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Urinary deoxypyridinoline is a BMD-independent marker for prevalent vertebral fractures in postmenopausal women treated with glucocorticoid

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Conflicts of interest None

Mini-Abstract: Urinary deoxypiridinoline (DPD) level was associated with prevalent vertebral fractures in glucocorticoid (GC)-treated postmenopausal women independently of lumbar spine bone mineral density (BMD).

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Running title: Glucocorticoid-induced osteoporosis and bone metabolic indices

Abstract

Introduction Bone metabolic indices are the potential predictors of bone fragility. However, their diagnostic efficiency for identifying the risk of GC-induced vertebral fractures is still unclear. We therefore evaluated whether bone metabolic indices would assess the risk of vertebral fractures in GC-treated women. *Methods* One hundred seventy-five women treated with GC for more than 6 months were enrolled in this study. *Results* Both premenopausal and postmenopausal women with vertebral fractures had significantly higher urinary DPD levels than those without vertebral fractures. When multivariable logistic regression analysis was performed with the presence of vertebral fractures as a dependent variable and each of DPD or osteocalcin level adjusted for age, weight, height, current and maximum doses of GC, duration of GC treatment, as well as lumbar spine BMD as an independent variable, DPD level was identified as a factor associated with the presence of vertebral fractures in postmenopausal women, but not in premenopausal women. *Conclusion* Urinary DPD level was significantly associated with prevalent vertebral fractures in

GC-treated postmenopausal women independently of lumbar spine BMD.

Key word: Glucocorticoid; Osteoporosis; Fracture; Bone metabolic index

Introduction

Glucocortiocid (GC)-induced osteoporosis (GIO) is a serious problem for patients taking GC therapy. GC administration causes bone loss and an increase in bone fragility, resulting in a great increase in fracture risk [1-5]. Excessive intrinsic GC due to Cushing's syndrome is associated with increased bone resorption markers, decreased bone mineral density (BMD) and increased fracture risk [6-10]. However, a meta-analysis of prior GC use and fracture risk suggested that fracture risk was explained only partly by BMD [3]. Moreover, the thresholds of BMD for vertebral fractures were higher in patients with oral GC treatment [11-13]. Thus, the factors other than BMD are considered to affect fracture risk in GC-treated patients. There have been several reports, which examined the risk factors for fractures in GIO. Age was an important and independent risk factor for vertebral deformity in patients taking long-term GC therapy [14]. Long duration and continuous pattern of GC use demonstrated a significant 5-fold increased risk of hip fractures and 5.9-fold increased risk of vertebral fractures [3]. Our previous study revealed that body composition is

related to vertebral fracture risk in GC-treated patients [15]. Bone quality is influenced by accumulated micro damage, bone turnover effects, anomalies of bone matrix proteins and degree of mineralization [16]. We previously reported that endogenous or exogenous GC excess affects bone geometry of forearms of premenopausal, but not postmenopausal women treated with GC, which might influence a decrease in bone strength [17]. Although bone metabolic indices are related to bone turnover and bone quality in primary osteoporosis [18], whether bone metabolic indices are useful to predict fracture risk in GC-treated patients remains still unknown.

In postmenopausal women, low-dose GC therapy significantly decreases osteocalcin (OCN), type I N-terminal procollagen, propeptide of type I C-terminal procollagen [19]. Several reports indicate that serum OCN levels are decreased in the patients treated with GC or Cushing's syndrome, although the controversy exists about the bone resorption indices [8, 9, 20-22]. However, how the changes in bone metabolic indices by GC excess influence vertebral fracture risk and their diagnostic efficiency for identifying the risk of GC-induced vertebral

fractures in the different estrogen state is still unclear. In the present study, we therefore evaluated whether bone markers would assess the risk of vertebral fractures in GC-treated women by separating premenopausal and postmenopausal subjects.

Subjects and methods

Subjects

One hundred seventy-five female patients who were treated with oral GC for more than 6 months (GC patients) participated in this study. Among GC patients, 85 and 90 patients were premenopausal and postmenopausal, respectively. The underlying diseases are shown in Table 1. The subjects with rheumatic arthritis were excluded, because bone metabolic indices might be influenced by rheumatic arthritis itself. We excluded those subjects whose activity of daily life was disturbed. The study was approved by the ethical review board of our institutions and was in compliance with the Helsinki declaration. 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 (IRMA) (Allegro Intact PTH IRMA kit; Nichols Institute Diagnostics, San Juan Capistrano, CA; normal range, 10-65 ng/L), as previously described [23].

Serum OCN was assayed by IRMA using tracer anti-OCN (12-33) antibody and solid-phase anti-OCN (30-49) antibody with synthetic human OCN (1-49) as a standard. Epitope mapping revealed that anti-OCN (12-33) antibody recognizes OCN (22-38), and anti-OCN (30-49) antibody recognizes OCN (38-43). This assay is expected to measure the major portions of bone-derived OCN, reflecting the bone formation process. The intra- and interassay variations for serum level of OCN were 4.6 % and 6.3 %, respectively. Normal range was 2.5-13 ng/ml.

Urinary level of free deoxypyridinoline (DPD) was measured by a competitive enzyme immunoassay utilizing a monoclonal anti-DPD antibody coated on the

strip to capture DPD. DPD in the sample competes with conjugated DPD-alkaline phosphatase for the antibody and the reaction is detected with a pNPP substrate. The data were corrected for urinary concentration by creatinine. The sensitivity of the assay is 1.1 nmol/l. The intra- and interassay variations for DPD were less than 10 %. Normal range of DPD was 2.8-7.6 nmol/mmol.Cr.

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 T_4 to L_4 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. 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 [24].

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

BMD values were measured by DXA using QDR-2000 (Hologic Inc., Waltham, MA) at 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. The coefficient of variation was obtained in vitro using ‘phantom’ with at least four time measurements for the same subject. Normative data were obtained from a population-based database for Japanese Society of Bone and Mineral Research in 1996.

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. Multivariable logistic regression analyses were performed to evaluate association between various indices and vertebral fractures. P values < 0.05 were considered significant.

Results

Background data

Baseline characteristics and bone metabolism data of premenopausal and postmenopausal women treated with GC are shown in Tables 2 and 3. Mean age of each group was 33.9 ± 8.6 and 61.4 ± 8.2 in premenopausal and postmenopausal women treated with GC, respectively. Body mass index (BMI)

was similar in both groups. Present dose and duration of treatment of GC were similar in both groups, although maximum dose of GC were a little lower in the postmenopausal group, compared to that in the premenopausal group. Mean present dose of predonisolone were 10.1 ± 5.1 and 10.8 ± 7.8 mg in premenopausal and postmenopausal women treated with GC, respectively. BMD values were significantly lower in postmenopausal women at all sites, compared to those in premenopausal women. Bone metabolic indices in postmenopausal women were significantly higher, compared to those in premenopausal women. There were no correlations between each of OCN or DPD level versus age or BMD values in either group (data not shown).

Comparison of various indices between subjects with and without vertebral fractures

We compared various indices between subjects with and without vertebral fractures in premenopausal and postmenopausal women separately. As shown in Table 4, premenopausal women with vertebral fractures were significantly shorter,

and had a longer duration of treatment, lower BMD values at all site, and higher urinary DPD levels than those without vertebral fractures. Postmenopausal women with vertebral fractures had lower lumbar spine BMD values and higher urinary DPD levels than those without vertebral fractures (Table 5). Serum OCN levels were similar with or without vertebral fractures in both premenopausal and postmenopausal women.

Associations between the presence of vertebral fractures and various indices

Multivariable logistic regression analysis was performed with the presence of prevalent vertebral fractures as a dependent variable and each of DPD or OCN level adjusted for age, weight, height, current and maximum doses of GC, duration of GC treatment, as well as lumbar spine BMD as an independent variable. As for postmenopausal women, current and maximum dose of GC was also included as an independent variable. As shown in Table 6, urinary DPD level was identified as a factor associated with the presence of vertebral fractures in postmenopausal women, but not in premenopausal women.

Discussion

Several studies indicated that bone formation indices, especially serum OCN is decreased and bone resorption indices are increased in the patients with Cushing's syndrome [8, 9, 20, 21], although several inconsistencies of data exist dependent on study design and populations. Moreover, Dovio et al [25] reported that high dose GC administration caused an immediate and persistent decrease in bone formation indices and a rapid and transient increase in bone resorption indices. Our recent prospective study revealed that serum OC level showed a marked decrease on the day 3 of GC therapy, and that both serum and urinary type I collagen cross-linked N-telopeptide levels significantly increased on day 7 of GC therapy [26]. These findings indicate that GC excess reduces serum OCN and increases bone resorption indices, including urinary Dpd , although serum bone-type alkaline phosphatase level does not seem to be sensitive to the effects of GC excess, compared to serum OCN. Numerous studies with long-term GC-treated patients indicate that serum OCN levels are significantly

reduced, although the changes of other bone metabolic indices are not apparent or inconsistent [27]. In the present study, urinary DPD levels seemed to be high in GC-treated postmenopausal women, although serum OCN levels were within normal range in both premenopausal and postmenopausal women treated with GC. These findings suggest that DPD level might be useful for the clinical assessment especially for postmenopausal women treated with GC.

In the present study, urinary DPD levels were significantly higher in the group with vertebral fractures, compared to those without vertebral fractures in both premenopausal and postmenopausal women treated with GC, although serum OCN levels were not significantly different between both groups. Moreover, in multivariable logistic regression analysis, urinary DPD, but not serum OCN, was significantly related to prevalent vertebral fractures independently of lumbar spine BMD, when age, body weight, body height, current and maximum dose of GC and duration of GC treatment were adjusted, in postmenopausal women treated with GC. These findings indicate that urinary DPD is useful as a predictor of vertebral fracture risk independently of BMD measurement in postmenopausal

women treated with GC. Although the data of the other bone resorption indices are not available in this study, the measurement of bone resorption indices might be important to assess the fracture risk in postmenopausal GC-treated patients. In primary osteoporosis, the measurement of bone resorption indices is useful to evaluate vertebral fracture risk independently of BMD and is considered to be one of the valuable tools to measure bone quality [18]. Since the efficacy of BMD measurement are relatively limited for the predictor of fracture risk in GIO, compared to that in primary osteoporosis, urinary DPD is expected as an important marker in GC-treated postmenopausal women for the prevention of fractures.

In the present study, urinary DPD was not significantly related to prevalent vertebral fractures in premenopausal women treated with GC, although urinary DPD levels were significantly higher in the group with vertebral fractures in those patients. These findings suggest that an increase in bone resorption are not directly linked to an increase in vertebral fracture risk in the presence of intrinsic estrogen in GC-treated patients. On the other hand, estrogen depletion by

menopause might lead to accelerated bone resorption directly linked to enhanced bone fragility, resulting in contributing an increase in vertebral fracture risk in GC-treated patients. It is possible that decreased bone trabecular connectivity by estrogen depletion accelerates an increase in bone fragility by enhanced bone resorption in these patients.

Serum OCN, a late osteoblast differentiation marker, decreases in the early term after the initiation of GC treatment [25, 26], and it is a sensitive marker in long-term GC-treated patients. However, whether a change in serum OCN would be related to fracture risk has been unknown in GC-treated patients. In the present study, serum OCN levels were not different between the groups with and without vertebral factures in both premenopausal and postmenopausal women treated with GC, which were compatible with our previous reports [15]. Moreover, serum OCN was not related to prevalent vertebral fractures in multivariable logistic regression analysis. These findings indicate that a decrease in serum OCN is not related to an increase in vertebral fracture risk in both premenopausal and postmenopausal women treated with GC.

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. Thirdly, we cannot rule out the possibility that vertebral fractures were overestimated by the criterion of 20 %, since it might be too low for thoracic fractures.

In conclusion, urinary DPD level was significantly associated with prevalent vertebral fractures in GC-treated postmenopausal women. This association was independent of lumbar spine BMD, suggesting that the marker might reflect bone strength rather than bone mass.

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Table 1. Basal disease of patients treated with GC

	Premenopausal group	Postmenopausal group
autoimmune diseases	68	33
dermatological diseases	6	16
neurological diseases	5	23
respiratory diseases	2	5
inflammatory bowel diseases	2	0
hematological diseases	1	5
granulomatous diseases	1	7
renal disease	0	1
total	85	90

Table 2. Baseline characteristics of subjects treated with GC

	Premenopausal women	Postmenopausal women
N	85	90
Age (yr)	33.9±8.6	61.4±8.2**
Body height (cm)	157.6±6.7	152.8±5.7**
Body weight (kg)	55.1±9.7	51.4±7.8**
BMI (kg/m^2)	22.2±3.6	22.0±3.1
Maximum dose (mg/day)	44.3±15.1	38.4±17.3*
Present dose (mg/day)	10.1±5.1	10.8±7.8
Duration of treatment (m)	83.0±78.8	83.0±92.1

*, $p<0.01$; **,$p<0.05$, compared to the premenopausal group

Table 3. Baseline bone metabolism data of subjects treated with GC

	Premenopausal women	Postmenopausal women
Lumbar BMD (g/cm^2)	0.919±0.144	0.797±0.147**
Z-Score	-0.721±1.257	-0.222±1.105**
Femoral BMD (g/cm^2)	0.713±0.116	0.606±0.095**
Z-Score	-0.489±1.055	-0.236±1.127
Radius BMD (g/cm^2)	0.681±0.072	0.546±0.086**
Z-Score	0.655±1.314	0.345±1.462
DPD (nmol/mmol· Cr)	5.9±2.9	7.8±4.1**
OCN (ng/ml)	3.3±1.7	4.9±3.0**

*, p<0.01; **,p<0.05, compared to the premenopausal group

Table 4. Comparison of various indices between premenopausal subjects with and without vertebral fractures

	Vertebral fractures (-)	Vertebral fractures (+)
N	79	6
Age (yr)	33.5±8.6	38.7±6.9
Body height (cm)	158.1±6.5	151.2±5.2*
Body weight (kg)	55.5±9.9	50.5±5.5
BMI (kg/m^2)	22.2±3.6	22.1±3.8
Maximum dose (mg/day)	43.6±14.8	53.3±16.3
Present dose (mg/day)	10.1±4.9	10.5±7.7
Duration of treatment (month)	76.1±71.7	174.3±116.2**
Lumber BMD (Z-Score)	-0.614±1.227	-2.132±0.722**
Femoral BMD (Z-Score)	-0.393±1.016	-1.745±0.742**
Radius BMD (Z-Score)	0.820±1.121	-1.517±1.828**
DPD (nmol/mmol· Cr)	5.7±2.7	8.8±4.6**
OCN (ng/ml)	3.3±1.7	3.3±1.8

*, $p<0.01$; **,$p<0.05$, compared to the group without vertebral fractures

Table 5. Comparison of various indices between postmenopausal subjects with and without vertebral fractures

	Vertebral fractures (-)	Vertebral fractures (+)
N	34	56
Age (yr)	60.8±7.8	62.3±8.8
Body height (cm)	153.4±5.4	151.8±6.1
Body weight (kg)	52.3±6.6	50.1±9.3
BMI (kg/m^2)	22.2±2.9	21.7±3.5
Maximum dose (mg/day)	36.8±15.8	41.2±19.6
Present dose (mg/day)	10.4±8.2	11.4±7.1
Duration of treatment (month)	87.4±87.2	75.8±100.4
Lumbar BMD (Z-Score)	0.041±1.136	-0.654±0.913**
Femoral BMD (Z-Score)	-0.145±1.029	-0.383±1.272
Radius BMD (Z-Score)	0.370±1.341	0.305±1.657
DPD (nmol/mmol · Cr)	6.9±3.0	9.3±5.2**
OCN (ng/ml)	5.2±3.0	4.5±2.9

**,p<0.05, compared to the group without vertebral fractures

Table 6. Associations between the presence of vertebral fractures and various indices in GC-treated women

Premenopausal	Odds Ratio (95%CI) P value	Postmenopausal	Odds Ratio (95%CI) P value
Lumbar BMD	0.03 (0.001-0.80) 0.036	Lumbar BMD	0.39 (0.20-0.77) 0.007
OCN	1.05 (0.13-8.59) 0.966	OCN	0.62 (0.35-1.11) 0.107
DPD	2.27 (0.55-9.42) 0.259	DPD	2.14 (1.22-3.74) 0.008

Multivariate analysis adjusted for age, body weight, body height, duration of treatment with GC and age, body weight, body height, current/maximum dose of GC, duration of treatment with GC for premenopausal and postmenopausal women, respectively