) Bone density threshold and other predictors of vertebral fracture in patients receiving oral glucocorticoid therapy. Arthr Rheum 48: 3224-3229
3. Van Staa TP, Leufkens HG, Abenhaim L, Zhang B, Cooper C (2000) Use of oral corticosteroids and risk of fractures. J Bone Miner Res 15: 993-1000
4. Steinbuch M, Youket TE, Cohen S (2004) Oral glucocorticoid use is associated with an increased risk of fracture. Osteoporos Int 15: 323-328
5. Van Staa TP, Leufkens HG, Cooper C (2002) The epidemiology of corticosteroid-induced osteoporosis: a meta-analysis. Osteoporos Int 13: 777-787
6. Kanis JA, Johansson H, Oden AM, Johnell O, de LaetC, Melton III LJ, Tenenhouse A, Reeve J, Silman AJ, Pols HAP, Eisman JA, McCloskey EV, Mellstrom D (2004) A meta-analysis of prior corticosteroid use and fracture risk. J Bone Miner Res 19: 893-899
7. Manelli F, Giustina A (2000) Glucocorticoid-induced osteoporosis. Trend Endocrinol Metab 11: 79-85
8. Kaltsas G, Manetti L, Grossman AB (2002) Osteoporosis in Cushing's syndrome. Front Horm Res 30: 60-72
9. Manning PJ, Evans MC, Reid IR (1992) Normal bone mineral density following cure of Cushing's syndrome. Clin Endocrinol 36: 229-234

10. Hermus AR, Smals AG, Swinkels LM, Huysmans DA, Pieters GF, Sweep CF, Corstens FH, Kloppenborg PW (1995) Bone mineral density and bone turnover before and after surgical cure of Cushing's syndrome. J Clin Endocrinol Metab 80: 2859-2865
11. Mancini T, Doga M, Mazziotti G, Giustina A (2004) Cushing's syndrome and bone. Pituitary 7: 243-246
12. Francucci CM, Pantanetti P, Garrapa GG, Massi F, Arnaldi G, Mantero F (2002) Bone metabolism and mass in women with Cushig's syndrome and adrenal incidentaloma. Clin Endocrinol 57: 587-593
13. Vestergaard P, Lindholm J, Jorgensen JOL, Hagen C, Hoeck HC, Laurberg P, Rejnmark L, Brixen K, Kristensen LO, Feldt-Rasmussen U, Mosekilde L (2002) Increased risk of osteoporotic fractures in patients with Cushing's syndrome. Eur J Endocrinol 146: 51-56
14. Nawata H, Soen S, Takayanagi R, Tanaka I, Takaoka K, Fukunaga M, Matsumoto T, Suzuki Y, Tanaka H, Fujiwara S, Miki T, Sagawa A, Nishizawa Y, Seino Y (2005) Guidelines on the management and treatment of glucocorticoid-induced osteoporosis of the Japanese Society for Bone and Mineral Research. J Bone Mineral Metab 23: 105-109
15. Kaji H, Yamauchi M, Chihara K, Sugimoto T (2006) The threshold of bone mineral density for vertebral fracture in female patients with glucocorticoid–induced osteoporosis. Endocr J 53: 27-34
16. NIH Consensus Development Panel on Osteoporosis. Prevention. Osteoporosis prevention, diagnosis, and the therapy. JAMA 285: 785-795

17. 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
18. Martin RB (1991) Determinants of the mechanical properties of bones. J Biomech 24(Suppl 1): 79-88
19. Smith RW Jr, Walker RR (1964) Femoral expansion in aging women: implications for osteoporosis and fractures. Science 145: 156-157
20. Ahlborg HG, Johnell O, Turner CH, Rannevik G, Karlsson MK (2003) Bone loss and bone size after menopause. N Engl J Med 349: 327-334
21. Chen Q, Kaji H, Iu MF, Nomura R, Sowa H, Yamauchi M, Tsukamoto T, Sugimoto T, Chihara (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: 4655-4658
22. Kaji H, Kosaka R, Yamauchi M, Kuno K, Chihara K, Sugimoto T (2005) 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 52: 659-666
23. Riggs BL, Melton III LJ, Robb RA, Camp JJ, Atkinson EJ, Peterson JM, Rouleau PA, McCollough CH, Bouxsein ML, Khosla S (2004) Population-based study of age and sex differences in bone volumetric density, size, geometry, and structure at different skeletal sites. J Bone Miner Res 19: 1945-1954

24. Tsugeno H, Fujita T, Goto B, Sugishita T, Hosaki Y, Ashida K, Mitsunobu F, Tanizaki Y, Shiratori Y (2002) Vertebral fracture and cortical bone changes in corticosteroid-induced osteoporosis. Osteoporos Int 13: 650-656
25. Lian KC, Lang TF, Keyak JH, Modin GW, Rehman Q, Do L, Lane NE (2005) Differences in hip quantitative computed tomography (QCT) measurement on bone mineral density and bone strength between glucocorticoid-treated and glucocortiocid-naïve postmenopausal women. Osteoporos Int 16: 642-650
26. Smith-Bindman R, Cummings SR, Steiger P, Genant HK (1991) A comparison of morphometric definitions of vertebral fractures. J Bone Miner Res 6: 25-34
27. Ruegsegger P, Durand E, Dambacher MA (1991) Localization of regional forearm bone loss from high-resolution computed tomographic images. Osteoporos Int 1: 76-80
28. Schiessl H, Ferretti JL, Tysarczyk-Niemeyer G (1996) Noninvasive bone strength index as analysis by peripheral quantitative computed tomography (pQCT). In: Schonau E (ed) Pediatric Osteology. New Developments in Diagnostics and Therapy. Elsevier, Amsterdam 147-160
29. 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 Phys 86: 1347-1351
30. Ørtoft G, Oxlund H (1996) Qualitative alterations of cortical bone in female rats after long-term administration of growth hormone and glucocorticoid. Bone 18: 581-590
31. Ikeda S, Morishita Y, Tsutsumi H, Ito M, Shiraishi A, Arita S, Asahoshi S, Narusawa K, Nakamura T (2003) Reductions in bone turnover, mineral, and

structure associated with mechanical properties of lumbar vertebra and femur in glucocorticoid-treated growing minipigs. Bone 2003 33: 779-787.

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

33. Michel BA, Bloch DA, Wolfe F, Fries JF (1993) Fractures in rheumatoid arthritis: an evaluation of associated risk factors. J Rheumatol 20: 1666-1669

34. Ramsey-Goldman R, Dunn JE, Huang CF, Dunlop P, Rairie JE, Fitzgerald S, Manzi S (1999) Frequency for fractures in women with systemic lupus erythematosus: comparison with United States population data. Arthr Rheum 42: 882-890

35. Faggiano A, Pivonello R, Filippella M, Di Somma C, Orio F Jr, Lombard G, Colao A (2001) Spine abnormalities and damage in patients cured from Cushing's disease. Pituitary 4: 153-161

36. Chiodini I, Carnevale V, Torlontano M, FusilliS, Guglielmi G, Peleri M, Modoni S, Di Giorgio A, Liuzzi A, Minisola S, Cammisa M, Trischotta V, Scillitani A (1998) Alterations of bone turnover and bone mass at different skeletal sites due to pure glucocorticoid excess: study in eumenorrheic patients with Cushing's syndrome. J Clin Endocrinol Metab 83: 1863-1867

37. Rubin MR, Bilezikian JP (2002) The role of parathyroid hormone in the pathogenesis of glucocorticoid-induced osteoporosis: a re-examination of the evidence. J Clin Endocrinol Metab 87: 4033-4041

38. Unsi-Rasi K, Semanick IM, Zanchetta JR, Bogado CZ, Eriksen EF, Sato M, Beck IJ (2005) Effects of teriparatide [rhPTH(1-34)] treatment on structural

geometry of the proximal femur in elderly osteoporotic women. Bone 36: 948-958

39. Ferretti JL, Capozza RF, Mondelo N, Zanchetta JR (1993) Interrelationships between densitometric, geometric, and mechanical properties of rat femora: inferences concerning mechanical regulation of bone modeling. J Bone Miner Res 8: 1389-1396
40. Myers ER, Hecker AT, Rooks DS, Hipp JA, Hayes WC (1993) Geometric variables from DXA of the radius predict forearm fracture load in vitro. Calcif Tissue Int 52: 199-204
41. Oleksik A, Ott SM, Vedi S, Bravenboer N, Compston J, Lips P (2000) Bone structure in patients with low bone mineral density with or without vertebral fractures. J Bone Miner Res 15: 1368-1375
42. Yamauchi M, Sugimoto T, Chihara K (2004) Determinants of vertebral fragility: the participation of cortical bone factors. J Bone Miner Metab 22: 79-85
43. Karavitaki N, Ioannidis G, Giannakopoulos F, Marvrokefalos P, Thalassinos N (2004) Evaluation of bone mineral density of the peripheral skeleton in pre- and postmenopausal women with newly diagnosed endogenous Cushig's syndrome. Clin Endocrinol 60: 264-270
44. Di Somma C, Pivonello R, Loche S, Faggiano A, Klain M, Salvatore M, Lombardi G, Colao A (2003) Effect of 2 years of cortisol normalization on the impared bone mass and turnover in adolescent and adult patients with Cushing's disease: a prospective study. Clin Endocrinol 58: 302-308
45. Di Somma C, Pivonello R, Loche S, Faggiano A, Marzullo P, Di Sarno A, Klain M, Salvatore M, Lombardi G, Colao A (2002) Severe impairment of bone mass

and turnover in Cushing's disease: comparison between childhood-onset and adulthood-onset disease. Clin Endocrinol56: 153-158

46. Ruegsegger P, Medici T, Anliker M (1983) Corticosteroid-induced bone loss: a longitudinal study of alternate therapy in patients with bronchial asthma using quantitative computed tomography. Eur J Clin Parmacol 25: 615-620
47. Seeman E (1997) From density to structure: growing up and growing old on the surfaces of bone. J Bone Miner Res 12: 509-521
48. Russo CR, Lauretani F, Bandinelli S, Bartali B, Di Iorio A, Volpato S, Guralnik JM, Harris T, Ferrucci L (2003) Aging bone in men and women: beyond changes in bone mineral density. Osteoporos Int 14: 531-538
49. Vanderschueren D, Venken K, Ophoff J, Bouillon, Boonen S (2006) Sex steroids and the periosteum-reconsidering the roles of androgens and estrogens in periosteal expansion. J Clin Endcocrinol Metab 91: 378-382
50. Saxon LK, Turner CH (2006) Low-dose estrogen treatment suppresses periosteal bone formation in response to mechanical loading. Bone 39: 1261-1267

Table 1. Basal diseases of GC-treated patients

	Premenopausal women	Postmenopausal women
Autoimmune diseases	40	22
Neurological diseases	3	16
Inflammatory bowel diseases	1	3
Dermatological diseases	0	3
Hematological diseases	1	2
Respiratory diseases	3	0
Granulomatous diseases	0	2
Total	48	48

Table 2. Baseline characteristics of control subjects and GC-treated patients

	Premenopausal women		Postmenopausal women	
	GC(-)	GC(+)	GC(-)	GC(+)
Age (yr)	33.5 ± 7.7	35.2 ± 8.2	62.8 ± 6.7	60.2 ± 8.2
Height (cm)	157.4± 5.3	156.5 ± 5.6	153.7±5.3	152.6 ± 5.4
Body weitht (kg)	53.8 ± 10.8	52.2 ± 8.0	52.2 ± 6.4	49.8 ± 7.6
BMI (kg/m^2)	21.7 ± 4.2	21.3 ± 3.1	22.1 ± 2.5	21.3 ± 3.0
Glucocorticoid treatment				
Present dose (mg/day)		10.3 ± 6.5		11.3 ± 9.5
Maximum dose (mg/day)		43.5 ± 12.9		40.3 ± 17.0
Duration of treatment(months)		87.5 ± 92.3		87.0 ± 89.0

All data are presented as means ± SD. GC, glucocorticoid.

Table 3. Baseline characteristics of control subjects or patients with Cushing's syndrome

	Premenopausal women		Postmenopausal women	
	Control	Cushing	Control	Cushing
N	25	4	38	6
Age (yr)	33.7 ± 8.4	34.0 ± 13.8	66.7 ± 7.8	66.7± 6.5
Height (cm)	157.2 ± 3.9	157.7 ± 6.0	149.5± 2.7	149.0± 2.3
Body weitht (kg)	53.6 ± 6.7	54.9 ± 1.7	50.9± 5.2	52.1± 7.8
BMI (kg/m^2)	21.7 ± 3.0	21.7 ± 1.1	22.8± 2.3	23.4± 3.2
Cortisol (mg/dl)		20.3 ± 3.8		15.7 ± 2.9
Urinary free cortisol (mg/day)		318 ± 139		193 ± 76
Urinary 17-OHCS (mg/day)		15.9 ± 4.7		13.0 ± 1.1

All data are presented as means ± SD.

Table 4. Comparison of various indices by pQCT between women with and without GC treatment

	Premenopausal women		Postmenopausal women	
	GC(-)	GC(+)	GC(-)	GC(+)
Total BMD (mg/cm^3)	396.5±50.9	382.9±77.6	293.1±67.7	297.1±64.6
Trabecular BMD (mg/cm^3)	183.1±37.6	179.1±50.7	112.5±38.5	122.4±43.0
Cortical BMD (mg/cm^3)	1166±33	1177±25	1081±62	1091±62
Total area (mm^2)	115.9±15.8	108.6±16.4*	111.5±17.5	115.5±16.4
Cortical area (mm^2)	68.8±8.61	65.4±9.1	51.8±8.9	55.6±10.3*
Cortical thickness (mm)	2.21±0.23	2.18±0.04	1.62±0.35	1.71±0.34
Periosteal circumferences (mm)	38.1±2.6	36.9±2.7*	37.5±3.1	38.0±2.7
Endocortical circumferences (mm)	24.2±2.7	23.1±2.8	27.3±4.3	27.2±3.5
SSIp (mm^3)	228.2±44.0	207.4±44.3*	179.1±34.5	193.9±39.2*

All data are presented as means ± SD. GC, glucocorticoid; pQCT, peripheral quantitative computed tomography; SSIp, polar strength strain index.

*:p<0.05, compared with each GC-untreated group

Table 5. Comparison of various indices by pQCT between control subjects and patients with Cushing's syndrome

	•Premenopausal •women		Postmenopausal women	
	Control	Cushing	Control	Cushing
Total BMD (mg/cm^3)	398.5±47.2	333.8±70.1**	285.6±54.8	262.3±41.8
Trabecular BMD (mg/cm^3)	178.2±37.9	145.8±31.1	102.2±35.7	99.4±22.8
Cortical BMD (mg/cm^3)	1165±35	1123±42**	1072±58	1054±61
Total area (mm^2)	119.7±12.4	105.0±18.3	112.8±19.3	110.2±9.4
Cortical area (mm^2)	70.3±6.5	58.3±11.4*	49.7±7.3	46.7±7.2
Cortical thickness (mm)	2.22±0.21	1.93±0.30**	1.54±0.29	1.45±0.29
Periosteal circumferences (mm)	38.7±2.1	36.2±3.1**	37.5±3.2	37.2±1.6
Endocortical circumferences (mm)	24.8±2.6	24.1±2.8	27.9±4.2	28.1±3.1
SSIp (mm^3)	237.8±35.8	184.7±50.5**	173.0±31.6	161.7±14.1

All data are presented as means ± SD. pQCT, peripheral quantitative computed tomography; SSIp, polar strength strain index.

*:$p<0.01$; **:$p<0.05$, , compared with each control group

Table 6. Comparison of various indices by pQCT between GC-treated women with and without vertebral fractures

	•Premenopausal •women		Postmenopausal women	
	Vertebral fracture (-)	Vertebral fracture(+)	Vertebral fracture(-)	Vertebral fracture(+)
Total BMD (mg/cm^3)	397.1±69.2	299.7±76.5*	291.4±59.2	306.8±73.4
Trabecular BMD (mg/cm^3)	188.2±47.7	125.4±31.4*	125.0±44.9	118.1±40.4
Cortical BMD (mg/cm^3)	1178±26	1169±15	1086±55	1099±73
Total area (mm^2)	110.8±16.5	95.8±8.4**	114.6±16.9	117.0±15.9
Cortical area (mm^2)	67.2±8.4	54.9±5.3*	54.6±9.5	57.1±11.6
Cortical thickness (mm)	2.23±0.23	1.92±0.18*	1.69±0.33	1.75±0.38
Periosteal circumferences (mm)	37.2±2.7	34.7±1.6**	37.9±2.8	38.3±2.6
Endocortical circumferences (mm)	23.2±2.9	22.6±1.7	27.2±3.7	27.3±3.2
SSIp (mm^3)	214.1±44.0	168.2±19.4**	190.0±37.1	200.5±42.7

All data are presented as means ± SD. GC, glucocorticoid; pQCT, peripheral quantitative computed tomography; SSIp, polar strength strain index.

*:p<0.01; **:p<0.05 , compared with each group without vertebral fracture

Table 7.Relationship between cortical bone parameters and various indices of GC treatment in premenopausal women

	Present dose (mg/day)		Maximum dose (mg/day)		Duration of treatment (months)	
	r	*p*	r	*p*	r	*p*
Total area (mm^2)	0.096	0.516	-0.085	0.565	-0.283	0.052
Cortical area (mm^2)	0.230	0.115	-0.085	0.566	-0.454	0.001*
Cortical thickness (mm)	0.262	0.073	-0.069	0.642	-0.443	0.002*
Periosteal circumferences (mm)	0.093	0.528	-0.088	0.552	-0.289	0.047**
Endocortical circumferences (mm)	-0.057	0.698	-0.046	0.754	-0.030	0.841

All data are presented as means ± SD. GC, glucocorticoid.

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

Table 8. Relationships between BMD and cortical thickness or area in women with and without GC treatment

		Premenopausal women				Postmenopausal women			
		GC(-)		GC(+)		GC(-)		GC(+)	
		C.T.	C.A.	C.T.	C.A.	C.T.	C.A.	C.T.	C.A.
Total BMD	r	0.535*	0.448*	0.578*	0.387*	0.772*	0.640*	0.764*	0.620*
	p	0.0006	0.0056	<0.0001	0.0061	<0.0001	<0.0001	<0.0001	<0.0001
Trabecular BMD	r	0.378	0.362	0.508*	0.302	0.632*	0.505*	0.617*	0.536*
	p	0.0245	0.0319	0.0002	0.0367	<0.0001	<0.0001	<0.0001	<0.0001
Cortical BMD	r	0.459*	0.088	0.508*	0.234	0.681*	0.867*	0.839*	0.664*
	p	0.0043	0.6116	<0.0001	0.1100	<0.0001	<0.0001	<0.0001	<0.0001

GC, glucocorticoid; pQCT, peripheral quantitative computed tomography; C.T., cortical thickness; C.A., cortical area.

*:p<0.01