Endocrine Journal 2006, **53** (1), 27–34

The Threshold of Bone Mineral Density for Vertebral Fracture in Female Patients with Glucocorticoid-induced Osteoporosis

HIROSHI KAJI, MIKA YAMAUCHI*, KAZUO CHIHARA AND TOSHITSUGU SUGIMOTO*

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

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

Abstract. Glucocorticoid (GC)-induced osteoporosis (GIO) is a serious problem for patients taking GC therapy. GC increases risk for fracture. However, there are controversies regarding the threshold of bone mineral density (BMD) in patients with GIO. The present study aimed to examine the relationship between the presence or absence of vertebral fracture and various indices including BMD in 136 female Japanese patients treated with oral GC (102 patients with autoimmune diseases). Moreover, we analyzed the cut-off values of BMD for incidence of vertebral fracture in patients with oral GC use and compared these values with those in control subjects. BMD was measured by dual-energy X-ray absorptiometry of the lumbar spine, femoral neck, and distal one third of radius. We compared various indices between patients taking oral GC with and without vertebral fracture. Age, body height, and body weight were significantly greater, shorter, and lower in the group with vertebral fracture, respectively. As for BMD, age-matched BMD seemed lower in the fracture group, although the differences were significant between both groups only at the femoral neck. Duration of GC treatment was longer in the fracture group. Cut-off values of BMD at lumbar spine, femoral neck, and distal radius were higher in patients with GC treatment compared with those of control group [GC vs control (g/cm^2): 0.807 vs 0.716 at lumbar spine; 0.611 vs 0.581 at femoral; 0.592 vs 0.477 at radius]. The sensitivity and specificity were lower in patients with GC treatment compared with those of control group. The present study demonstrated that the thresholds of BMD for vertebral fracture were higher in Japanese female patients with oral GC treatment at any site compared with postmenopausal subjects. The factors other than BMD were considered to affect bone strength and vertebral fracture risk.

Key words: Glucocorticoid, Vertebral fracture, Bone mineral density, Fracture threshold, Osteoporosis

(*Endocrine Journal* **53**: 27–34, 2006)

GLUCOCORTICOID (GC) is used for the treatment of various serious diseases, such as rheumatic, collagen, and respiratory diseases. GC-induced osteoporosis (GIO) is a serious problem for patients taking GC therapy and many patients suffer from decrease in the activity of daily life and quality of life. About 50% of patients with Cushing syndrome and 30–50% of patients taking long-term GC have atraumatic fracture due to osteopenia [1–3]. Histomorphometric studies of GIO revealed an increase in the number of osteoclasts and bone resorption sites as well as a reduction in bone formation [4]. The effect of GC on bone formation seems to be more crucial in the pathogenesis of GIO [5].

Glucocorticoid (GC) causes bone loss and an increase in bone fragility, resulting in the great increase in fracture risk. Van Staa *et al.* [6] reported that the relative risk during oral GC treatment of non-vertebral fracture was 1.33, hip fracture of 1.61, forearm fracture of 1.09, and vertebral fracture of 2.60. Other studies also confirmed the enhanced risk of vertebral and hip fractures in GIO [2, 7–10]. Lower bone mineral density (BMD) was found in the hip and vertebrae of patients under oral GC therapy [9, 11–14]. However, a meta-

Received: April 19, 2005
Accepted: October 24, 2005
Correspondence to: Dr. Hiroshi KAJI, 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

analysis of prior GC use and fracture risk suggested that fracture risk was only partly explained by BMD [7]. In patients with GC-treated rheumatoid arthritis, lumbar BMD could not be used to predict the risk of vertebral fracture [15]. Moreover, controversies exist about the threshold of BMD in patients with GIO. Selby *et al.* reported that GC did not alter the threshold for vertebral fracture in 391 patients [16]. However, several studies indicated that the threshold of BMD for fracture in patients taking oral GC is increased [17, 18].

The present study was, therefore, performed to examine the relationship between the presence or absence of vertebral fracture and various indices including BMD in 136 female Japanese patients treated with oral GC because of collagen, neurological, dermatological or respiratory diseases. Moreover, we analyzed the cut-off values of BMD for the incidence of vertebral fractures in patients with oral GC use and compared these values with those in control subjects.

Subjects and Methods

Subjects

One hundred thirty-six female Japanese patients who were treated with oral GC for more than 6 months (GC group), and 716 control subjects participated in this study. Basal diseases of GC-treated patients are shown in Table 1. We excluded subjects whose performance status was disturbed. Among 136 patients, 102 patients (75%) were included due to autoimmune diseases. Control subjects were women who visited our outpatient clinic for assessment of metabolic bone diseases, including osteoporosis. Postmenopausal subjects numbered 71 and 622 in GC and control groups, respectively. 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.

Table 1. Basal diseases of GC-treated group

	n
Autoimmune diseaes	102
Neurological diseases	15
Dermatological diseases	6
Respiratory diseases	5
Inframatory bowel diseases	5
Hematological diseases	5
Total	136

Biochemical measurements

Routine serum and urinary chemistry determinations were performed by standard automated techniques. Serum concentrations of intact parathyroid hormone (PTH) were measured by immunoradiometric assay (Allegro Intact PTH IRMA kit; Nichols Institute Diagnostics, San Juan Capistrano, CA; normal range, 10–65 ng/liter), as previously described [19]. Serum level of osteocalcin and urinary level of deoxypyridinoline (Dpd) were measured as described [20].

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 fracture was 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 to the height of the nearest uncompressed vertebral body. On this criterion, 34 and 158 women were diagnosed as having one or more vertebral fractures in the GC and control groups, respectively. Defining vertebral fracture from radiographs of the spine is difficult because there is no gold standard for the types of deformities of vertebral shape resulting from the breakage of bone. Definitions of vertebral fracture 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 [21].

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, femoral neck and distal one third of radius. 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 a given measurement differs from the mean for a sex-, age-, and race-matched reference population. The T-score is the number of SD 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.

Statistical analysis

All data were expressed as the mean ± SD for each index. Comparisons of each group were made with the nonparametric Mann-whitney U-test. P values <0.05 were considered significant. To compare the strength of association between BMD at each of the measurement sites and fractures, we analyzed the areas under receiver operating characteristic (ROC) curves for each site [22]. For each of the BMD measurements at the radius, femoral and lumbar spine sites and for each of the vertebral fracture group, all possible cut-off points were defined and the proportion of subjects without fractures above each point (the specificity) and the proportion of subjects with fractures below each point (the sensitivity) were calculated. This yielded an ROC curve which displayed the relationship between sensitivity and specificity for each BMD measurement as a discriminator between the normal and fracture groups. The optimal criterion, which attempts to maximize both sensitivity and specificity, is usually defined as the point closest to 100 % sensitivity and 100 % specificity.

Table 2. Background data in control and GC-treated groups

	Control	GC-treated
No. of subjects	716	136
No. of subjects with vertebral fracture	158 (22.1%)	34 (25.0%)
No. of postmenopausal women	622	71
Age (years)	61.2±10.9	49.6±15.5**
Body height (cm)	152.5±5.8	154.5±6.1**
Body weight (kg)	51.0±7.9	51.4±8.2
BMI (kg/m^2)	21.9±3.0	21.5±3.1
L2-4BMD (g/cm^2)	0.781±0.157	0.842±0.164**
Zscore	–0.028±1.285	–0.484±1.257**
FN BMD (g/cm^2)	0.617±0.110	0.650±0.118**
Zscore	0.096±1.307	–0.434±1.151**
Rad1/3 BMD (g/cm^2)	0.508±0.086	0.630±0.100**
Zscore	–0.464±1.400	0.653±1.428**

BMI: body mass index; FN: femoral neck; Rad1/3: distal radius
**, control vs GC,; *p<0.01*

Table 3. Background data in GC-treated group

	GC-treated
Serum calcium (mg/dl)	9.64±0.42
Serum phosphorus (mg/dl)	3.40±0.59
ALP [100–303] (IU/l)	196.5±73.1
intact PTH [10–65] (pg/ml)	34.5±13.7
Osteocalcin [2.5–13] (ng/ml)	3.99±2.63
u-Ca/u-Cr	0.28±0.20
u-Dpd [2.8–7.6] (nmol/mmol · Cr)	7.74±7.13
Current dose of prednisolone (mg/day)	10.1±7.4
Maximum dose of prednisolone (mg/day)	40.6±16.3
Duration of glucocorticoid treatment (month)	82.5±82.0

Results

Background data

Baseline indices are shown in Table 2 and 3 in GC and control groups. The incidences of vertebral fracture were 22.1 and 25.0% in control and GC groups, respectively. Younger age was found in GC group. Body weight and body mass index (BMI) were similar in both groups, although body height was higher in GC group, probably due to younger age. BMD, as well as Z-score were higher in GC group at the lumbar spine, femoral neck, and radius. These differences were considered to be due to a younger age in GC group.

As shown in Table 3, serum levels of calcium, intact PTH, and non-specific alkaline phosphatase (ALP) were within normal range in patients under GC treatment, suggesting that GC did not induce secondary hyperparathyroidism in GC-treated group. Serum level of osteoclacin was relatively lower in patients taking GC which signified that the drug reduced bone formation. On the other hand, urinary level of Dpd was higher in the same group of patients which indicated increased bone resorption due to the effects of GC.

Comparison of various indices between patients taking oral GC with or without vertebral fracture

We compared various indices between patients taking oral GC with or without vertebral fracture. As shown in Table 4, age, body height, and body weight were significantly greater, shorter, and lower in the

Table 4. Comparison of various indices between women with and without vertebral fracture in GC-treated group

GC-treated	Vertebral fracture		*p*
	(–)	(+)	
Age (years)	45.8±15.7	57.1±12.6	<0.001**
Body height (cm)	155.7±5.6	150.6±5.9	<0.001**
Body weight (kg)	52.8±7.8	47.6±8.2	<0.001**
BMI (kg/m^2)	21.7±2.9	20.9±3.8	0.238
L2-4BMD Zscore	–0.37±1.31	–0.81±1.03	0.079
FN BMD Zscore	–0.29±1.18	–0.88±0.94	0.010*
Rad1/3 BMD Zscore	0.77±1.21	0.30±1.92	0.099
intact PTH (pg/ml)	33.1±13.2	36.8±16.2	0.193
osteocalcin (ng/ml)	4.12±2.61	3.59±2.70	0.345
u-Ca/u-Cr	0.27±0.21	0.32±0.18	0.342
u-Dpd (nmol/mmol · Cr)	7.21±7.60	9.29±5.32	0.163
Current dose of prednisolone (mg/day)	9.7±7.2	11.5±8.3	0.235
Maximum dose of prednisolone (mg/day)	39.2±14.7	45.0±20.1	0.086
Duration of glucocorticoid treatment (M)	70.1±70.5	118.1±102.3	0.013*

BMI: body mass index; FN: femoral neck; Rad1/3: distal radius **; $p<0.01$, *; $p<0.05$

group with vertebral fracture, respectively. As for BMD, Z-score seemed lower in the fracture group, although the differences were significant between both groups only at the femoral neck. On the other hand, the differences were not significant about serum levels of PTH and osteocalcin as well as urinary level of Dpd between patients with or without vertebral fractures. As regards the usage of GC, the duration of treatment was longer in the fracture group, although current and maximum doses were not significantly different between both groups.

Cut-off values for vertebral fracture

Table 5 shows cut-off values of BMD for vertebral fracture at the point of coincidence between sensitivity and specificity calculated by ROC analyses. Cut-off value discriminates the patients with vertebral fracture from those without fractures. Cut-off values of BMD at the lumbar spine, femoral neck and distal radius were higher in patients with GC treatment compared with those of control group. The sensitivity and specificity were lower in patients with GC treatment compared with those of control group.

Since age was greater in the control group, we performed ROC analyses in the age- and body size-matched GC-treated and control subgroups (110 subjects in each group; age: 53.0 ± 13.8 vs 53.0 ± 13.9 for control vs GC-treated; Height :154.2 ± 6.1 vs 153.9 ± 6.0 for control vs GC-treated; Weight: 51.6 ± 8.2 vs 51.7 ± 8.5 for control vs. GC-treated; BMI: 21.8 ± 2.8 vs 21.8 ± 3.1 for control vs GC-treated). Table 6

Table 5. Cut-off values for vertebral fracture at the point of coincidence between sensitivity and specificity

	Cut-off value			Sensitivity (%)	Specificity (%)
	(g/cm^2)	T-score	(%)		
Control					
L2-4	0.716	–2.66	71	74.8	74.8
Femoral neck	0.581	–1.89	74	75.3	75.3
Radius 1/3	0.477	–3.63	72	72.8	72.8
GC treated					
L2-4	0.807	–1.84	80	66.7	66.7
Femoral neck	0.611	–1.62	78	70.9	70.9
Radius 1/3	0.592	–1.37	89	62.2	62.2

Table 6. Cut-off value for vertebral fracture at the point of coincidence between sensitivity and specificity in age-matched subgroups

	Cut-off value			Sensitivity (%)	Specificity (%)
	(g/cm^2)	T-score	(%)		
Control					
L2-4	0.749	–2.36	75	83.3	83.3
Femoral neck	0.598	–1.74	76	72.2	72.2
Radius 1/3	0.544	–2.12	83	72.3	72.3
GC treated					
L2-4	0.802	–1.88	81	61.5	61.5
Femoral neck	0.606	–1.67	77	66.8	66.8
Radius 1/3	0.583	–1.55	87	56.9	56.9

shows cut-off values of BMD for vertebral fractures at the point of coincidence between sensitivity and specificity calculated by ROC analyses in these age-matched subgroups. Cut-off values of BMD at the lumbar spine and distal radius were higher in patients with GC treatment compared with those of control group, although the differences were less. The sensitivity and specificity were lower in patients with GC treatment compared with those of control group.

Discussion

The incidence of vertebral fracture was higher in the GC group compared with control group, although the subjects of GC group had higher BMD and younger age in the present study. This finding is compatible with previous reports, indicating the increased risk of vertebral fracture in patients taking oral GC [2, 6–10].

In the present study, we compared various indices between women with and without vertebral fracture in patients taking oral GC. Age, body height, and body weight were greater, shorter, and lower in the fracture group, respectively. Age was included in the risk factors for osteoporosis-related vertebral fractures, including GIO [7], which was compatible with the present evidence. Shorter height in the group with vertebral fracture is considered to be partly due to the vertebral deformity by fractures themselves, leading to significant loss of body height. Higher body weight induces the positive impact on bone mass. Moreover, our previous study revealed that lean body mass and serum level of albumin were selected as useful markers, which predicted the risk of osteoporosis vertebral fracture in postmenopausal Japanese women [20], suggesting that the sustained nutritional deficiency affects osteoporosis or vertebral fracture. These findings might explain the reason why the body weight of fracture group was lower in the present study. As for BMD, Z-score at any measured site seemed less in fracture group. However, the difference was significant only at the femoral neck. In previous studies about GC-treated patients [15], BMD at femoral neck was best predictable for fracture risk than the other sites, such as the lumbar spine or the distal radius. These findings were compatible with the present results. Since the differences in BMD were less between patients taking oral GC treatment with and without vertebral fracture, factors other than BMD are considered important, compared with postmenopausal osteoporosis. Duration of GC treatment was significantly longer in fracture group in the present study, which was compatible with previous reports [7, 23, 24]. In several studies, the daily dose of GC was selected to predict fractures [8, 25]. Since most of the present subjects suffer from autoimmune diseases and the differences of daily dose of GC were relatively less among the subjects, the difference of daily dose of GC might not be significant.

The present study revealed that the thresholds of BMD for vertebral fracture were higher at any measured site in patients with oral GC treatment, compared with control group. These findings support previous reports [17, 18]. Moreover, the sensitivity and specificity of cut-off values were lower in patients with oral GC treatment compared with control group, suggesting that BMD is not a very reliable marker for the prediction of fracture risk, compared with postmenopausal osteoporosis. Factors other than BMD might influence the bone strength in patients with oral GC treatment.

The reasons for increased threshold, as well as decreased sensitivity and specificity in patients with oral GC treatment, are still unknown. Bone strength is affected by BMD as well as bone quality, including bone structure, accumulation of micro damage, bone turnover state, bone matrix protein, and mineralization [26]. Several reports revealed the change of bone metabolic indices in patients with GIO or Cushing syndrome [27, 28]. Thus, the change in bone turnover may affect bone strength in patients with GC treatment. However, the differences in bone metabolic indices, such as serum osteocalcin and urinary Dpd were not significant between patients with GC treatment with and without vertebral fracture in the present study. Therefore, the effects of GC on bone turnover are not considered the main reason of increased threshold for vertebral fracture in patients with GC treatment. At the histological level, a decrease in wall thickness of trabecular packets and as a consequence in the trabecular thickness and trabecular bone volume were reported in GIO patients [29]. In the analysis of transiliac biopsy specimens, patients with GIO were characterized by lower bone formation and higher resorption than patients with postmenopausal osteoporosis, and these changes were associated with bone loss caused by a major loss of trabecular connectivity [30]. Moreover, Aaron *et al.* reported plate perforations and disruption of the three-dimensional trabecular architec-

ture in GIO patients [31]. On the other hand, GC decreases the number of osteoblasts and osteocytes by enhanced apoptosis as well as suppressed turnover of cell cycle [32, 33]. Moreover, GC inhibits the synthesis of bone matrix proteins, such as type I collagen and osteocalcin. The apoptosis of osteoblasts and osteocytes induced by GC and subsequently a marked alteration in bone turnover might result in the induction of microarchitechtural changes in bone quality [34]. These findings indicate that the disrupted bone structure might decrease bone strength in patients with GC treatment resulting in the increased fracture threshold of BMD. Alternatively, the change of bone geometry might affect the bone strength in patients with GC treatment. Our previous study revealed that total bone area and external circumferences were weakly but significantly higher in the postmenopausal subjects with fractures, although the fracture group had a significantly larger endocortical circumference and a net reduction of cortical thickness and cortical bone area in the analysis with peripheral quantitative computed tomography [35]. These differences did not seem to be observed in postmenopausal patients with GC use. Therefore, the disruption of the adapted change of bone geometry by GC might partly augment a decrease in bone strength induced by low BMD. Moreover, the increased fall by GC use or the nature of the underlying diseases for which GC were prescribed may affect the risk of fracture risk.

Cut-off values of BMD for vertebral fractures in Japanese were recently analyzed in several studies [36, 37]. Nawata *et al.* recently reported guidelines on the management and treatment of GC-induced osteoporosis of the Japanese Society for Bone and Mineral Research [36]. In that study, they showed cut-off values of BMD to separate fracture and nonfracture cases by analyzing 692 patients including 627 women. Our data confirmed their evidence. However, in our study, the proportion of basal disease is different, since our study did not include patients with rheumatoid arthritis, compared with the previous study. Moreover, we separately analyzed cut-off values of BMD at three sites (lumbar spine, femoral neck, and distal radius).

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 fracture. Namely, the patients with autoimmune diseases may possess the susceptibility for vertebral fractures to oral GC treatment compared with other diseases. Moreover, subjects enrolled in the present study may not represent the general patients undergoing oral GC treatment. Consequently, assessment of large numbers of patients will be necessary.

In conclusion, the present study demonstrated that the thresholds of BMD for vertebral fracture were higher in Japanese female patients with oral GC treatment as compared with postmenopausal subjects. The factors other than BMD are considered to affect bone strength and vertebral fracture risk.

References

1. Ross EJ, Linch DC (1982) Cushing's syndrome-killing disease: discrimininatory value of signs and symptoms aiding early diagnosis. *Lancet* 2: 646–649.
2. Adinoff AD, Hollister JR (1983) Steroid-induced fractures and bone loss in patients with asthma. *N Engl J Med* 309: 265–268.
3. Ohmori N, Nomura K, Ohmori K, Kato Y, Itoh T, Takano K (2003) Osteoporosis is more prevalent in adrenal than in pituitary Cushing's syndrome. *Endocr J* 50: 1–7.
4. Bressot C, Meunier J, Lejeune E, Edouard C, Darby A (1979) Histomorphometric profile, pathophysiology and reversibility of of glucocorticoid-induced osteoporosis. *Metab Bone Dis Rel Res* 1: 303–311.
5. Canalis E (1996) Clinical review 83: Mechanisms of glucocorticoid action in bone: implications to glucocorticoid-induced osteoporosis. *J Clin Endocrinol Metab* 81: 3441–3447.
6. Van Staa TP, Leufkens HGM, Abenhaim L, Zhang B, Cooper C (2000) Use of oral corticosteroids and risk of fractures. *J Bone Miner Res* 15: 993–1000.
7. Steinbuch M, Youket TE, Cohen S (2004) Oral glucocorticoid use is associated with an increased risk of fracture. *Osteopors Int* 15: 323–328.
8. Kanis JA, Johansson H, Oden Am Johnell O, de Laet C, 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.
9. Van Staa TP, Leufkens HGM, Cooper C (2002) The epidemiology of corticosteroid-induced osteoporosis: a meta-analysis. *Osteopors Int* 13: 777–787.
10. Luengo M, Picado C, Del Rio L, Guanabens N, Montserrat JM, Setoain J (1991) Vertebral fractures in

steroid dependent asthma and involutional osteoporosis: a comparative study. *Thorax* 46: 803–806.
11. Laan RF, van Riel PL, van Erning LJ, Lemmens JA, Ruijs SH, van de Putte LB (1992) Vertebral osteoporosis in rheumatoid arthritis patients: effect of low dose prednisone therapy. *Brit J Rheumatol* 31: 91–96.
12. Buckley LM, Leib ES, Cartularo KS, Vacek PM, Cooper SM (1995) Effects of low dose corticosteroids on the bone mineral density of patients with rheumatoid arthritis. *J Rheumatol* 22: 1155–1159.
13. Laan RF, van Riel PL, van de Putte LB, van Eming LJ, van Hof MA, Lemmens JA (1993) Low-dose prednisone induces rapid reversible axial bone loss in patients with rheumatoid arthritis: a randomized, controlled study. *Ann Int Med* 119: 963–968.
14. 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.
15. Peel NF, Moore DJ, Barrington NA, Bax DE, Eastell R (1995) Risk of vertebral fracture and relationship to bone mineral density in steroid treated rheumatoid arthritis. *Ann Rheu Dis* 54: 801–806.
16. Selby PL, Halsey JP, Adams KRH, Klimiuk P, Knight SM, Pal B, Stewart IM, Swinson DR (2000) Corticosteroids do not alter the threshold for vertebral fracture. *J Bone Miner Res* 15: 952–956.
17. 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. *Osteopors Int* 13: 650–656.
18. Wallach S, Cohen S, Reid DM, Highes RA, Hosking DJ, Laan RF, Doherty SM, Maricic M, Rosen C, Brown J, Barton I, Chines AA (2000) Effects of risedronate treatment on bone density and vertebral fracture in patients on corticosteroid therapy. *Calcifi Tis Int* 67: 277–285.
19. 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: 2655–4658.
20. Nakaoka D, Sugimoto T, Kaji H, Kanzawa M, Yano S, Yamauchi M, Sugishita T, Chihara K (2001) Determinants of bone mineral density and spinal fracture risk in postmenopausal Japanese women. *Osteopors Int* 12: 548–554.
21. 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.
22. Hanley JA, McNail BJ (1982) The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* 143: 29–36.
23. Michel BA, Bloch DA, Wolfe F, Fries JF (1993) Fractures in rheumatoid arthritis: an evaluation of associated risk factors. *J Rheumatol* 20: 1666–1669.
24. 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.
25. 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.
26. NIH Consensus Development Panel on Osteoporosis Prevention (2001) Osteoporosis prevention, diagnosis, and the therapy. *JAMA* 285: 785–795.
27. Prummel MF, Wiersinga WM, Lips P, Sanders TB, Sauerwein HP (1991) The course of biochemical parameters of bone turnover during treatment with corticosteroids. *J Clin Endocrinol Metab* 72: 382–386.
28. Osella G, Terzolo M, Reimondo G, Piovesan A, Pia A, Termine A, Paccotti P, Angeli A (1991) Serum markers of bone and collagen turnover in patients with Cushing's syndrome and in subjects with adrenal incidentalomas. *J Clin Endocrinol Metab* 82: 3303–3307.
29. Chapard D, Legerand E, Basle MF, Fromont P, Racineux JL, Rebel A, Audran M (1996) Altered trabecular architecture induced by corticosteroids: a bone histomorphometric study. *J Bone Miner Res* 11: 676–685.
30. Carbonare LD, Arlot ME, Chavassieux PM, Roux JP, Portero NR, Meunier PJ (2001) Comparison of trabecular bone microarchitecture and remodeling in glucocorticoid-induced and postmenopausal osteoporosis. *J Bone Miner Res* 16: 97–103.
31. Aaron JE, Francis RM, Peacock M, Makins NB (1989) Contrasting microanatomy of idiopathic and corticosteroid-induced osteoporosis. *Clin Orthoped* 243: 294–305.
32. Weistein RS, Jika RL, Parfitt AM, Manolagas SC (1998) Inhibition of osteoblastogenesis and promotion of apoptosis of osteoblasts and osteocytes by glucocorticoids. Potential mechanisms of their deleterious effects on bone. *J Clin Invest* 102: 274–282.
33. Smith E, Redman RA, Logg CR, Coetzee GA, Kasahara N, Frenkel B (2000) Glucocorticoids inhibit developmental stage-specific osteoblast cell cycle. Dissociation of cyclin A-dependent kinase 2 from E2F4-p130 complexes. *J Biol Chem* 275: 19992–20001.
34. Manolagas SC (2000) Corticosteroids and fractures: a close encounter of the third cell kind. *J Bone Miner Res* 15: 1001–1005.
35. Yamauchi M, Sugimoto T, Chihara K (2004) Determinants of vertebral fragility: the participation of cortical bone factors. *J Bone Miner Metab* 22: 79–85.

36. 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) Guldelines on the management and treatment of glucocorticoid-induced osteoporosis of the Japanese Society for Bone and Mineral Research. *J Bone Miner Metab* 23: 105–109.
37. Tanaka I, Oshima H (2003) A longitudinal study of diagnosis and treatment for glucocorticoid-induced osteoporosis. *Osteoporosis Jpn* 11: 11–14.