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Analysis of Factors Affecting Increase in Bone Mineral Density at Lumbar Spine by Bisphosphonate Treatment in Postmenopausal Osteoporosis

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Abstract

Bisphosphonate is an effective drug to reduce the fracture risk in osteoporotic patients; however, the factors that affect the efficacy of bisphosphonate treatment are not fully known, especially in Japanese patients. In the present study, we examined the relationships between an increase in lumbar spine bone mineral density (BMD) by bisphosphonates and several pretreatment parameters, including biochemical, bone/mineral and body composition indices in 85 postmenopausal osteoporotic patients treated with alendronate or risedronate. BMD increase was measured by dual-energy x-ray absorptiometry at the lumbar spine before and 2 years after treatment. BMD increase at the lumbar spine was observed as independent of age, height, weight, body mass index and fat mass, although lean body mass seemed slightly related. On the other hand, fasting plasma glucose (FPG) levels were significantly and positively related to BMD increase at the lumbar spine. In multiple regression analysis, FPG levels were not significantly related to BMD increase at the lumbar spine when lean body mass was considered. As for bone/mineral parameters, BMD increase at the lumbar spine was not significantly related to serum levels of calcium, PTH and alkaline phosphatase or urinary levels of deoxypyridinoline and calcium excretion. As for BMD parameters, Z scores of BMD at any site and bone geometry parameters obtained by forearm peripheral quantitative computed tomography were not significantly related to BMD increase at the lumbar spine. BMD increases at the lumbar spine were similar between groups with or without vertebral fractures. In conclusion, BMD increase at the lumbar spine by bisphosphonate treatment was not related to any pretreatment parameters, including body size, body composition and bone/mineral metabolism in postmenopausal Japanese women with primary osteoporosis, although FPG correlated to BMD partly through lean body mass.

Key words: Osteoporosis; bisphosphonate; bone mineral density; glucose; body composition

Introduction

Treatment of osteoporosis will be important as the number of elderly patients increases. In the recent decade, the development of drugs for osteoporosis has rapidly progressed. Among them, bisphosphonates are one of the most important agents for the reduction of osteoporotic fractures. Alendronate and risedronate are aminobisphosphonates, clinically used for osteoporosis, and numerous lines of evidence report a strong increase in bone mineral density (BMD) by bisphosphonates by suppressing bone resorption, resulting in reduced fracture risk in osteoporotic patients [1–3]. However, the factors affecting the efficacy of bisphosphonate treatment are not fully clear, especially in Japanese patients.

Several researchers have examined the effects of preexisting factors on bisphosphonate treatment in postmenopausal osteoporosis [4–7]. In most reports, the effects of aminobisphosphonates were evident, independent of age, gender, and preexistent fractures [4–7]. Moreover, bisphosphonates were effective even in secondary osteoporosis, such as primary hyperparathyroidism, glucocorticoid-induced osteoporosis, hypogonadism and chronic renal failure [8–11]. On the other hand, some bone metabolic indices, such as N-terminal propeptide of type 1 collagen (PINP), are good predictors to increase bone mineral density or reduce fracture risk by bisphosphonates [12].

In the present study, we examined the relationships between the increase in lumbar spine BMD by bisphosphonates and several pretreatment parameters, including biochemical, bone/mineral and body composition indices in 85 postmenopausal osteoporotic patients treated with alendronate or risedronate.

Materials and methods

Subjects

The subjects were 85 Japanese postmenopausal women aged 48–84 years (mean 69.1 ± 7.5 years) who visited our outpatient clinic, and were diagnosed with primary osteoporosis, based on diagnostic criteria by the Japanese Society for Bone and Mineral Research [13]. We excluded subjects whose daily activities were found to be diminished by medical review and physical examination. Patients were treated with bisphosphonates (alendronate or risedronate) for 2

years. Nineteen subjects were simultaneously treated with 0.5–1 µg of alfacalcidol. None had hepatic or renal dysfunction, thyroid diseases or systemic diseases which might affect bone metabolism. All subjects were free of drugs known to influence bone metabolism or body composition until the time of the present study.

The study was approved by the ethics 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; normal range, 10–65 ng/liter), as previously described [14]. Urinary level of deoxypyridinoline (Dpd) was measured as previously described [14].

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 based on diagnostic criteria in the Japanese Society for Bone and Mineral Research [13].

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 (cm²) and bone mineral content (BMC) (g) and expressed absolutely in g/cm². BMD at the lumbar spine was calculated by eliminating vertebral bodies with vertebral fractures. 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 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' with at least four time measurements for the same subject. Normative data were obtained from a population-based database for the Japanese Society of Bone and Mineral Research in 1996.

Measurement of body composition

Bone mineral content (BMC), lean body mass (LBM) and fat mass were measured by DXA (QDR-2000 Hologic Inc, Boston, MA, USA), using whole-body absorptiometry software and expressed in kg. A strong correlation between weight and total body mass measured by DXA ($r=0.98$) was obtained in a preliminary study. Coefficients of variation of measurements of BMC, LBM and fat mass were 0.9, 1.0 and 2.0 %, respectively. The coefficient of variation was obtained in vitro using a 'phantom'.

BMD measurements by pQCT

pQCT analysis was performed on the non-dominant forearm using an XCT-960 device (Stratec, Pforzheim, Germany) with a single energy X-ray source, as previously described [15]. 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 the distal radius and midradius, respectively. To calculate the structural properties of the cortical shell, trabecular and cortical bones were separated. To separate the cortical bone, all voxels ($0.295 \text{ mm} \times 0.295 \text{ mm} \times 1 \text{ mm}$) of the scanned image with a BMD lower than the threshold of 267 mg/cm^3 were eliminated. Cortical BMD and bone geometry indices were measured at the midradius. The cortical area is the region with linear attenuation. Cortical thickness was defined as the mean distance between inner and outer edges of the cortical shell.

Statistical analysis

All data are expressed as the mean $\pm$ SD for each index. 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 Pearson's correlation coefficients were calculated. Multiple regression analysis was performed to determine whether BMD increases at the lumbar spine were independently and significantly associated with FPG when LBM was considered. Comparisons between two 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 1. The incidences of preexisting vertebral fractures were 40% (34 patients). Mean age was 69.1 ± 7.5 . Urinary Dpd levels were high (normal range: 2.8–7.6), although serum levels of calcium and non-specific alkaline phosphatase (ALP) were within the normal range. BMD at any site was low.

Relationships between various parameters and BMD increase at the lumbar spine by bisphosphonates

BMD increase at the lumbar spine was measured by DXA at the lumbar spine before and 2 years after bisphosphonate treatment and expressed as a percentage to the baseline before treatment. The mean BMD increase at the lumbar spine was 6.8 ± 5.3 %. Height, weight and body mass index (BMI) as well as age were not significantly related to BMD increase at the lumbar spine in patients with postmenopausal osteoporosis (age: $r = -0.062$, $p = 0.5766$; height: $r = 0.103$, $p = 0.4388$; weight: $r = 0.163$, $p = 0.2195$; BMI: $r = 0.129$, $p = 0.3311$). As for the relationships between nutritional factors or lipid metabolism indices and BMD increase at the lumbar spine, serum levels of albumin, total cholesterol, HDL-cholesterol and triglyceride were not significantly related to BMD increase at the lumbar spine (albumin: $r = 0.175$, $p = 0.1251$; total cholesterol: $r = 0.082$, $p = 0.4894$; HDL-cholesterol: $r = 0.003$, $p = 0.9792$; triglyceride: $r = -0.036$, $p = 0.7984$). DXA enabled the analysis of body composition in terms of LBM and fat mass easily and precisely [16]; therefore, we examined the relationships between body composition indices (BMC, LBM and fat mass) and BMD increase at the lumbar spine. BMC and fat mass were not related to BMD increase at the lumbar

spine, although LBM seemed slightly related (BMC: $r=0.108$, $p=0.5294$; LBM: $r=0.224$, $p=0.0974$; fat mass: $r=0.083$, $p=0.5426$). Moreover, we assessed the relationship between fasting plasma glucose (FPG) and BMD increase at the lumbar spine. As shown in Figure 1, FPG levels were significantly and positively related to BMD increase at the lumbar spine.

Relationships between various bone/mineral parameters and BMD increase at the lumbar spine by bisphosphonates

We examined the relationships between various bone/mineral parameters and BMD increase at the lumbar spine. Serum levels of calcium and PTH as well as urinary calcium excretion were not significantly related to BMD increase at the lumbar spine (serum calcium: $r=-0.090$, $p=0.4859$; U-Ca/U-Cr: $r=0.116$, $p=0.4671$). Moreover, serum levels of ALP and urinary levels of Dpd were also not significantly related to BMD increase at the lumbar spine (ALP: $r=0.102$, $p=0.4053$; Dpd: $r=0.109$, $p=0.4679$). As for BMD parameters, Z scores of BMD at any site were not significantly related to BMD increase at the lumbar spine (L2-4: $r=-0.151$, $p=0.1739$; FN: $r=-0.049$, $p=0.6684$; R1/3: $r=-0.051$, $p=0.6740$). Among the measured sites, coefficient correlations seemed to be negatively and slightly higher at the lumbar spine, compared with the femoral neck and mid-radius. Bone geometry parameters also affect bone strength and we therefore examined the relationships between various bone geometry parameters obtained by forearm pQCT and BMD increase at the lumbar spine by bisphosphonates. Cortical volumetric BMD was not significantly related to BMD increase at the lumbar spine ($r=-0.078$, $p=0.5611$). Moreover, total area, cortical area and thickness as well as periosteal and endocortical circumferences were not significantly related to BMD increase at the lumbar spine (periosteal circumferences: $r=0.132$, $p=0.3262$; endosteal circumferences: $r=0.113$, $p=0.3982$; total area: $r=0.137$, $p=0.3059$; cortical area: $r=0.022$, $p=0.8684$; cortical thickness: $r=-0.038$, $p=0.7802$).

Effects of preexistent vertebral fracture and alfacalcidol cotreatment on BMD increase at the lumbar spine by bisphosphonates

As shown in Figure 2, BMD increases at the lumbar spine were similar between groups with or without vertebral fractures. On the other hand, BMD increases at

the lumbar spine in groups with alfacalcidol cotreatment were a little higher than that of the group with bisphosphonate alone, although the differences were not significant (Figure 3).

Relationships between various parameters and FPG

Since FPG levels were significantly related to BMD increase at the lumbar spine, we examined which factors would have an influence. As shown in Table 2, LBM as well as height and weight were significantly related to FPG levels. In multiple regression analysis, FPG levels were not significantly related to BMD increase at the lumbar spine when LBM was considered ($r=0.176$, $p=0.2205$), indicating that FPG levels were related to BMD increase at the lumbar spine partly through LBM. Basal BMD at the lumbar spine was significantly related to weight, BMI, BMC, LBM, BMD at femoral neck and cortical area (weight: $r=0.378$, $p=0.0029$; BMI: $r=0.373$, $p=0.0034$; BMC: $r=0.489$, $p<0.0001$; LBM: $r=0.308$, $p=0.0205$; BMD at the femoral neck: $r=0.462$, $p<0.0001$; cortical area: $r=0.280$, $p=0.0326$), although it was not significant related to the other parameters examined.

Discussion

In several studies [17–19], significantly increased BMD was observed, presumably due to low bone turnover in aged women with type 2 DM, compared with age-matched non-diabetic women. On the other hand, fracture risk was higher in type 2 DM women than in non-diabetic women in most studies [17–21]. High glucose affects bone mineral metabolism. In DM patients, hyperglycemia, insulin insufficiency and advanced glycation endproducts induced osteoblast dysfunction, including the inhibition of differentiation and the increase of apoptosis as well as osteoclast dysfunction, resulting in low bone turnover [22–24]. Several studies showed a decrease in bone formation indices in patients with type 2 DM [17]. In nursing home patients with type 2 DM or controls, glucose modulates bone turnover within a physiological range of glycemia [25]. In the present study, FPG levels were significantly related to BMD increase at the lumbar spine by bisphosphonates. Taken together, physiological elevation of serum glucose might cause low turnover in bone, leading to a relative increase

of BMD. This mechanism may modulate the response of BMD to bisphosphonate treatment.

Lean body mass or fat mass affects BMD, and the nutritional state, such as serum albumin and insulin-like growth factor-1 levels, was related to BMD in postmenopausal women [26, 27]. In addition, several studies suggested that metabolic factors and lipid metabolism also affect BMD [28, 29]; however, serum albumin, total cholesterol, HDL-cholesterol, triglyceride and fat mass were not significantly related to BMD increase at the lumbar spine by bisphosphonate in the present study, although LBM seemed slightly, but not significantly, related to BMD increase at the lumbar spine by bisphosphonates. Moreover, FPG levels were significantly related to BMD increase at the lumbar spine by bisphosphonates. Since FPG levels were significantly related to LBM, weight and height, some factors, which affect muscle volume, may be responsible for the efficacy of bisphosphonates. For example, exercise or physical activity might be important to increase the efficacy of bisphosphonates in postmenopausal osteoporosis.

Efficacy and its influencing factors with bisphosphonate treatment have been investigated in osteoporotic patients. In the present study, age was not significantly related to BMD increase at the lumbar spine by bisphosphonate treatment, which was compatible with previous findings [4, 5]. Non-vertebral fracture efficacy was greater in both osteoporotic and nonosteoporotic women with high pretreatment PINP, although vertebral fracture treatment efficacy in osteoporotic women did not differ significantly according to pretreatment bone metabolic marker levels [12]. On the other hand, baseline levels of urinary Dpd did not influence the anti-vertebral fracture efficacy of risedronate in postmenopausal osteoporotic women [30]. Thus, controversy exists about the effects of bone turnover on the efficacy of bisphosphonates dependent on the study design, bone metabolic indices used and so on. In the present study, urinary Dpd levels and serum non-specific ALP levels were not significantly related to BMD increase at the lumbar spine by bisphosphonates, compatible with the previous study [12, 30]; however, we cannot rule out the possibility that other markers, such as PINP, might predict BMD change by bisphosphonates. In the present study, BMD at any site was not significantly related to BMD increase at the lumbar spine by bisphosphonates, although the Z score of BMD at the

lumbar spine seemed to be weakly, but not significantly, related. The efficacy of bisphosphonate was greater in women with BMD T scores below -2.5 [5, 7]. These and present findings suggest that BMD decrease at the lumbar spine might partly predict the efficacy of bisphosphonates, and lower BMD at the lumbar spine suggests a good indication for bisphosphonate treatment. Bone geometry changes are useful for evaluating bone fragility; however, no pQCT parameters were related to BMD increase at the lumbar spine by bisphosphonate treatment in the present study, indicating that bone geometry change did not affect the response to bisphosphonate treatment in postmenopausal women.

Increased PTH by vitamin D insufficiency may increase bone turnover and bone loss, and several studies have indicated that vitamin D insufficiency is related to reduced BMD and increased fracture risk [31, 32]. In the present study, the group receiving alfacalcidol and bisphosphonates seemed to have a slightly greater BMD increase at the lumbar spine, compared with the group receiving only bisphosphonates, although the differences were not significant, although serum levels of calcium and PTH as well as urinary calcium excretion were not related to BMD increase at the lumbar spine by bisphosphonates. Therefore, vitamin D insufficiency might affect the efficacy of bisphosphonates in postmenopausal osteoporosis. Active vitamin D suppresses the secretion of PTH from the parathyroid gland in a negative feedback manner, and several studies have revealed that serum levels of 25-hydroxyvitamin D₃, the most clinically reliable indicator of vitamin D insufficiency or deficiency, is inversely correlated to serum PTH levels [31, 33]. However, other factors, such as calcium negative balance or bone resorption status, also affect serum PTH levels, which might explain the absence of a negative correlation between serum PTH levels and BMD increase at the lumbar spine by bisphosphonates in the present study. Alternatively, PTH increase might lead to BMD decrease by vitamin D

insufficiency or accelerated bone resorption, resulting in greater increased BMD by bisphosphonate treatment.

Since BMD at the lumbar spine decreased in only 5 subjects, the differences in all parameters measured were not significant between the two groups with BMD increase and BMD decrease at the lumbar spine (data not shown). For example, FPG levels were 91.5 ± 13.4 and 83.4 ± 6.0 mg/dl, respectively ($p=0.1413$). Moreover, the relationships between each parameter and BMD increase at the lumbar spine were similar, even when subjects with BMD decrease were eliminated from the analysis (data not shown).

The present study has some limitations. First, the sample size was not large enough to reach definitive conclusions. Watts et al. reported that changes in BMD did not influence the magnitude of risedronate's effect on nonvertebral fractures [34]; however, Hochberg et al. suggested that larger increases in BMD during treatment appeared to be associated with greater reduction in the risk of nonvertebral fractures [35]. These findings indicate that BMD increase might not represent the efficacy of bisphosphonates, although a large-scale study is necessary to examine the effects of bisphosphonates on fracture risk. Also, hemoglobin A1c or postprandial glucose or responsive insulin secretion in the oral glucose tolerance test might be more suitable for evaluating glucose metabolism, although these data were not available in the present study.

In conclusion, BMD increase at the lumbar spine by bisphosphonate treatment was not related to any pretreatment parameters, including body size, body composition and bone/mineral metabolism in postmenopausal Japanese women with primary osteoporosis; however, it seems likely that FPG is correlated to BMD increase at the lumbar spine by bisphosphonate treatment partly through

LBM.

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Figure Legends

Fig. 1. Relationships between FPG and BMD increase at the lumbar spine by bisphosphonate treatment.

Simple regression analysis was performed, and Pearson's correlation coefficients (r) were calculated. P values <0.05 were considered significant.

Fig. 2. Comparisons of BMD increase at the lumbar spine by bisphosphonate treatment between groups with or without preexistent vertebral fractures.

Data are expressed as the mean $\pm$ standard error.

Fig. 3. Comparisons of BMD increase at the lumbar spine by bisphosphonate treatment between groups with or without alfacalcidol cotreatment.

Data are expressed as the mean $\pm$ standard error.

Table 1. Baseline indices in postmenopausal patients with osteoporosis

Age	69.1 $\pm$ 7.5
Height (cm)	151.6 $\pm$ 6
Weight (kg)	49 $\pm$ 8
BMI	21.7 $\pm$ 3.0
Serum Ca (mg/dl)	9.3 $\pm$ 0.4
ALP (IU/L)	260 $\pm$ 76
Dpd (nmol/mmol.Cr)	7.5 $\pm$ 2.7
L₂₋₄ BMD (g/cm²)	0.672 $\pm$ 0.082
FN BMD (g/cm²)	0.557 $\pm$ 0.089
1/3R BMD (g/cm²)	0.489 $\pm$ 0.065

Data are expressed as the mean $\pm$ SD

Table 2. Relationships between various parameters and FPG

	r	p
Age	0.095	0.4340
Height	0.311	0.0180*
Weight	0.351	0.0070*
BMI	0.228	0.0881
L2-4 BMD	-0.079	0.5124
FN BMD	-0.010	0.9350
R1/3 BMD	-0.080	0.5260
BMC	0.328	0.0132*
LBM	0.339	0.0103*
Fat mass	0.234	0.0827

***, p<0.05**

Figure 1

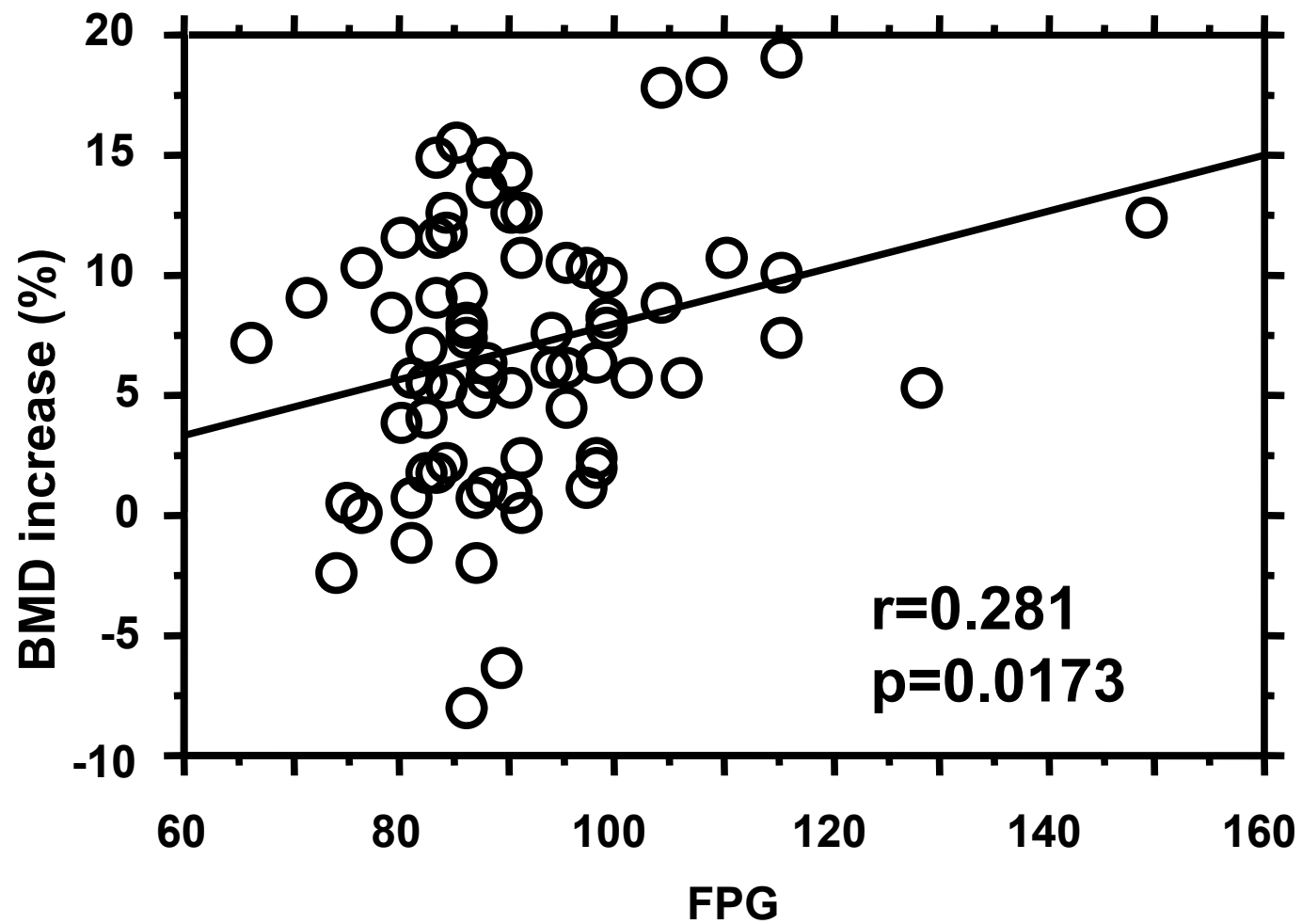


Figure 2

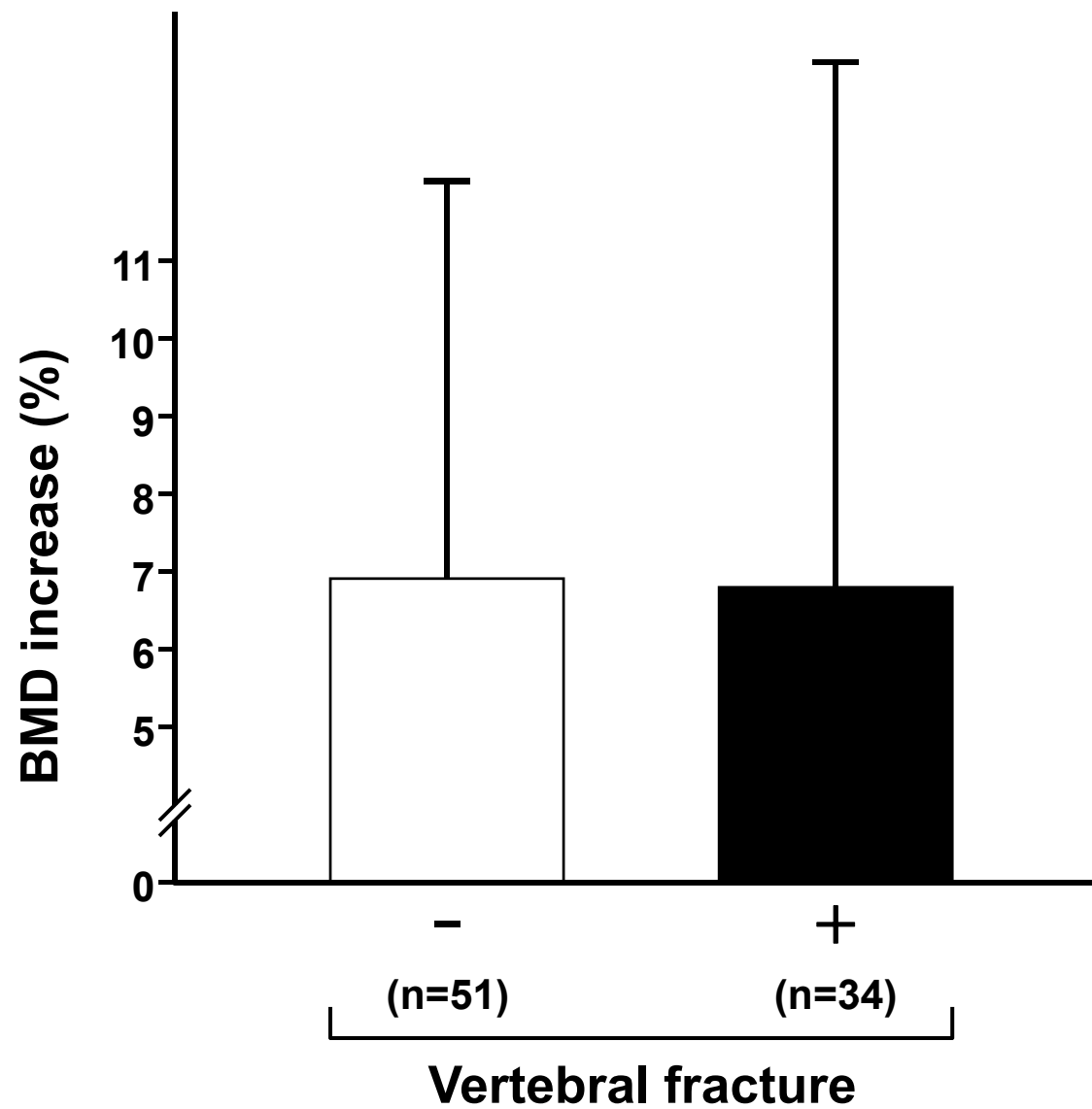


Figure 3

