Table 2 The correlations between serum adiponectin versus bone mineral density, bone metabolic marker, or other variables.

	Men				Postmenopausal women			
	Log (total adiponectin)		Log (HMW adiponectin)		Log (total adiponectin)		Log (HMW adiponectin)	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Age	0.292	<0.0001	0.202	0.0021	0.323	<0.0001	0.264	0.0005
Duration of diabetes	0.203	0.0022	0.214	0.0012	0.310	0.0001	0.288	0.0003
Body height	−0.143	0.0295	−0.074	0.2650	−0.139	0.0711	−0.108	0.1613
Body weight	−0.409	<0.0001	−0.229	0.0005	−0.344	<0.0001	−0.322	<0.0001
BMI	−0.432	<0.0001	−0.247	0.0001	−0.314	<0.0001	−0.306	<0.0001
HbA1c	−0.102	0.1223	−0.053	0.4251	0.077	0.3194	0.138	0.0743
Creatinine	0.081	0.2190	0.053	0.4231	0.120	0.1178	−0.034	0.6591
Total BMD	−0.301	<0.0001	−0.173	0.0145	−0.264	0.0012	−0.194	0.0195
L2-4 BMD	−0.220	0.0009	−0.180	0.0072	−0.205	0.0072	−0.128	0.0954
Z score	−0.163	0.0150	−0.112	0.0949	−0.085	0.2748	−0.034	0.6601
F BMD	−0.326	<0.0001	−0.209	0.0019	−0.293	0.0002	−0.297	0.0001
Z score	−0.211	0.0017	−0.138	0.0411	−0.184	0.0193	−0.225	0.0041
1/3R BMD	−0.252	0.0002	−0.136	0.0477	−0.286	0.0003	−0.203	0.0110
Z score	−0.041	0.5551	−0.051	0.4629	−0.099	0.2176	−0.054	0.5052
Osteocalcin	0.183	0.0083	0.084	0.2300	0.196	0.0156	0.051	0.5351
uNTX	0.189	0.0045	0.107	0.1124	0.113	0.1540	0.177	0.0241

BMI, body mass index; HbA_{1c}, hemoglobin A_{1c}; BMD, bone mineral density; L, lumbar; F, femoral neck; 1/3R, one-third of the radius; uNTX, urinary N-terminal cross-linked telopeptide of type-I collagen; HMW, high molecular weight.

creatinine, and HbA_{1c} (Table 3). In men, log (total adiponectin) was significantly and negatively correlated with T-, L-, and F-BMD ($P<0.05$) and positively correlated with uNTX ($P<0.05$), while log (HMW adiponectin) was only significantly and negatively correlated with L-BMD ($P<0.05$). On the other hand, in post-menopausal women, neither log (total adiponectin) nor log (HMW adiponectin) were correlated with BMD at any site or any bone metabolic markers, except that log(total adiponectin) was significantly and positively correlated with osteocalcin ($P<0.01$).

Comparison of serum adiponectin levels and other variables between patients with and without vertebral fractures

Next, we compared serum total and HMW adiponectin levels and other parameters between patients with and without vertebral fractures or with moderate or severe vertebral fractures (Table 4). The male and post-menopausal female patients with vertebral fractures or with moderate or severe vertebral fractures were significantly older ($P<0.05$), shorter in height ($P<0.05$), lower in absolute values of T-BMD ($P<0.05$), and L-BMD ($P<0.05$) than their counterparts without fractures. The post-menopausal female patients with vertebral fractures or with moderate or severe vertebral fractures had significantly lower absolute F-BMD and 1/3R-BMD than those without fractures ($P<0.05$). The post-menopausal female patients with moderate or severe vertebral fractures had significantly lower Z score of F-BMD than those without fractures ($P<0.05$). Serum total adiponectin level was significantly higher in men and post-menopausal women with vertebral fractures or with moderate or severe vertebral fractures than in those

Table 3 The correlations between serum adiponectin versus bone mineral density or bone metabolic marker.

	Men				Postmenopausal women			
	Log (total adiponectin)		Log (HMW adiponectin)		Log (total adiponectin)		Log (HMW adiponectin)	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Total BMD	−0.165	0.0356	−0.058	0.4293	−0.118	0.1741	−0.056	0.5156
L2 − 4 BMD	−0.187	0.0133	−0.146	0.0382	−0.071	0.4028	−0.016	0.8517
F BMD	−0.136	0.0480	−0.086	0.1763	−0.096	0.2216	−0.150	0.0557
1/3R BMD	−0.129	0.0715	−0.040	0.5475	−0.098	0.2237	−0.038	0.6383
Osteocalcin	0.078	0.3020	0.025	0.7264	0.269	0.0033	0.105	0.2554
UNTX	0.148	0.0489	0.074	0.2920	0.053	0.5293	0.075	0.3789

Multiple regression analysis was performed between adiponectin versus BMD at each skeletal site and bone markers adjusted for age, duration of diabetes, BMI, creatinine, and HbA1c. BMI, body mass index; HbA_{1c}, hemoglobin A_{1c}; BMD, bone mineral density; L, lumbar; F, femoral neck; 1/3R, one-third of the radius; uNTX, urinary N-terminal cross-linked telopeptide of type-I collagen; HMW, high molecular weight

Table 4 Comparison of demographic and biochemical parameters including serum total and high molecular weight adiponectins between subjects with and without vertebral fractures.

	Men					Postmenopausal women				
Vertebral fracture	**No**	Yes		Moderate or severe		**No**	Yes		Moderate or severe	
Number of patient	151	80	*P*	19	*P*	118	52	*P*	21	*P*
Age	57.8±13.3	63.0±12.7	0.0052	65.1±10.0	0.0240	64.7±9.8	71.3±9.8	<0.0001	74.2±10.3	0.0001
Duration of diabetes	10.2±9.2	11.4±8.7	0.3421	15.7±10.3	0.0199	11.5± 9.6	14.2±10.3	0.1172	16.0±10.3	0.0717
Body height	167.1±6.5	163.8±6.7	0.0004	163.8 ± 5.2	0.0380	151.3±5.7	148.3±6.0	0.0029	145.3±6.1	<0.0001
Body weight	67.0±17.3	62.3±12.0	0.0339	63.1 ±7.6	0.3352	56.2±10.8	53.6±11.5	0.1545	51.1±13.8	0.0658
BMI	23.9±5.2	23.1±3.6	0.2795	23.5 ±2.7	0.7684	24.5±4.3	24.3± 5.0	0.8000	24.2±6.0	0.7546
HbA1c	8.9±2.8	8.8±2.2	0.7644	8.5±1.9	0.5694	8.8±2.3	8.8±2.6	0.9720	8.8±2.5	0.9919
Creatinine	0.79±0.18	0.80±0.19	0.8403	0.83±0.23	0.4664	0.63±0.17	0.68±0.17	0.0709	0.65±0.14	0.5123
Total adiponectin	5.84±3.78	7.19±4.55	0.0165	8.39 ±4.50	0.0073	8.04± 4.98	10.53±7.22	0.0101	10.82±7.51	0.0353
HMW adiponectin	5.88±4.86	6.97±6.77	0.1581	9.72 ±7.73	0.0030	8.38±6.80	10.67±8.24	0.0599	10.67±8.71	0.1839
Total BMD	1.094±0.115	1.053±0.103	0.0137	1.030 ±0.103	0.0317	0.944±0.113	0.882±0.103	0.0021	0.853±0.093	0.0035
L2-4 BMD	1.063±0.203	1.009±0.154	0.0432	0.966±0.153	0.0464	0.902±0.172	0.832±0.219	0.0246	0.767±0.272	0.0037
Z score	0.56±1.26	0.33±0.93	0.1444	0.07±0.87	0.1004	0.70 ± 1.14	0.45±1.40	0.2234	0.11±1.84	0.0556
F Neck BMD	0.798±0.137	0.764±0.122	0.0764	0.745±0.107	0.1104	0.661±0.124	0.603±0.138	0.0085	0.537±0.162	0.0003
Z score	0.38±1.17	0.25±0.92	0.4152	0.19±0.91	0.5097	0.58±1.18	0.31±1.31	0.2010	−0.16±1.70	0.0224
1/3R BMD	0.716±0.072	0.704±0.063	0.2191	0.702±0.069	0.4166	0.544±0.090	0.509±0.087	0.0292	0.497±0.077	0.0432
Z score	−0.56±1.18	−0.64±1.09	0.6528	−0.47±0.99	0.7548	0.64±1.57	0.61±1.33	0.9230	0.77±1.42	0.7471
Osteocalcin	5.1±2.5	4.8±2.3	0.4558	5.3±3.0	0.7760	7.1±3.0	7.2±2.8	0.8527	6.5±2.4	0.3940
uNTX	32.4±18.0	33.0±16.2	0.7975	34.5±20.1	0.6411	52.4±28.4	60.5±43.5	0.1568	60.3±42.5	0.2945

BMI, body mass index; HbA_{1c}, hemoglobin A_{1c}; HMW, high molecular weight; BMD, bone mineral density; L, lumbar; F, femoral neck; 1/3R, one-third of the radius; uNTX, urinary N-terminal cross-linked telopeptide of type-I collagen.

without fractures ($P<0.05$). Serum HMW adiponectin was significantly higher in men with moderate or severe vertebral fractures than in those without fractures ($P<0.01$). No difference was found in serum osteocalcin or uNTX between those with and without fractures.

When multivariate logistic regression analysis was performed with the presence of vertebral fractures as a dependent variable and serum total and HMW adiponectin levels, bone markers, and absolute BMD values at each site adjusted for age, BMI, duration of diabetes, serum creatinine, and HbA_{1c} as independent variables (Table 5), total adiponectin in men was selected as an index affecting the presence of vertebral fractures ($P<0.05$), as well as T-BMD and L-BMD ($P<0.05$). Moreover, serum total and HMW adiponectin levels as well as T-BMD and L-BMD were associated with the presence of moderate or severe vertebral fractures in men ($P<0.05$) (Table 5). By contrast, no parameters were selected in post-menopausal women.

Discussion

In this study, we found that serum total adiponectin level was negatively correlated with T-, L-, and F-BMD and positively with uNTX, and serum HMW adiponectin level was negatively correlated with L-BMD in diabetic men, while it was positively correlated with serum osteocalcin level, but not with uNTX or BMD at any site in post-menopausal women. Logistic regression analysis showed that total and HMW adiponectin were significantly and positively associated with the presence of vertebral fractures in type 2 diabetic men, suggesting that they are not only correlated with BMD or uNTX but also are useful markers for assessing the risk of vertebral fractures specifically in diabetic males.

Several studies investigated the relationship between serum adiponectin and BMD in subjects without diabetes. In non-diabetic men, Oh *et al.* showed that serum adiponectin level had no significant correlation with BMD in 80 adults (19). By contrast, Peng *et al.* showed that the hormonal level was significantly and negatively correlated with T-, L-, and F-BMD in 232 men (15). Moreover, Michaëlsson *et al.* recently showed that a negative association between adipinectin and BMD was found in two cohorts, one recruited 441 men and another 314 men (21). Our finding was consistent with the latter two reports. In non-diabetic women, serum adiponectin level was reported to be negatively correlated with BMD (12–14), while other studies showed no significant correlation (16–18). Our finding that the hormone level was not significantly correlated with BMD at any site in diabetic women seems to accord with the latter observation. By contrast, few studies were performed in diabetic subjects with regard to the relationship between serum adiponectin level and BMD. Lenchik *et al.* showed that after adjusting for age, gender, race, smoking, and diabetes status, serum adiponectin was inversely associated with BMD in 38 women and 42 men (86% with type 2 diabetes) (11). Tamura *et al.* showed that there were a significant positive correlation between serum adiponectin level and Z score at R-BMD, but not at L- or F-BMD in 40 Japanese patients (28 men and 12 women) with type 2 diabetes (20). Although, they investigated men and women together, some adiponectin variability is suggested to be sex related: Serum total and HMW adiponectins have been reported to be higher in post-menopausal women

Table 5 Associations between the presence of vertebral fractures and serum adiponectin.

	Men		Postmenopausal women	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Presence of vertebral fractures				
Total adiponectin	1.396 (1.020–1.911)	0.0371	1.341 (0.916–1.964)	0.1310
HMW adiponectin	1.199 (0.895–1.608)	0.2235	1.214 (0.828–1.780)	0.3208
Total BMD	0.700 (0.501–0.979)	0.0372	0.743 (0.469–1.178)	0.2061
L2-4 BMD	0.709 (0.522–0.963)	0.0280	0.835 (0.553–1.262)	0.3922
F BMD	0.831 (0.593–1.166)	0.2846	0.826 (0.523–1.305)	0.4136
1/3R BMD	1.011 (0.728–1.403)	0.9496	1.013 (0.631–1.623)	0.9588
Osteocalcin	0.844 (0.606–1.176)	0.3163	0.957 (0.626–1.464)	0.8405
uNTX	0.998 (0.743–1.342)	0.9908	1.233 (0.831 – 1.829)	0.2976
Presence of moderate or severe vertebral fractures				
Total adiponectin	1.709 (1.048–2.787)	0.0316	1.395 (0.824–2.360)	0.2150
HMW adiponectin	1.810 (1.112–2.946)	0.0169	1.150 (0.661–2.001)	0.6208
Total BMD	0.527 (0.296–0.938)	0.0295	0.473 (0.198–1.129)	0.0918
L2-4 BMD	0.527 (0.303–0.916)	0.0233	0.538 (0.259–1.114)	0.0952
F BMD	0.719 (0.410–1.259)	0.2479	0.551 (0.262–1.157)	0.1152
1/3R BMD	1.165 (0.692–1.962)	0.5655	0.950 (0.434–2.082)	0.8984
Osteocalcin	1.096 (0.666–1.804)	0.7173	0.762 (0.389–1.494)	0.4287
uNTX	1.115 (0.682–1.823)	0.6641	1.288 (0.692–2.396)	0.4244

Multivariate logistic regression analysis was performed with the presence of vertebral fractures as a dependent variable and each of levels of adiponectin adjusted for age, duration of diabetes, BMI, creatinine, and HbA1c as independent variables. HMW, high molecular weight; BMD, bone mineral density; L, lumbar; F, femoral neck; 1/3R, one-third of the radius; uNTX, urinary N-terminal cross-linked telopeptide of type-I collagen; OR, odds ratio; CI, confidential intervals. Unit of change; Standard deviation per increase.

than in men (29, 30). Therefore, it would be more suitable to perform clinical studies on adiponectin after separating between men and women in order to avoid such sex-related differences. In the present study, we investigated correlation between adiponectin and BMD in a larger population of each gender. Our findings of significant negative correlation between total and HMW adiponectin and BMD in the diabetic males seem to accord with those of Lenchik *et al.*

To our knowledge, the present study is the first one that investigated the association between the difference in molecular sizes of adiponectin versus BMD, bone metabolic markers, and the presence of vertebral fractures. We found that serum total adiponectin level was associated with BMD, uNTX, and the presence of vertebral fractures more potently than HMW adiponectin, while both serum total and HMW adiponectin were associated with the presence of moderate or severe vertebral fractures. However, little is known about the distribution and function of each adiponectin isoform in the bone microenvironment, and further studies are needed to clarify the significance of adiponectin molecular sizes in bone metabolism.

Adiponectin has recently attracted widespread attention, especially in diabetes field, due to their beneficial anti-diabetic and anti-atherosclerotic effects. We and other researchers have also shown that adiponectin stimulates osteoblastogenesis and bone formation in cultured osteoblasts (9, 10, 35). Luo *et al.* have shown that adiponectin regulated bone turnover via enhancing the receptor activator of nuclear factor-κB ligand (RANKL) expression and suppressing its decoy receptor, osteoprotegerin (OPG) (36). Thus, agents that are able to increase circulating adiponectin may improve not only energy metabolism or aterosclerosis but also bone metabolism. Indeed, in clinical studies, several researchers documented the significant relationship between serum adiponectin and bone metabolic markers in normal subjects. Peng *et al.* showed that serum adiponectin was positively correlated with BAP and uNTX in 232 men after adjustment for age and fat mass (15). Richard *et al.* showed that serum adiponectin was positively associated with osteocalcin in 1208 women after adjustment for age, BMI, central fat mass, insulin levels, smoking, menopause, and HRT status (12). The present study also showed that total adiponectin level was positively associated with uNTX and osteocalcin in the diabetic males and post-menopausal females respectively. These clinical observations seem to accord with a recent *in vitro* study reporting that osteocalcin increases adiponectin expression in adipocytes (37). Taken together, both experimental and clinical studies suggest that adiponectin could accelerate bone turnover and might improve low bone turnover-associated bone fragility that is typically seen in diabetic patients (38).

The present study indicated a negative correlation between serum adiponectin level and BMD in diabetic men. This finding seems a little contradictory, given that we and other researchers have shown the stimulatory action of adiponectin on osteoblastogenesis and bone formation by *in vivo* and *in vitro* experiments (9, 10, 35). One possible explanation is that serum adiponectin level in subjects with osteoporosis reactively elevates through its up-regulated synthesis and secretion, in order to protect bone from osteopenia. This explanation is supported by the observation that serum OPG level is also negatively correlated with BMD, although it acts as a decoy receptor for RANKL and protects bone from osteopenia through inhibiting osteoclastic activities (39).

This study has some limitations. First, the sample size was not large enough to make definite conclusions. Second, we analyzed only subjects who visited Shimane University Hospital, a tertiary center, for the evaluation or treatment of diabetes mellitus and osteoporosis. Therefore, the patients enrolled in this study might have relatively severe states of the disorders and might not be representative of Japanese men and post-menopausal women with the disorders. Consequently, assessment of larger numbers of patients is necessary to determine the usefulness of serum adiponectin levels for predicting the risk of vertebral fractures. Third, vertebral fracture rates in the present populations (34.6% in male and 30.6% in female) seem to be higher than those observed in Western counterparts. However, we found the similar fracture rate (31.6%) in 193 non-diabetic post-menopausal women in a previous study (40), and comparison of vertebral fracture rates between one Japanese and two European cohorts show that Japanese have a higher fracture rate than Europeans (41–43). Fourth, BMI in the present populations (mean; 23.6 in male and 24.5 in female) were lower than those observed in Western people. It is because the capacity of insulin secretion and the degree of obesity in Asian populations are known to be different from Western people (44). Therefore, further studies are needed to examine whether or not our findings are also seen in Western populations. Fifth, the significant difference in age between men and women found in this study could reduce the significance of comparisons because adiponectin is markedly influenced by age. Finally, a previous genetic study has shown that low serum adiponectin levels might be influenced by genetic factors (45), and thus it is possible that genes for adiponectin may predetermine its serum levels independent of bone status, and the hormone levels may not reflect the bone microenvironment. On the contrary, strengths of our study are that the number of subjects was relatively larger than those of previous studies in type 2 diabetes, and that we measured both of total and HMW adiponectins and examined their relationship with bone parameters in separate genders. We also for the first time showed the association between serum adiponectin levels and the presence of vertebral fractures.

In conclusion, the present study showed that serum adiponectin was associated with BMD, uNTX, and the presence of vertebral fractures in men, and that serum adiponectin was positively associated with serum osteocalcin in post-menopausal women. These findings suggest that serum adiponectin was involved in bone metabolism and that the hormonal level may be as efficient as BMD in assessing the risk of vertebral fractures in diabetic males.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Bone fragility in male glucocorticoid-induced osteoporosis is not defined by bone mineral density

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Mini abstract

Eighty-seven male Japanese subjects taking prednisolone ≥ 5 mg for more than 6 months and 132 age- and BMI-matched control subjects were examined. Multiple regression analysis adjusted for age and BMI showed that spinal BMD in the prednisolone group was not associated with prevalent vertebral fractures. (46 words)

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Abstract

Introduction: Glucocorticoid (GC) treatment is known to increase the risk for bone fractures. However, the association between vertebral fractures (VFs) and bone mineral density (BMD) in GC-treated male patients remains unclear.

Methods: Eighty-seven male subjects taking prednisolone ≥ 5 mg for more than 6 months and 132 age- and BMI-matched control subjects were examined using lateral thoracic and lumbar spine radiographs and spine dual energy X-ray absorptiometry.

Results: The presence of GC use was an independent risk factor for VFs adjusted for age and BMI (odds ratio 10.93, $P < 0.001$). By receiver operating characteristic analysis, the absolute BMD values for detecting VFs were higher and the sensitivity and specificity were lower in the GC group than in the control group (0.936 g/cm^2 vs. 0.825 g/cm^2 and 53.5% vs. 74.0%, respectively). Multiple regression analysis adjusted for age and BMI showed that spinal BMD in the GC group was not associated with prevalent VFs, even after adding current and past maximum GC doses as independent variables.

Conclusions: These results show that lumbar BMD values are not associated with prevalent vertebral fractures in GC-treated male patients, suggesting that bone fragility in male GC users is affected by bone quality rather than by BMD.

Key words: glucocorticoid, osteoporosis, men, vertebral fractures, bone mineral density

Introduction

Oral glucocorticoids (GC) have been used for the treatment of a range of autoimmune, respiratory, hematological, and renal diseases. A meta-analysis showed that patients treated with GC had a higher risk of fractures of the hip, vertebra, forearm, or any other site compared to control subjects (1). Low BMD is a key predictor of fractures related to primary osteoporosis in both men and women (2); however, vertebral fractures (VFs) occurred at much higher rates than expected on the basis of BMD (1), suggesting that the bone fragility of glucocorticoid users is not defined by BMD. Indeed, the cut-off values of BMD at the lumbar spine (L), femoral neck (FN), and one third of radius (R) for VFs in female Japanese patients treated with GC were higher than those of controls in our previous study (3). However, the relationship between BMD and fracture risk in GC-treated male patients is still unknown.

Several clinical aspects of male osteoporosis differ from those of female osteoporosis. Approximately half the male patients with osteoporosis presenting with symptomatic VFs have identifiable secondary causes (4); GC therapy is a common cause of osteoporosis in older men (5). The prevention of fractures in men seems to be much more important than in women because male mortality rates within one or two years after a fracture are higher than in females (6, 7). In this study, to clarify the relationship between BMD and bone fragility in male GC users, we measured L-BMD in male GC users and age- and BMI-matched control subjects and compared the values of BMD Z scores between subjects with and without VFs. We also compared BMD cut-off levels and odds ratios for VFs between GC users and controls.

Subjects and Methods

Subjects

We enrolled eighty-seven Japanese male patients (age range: 20-85 years, mean 52.1 years; BMI: 16.3-29.7 kg/m^2, mean 22.4 $\pm$ 2.8 kg/m^2) who were diagnosed with autoimmune disease, except for rheumatoid arthritis, who were treated with an oral GC (prednisolone (PSL) $\geq$ 5 mg/day) for more than 6 months (GC group), and who underwent L-BMD measurements at the outpatient clinic of Shimane University Hospital. We excluded patients with renal dysfunction who had serum creatinine levels higher than the normal range (0.56 - 1.23 mg/dl) and patients whose performance status was disturbed. We investigated patients' history of GC treatment with regard to the duration of GC treatment and the current and past maximum dose. No patients were taking any drugs or hormones that are known to

affect bone metabolism, including sex steroids, warfarin, or bisphosphonates. Basal diseases of the GC-treated patients were systemic lupus erythematosus (11 cases), polymyositis (11 cases), Behcet's syndrome (7 cases), ulcerative colitis (7 cases), dermatomyositis (4 cases), myasthenia gravis (3 cases) and others (dermatological diseases, hematological diseases, granulomatous and respiratory diseases). For the control group, 132 age- and BMI-matched men (age range: 22 - 86 years, mean 53.4 years; BMI: 14.0-32.9 kg/m^2, mean 22.9 $\pm$ 3.7 kg/m^2), who were suffering from lumbago or suspected osteoporosis without underlying conditions affecting the skeleton, were recruited. To verify that patients in the GC group have a higher risk of VFs than control subjects (expected fracture rate: GC group, 30%; control group, 10%, respectively), 122 control and 81 GC subjects were needed to reach the sufficient statistical power ($\alpha = 0.05$ and $1-\beta = 0.8$). No patients were taking drugs or hormones that affect bone metabolism, including sex steroids and calcitonin. Baseline characteristics of subjects are shown in Table 1. The mean current dose and past maximum dose of prednisolone were 11.1 $\pm$ 9.8 and 41.5 $\pm$ 21.0 mg/day, respectively, in the GC group. This study was cross-sectional, was approved by the ethical review board of our institution, and was in compliance with the Helsinki declaration. All subjects agreed to participate in the study and gave written informed consent.

Densitometry

BMD values were measured by dual-energy X-ray absorptiometry using the QDR-4500 DEXA system (Hologic, Waltham, MA) at L in all GC-treated and control subjects, and BMD measurements of the FN and R were performed in 73 and 58 GC subjects, respectively. Vertebrae with fractures or overt osteoarthritis were excluded from the analysis of L-BMD because these factors may increase BMD through artifacts. BMD was automatically calculated from the bone area (cm^2) and bone mineral content (BMC, g). Values were also expressed relative to the standard deviation (SD) of age- and sex-matched normal Japanese mean values of BMD provided by the manufacturer (BMD Z score) (8). The coefficients of variation of the L, FN, and R measurements were 1.0, 1.0, and less than 1%, respectively.

Assessment of fractures

In all subjects, conventional thoracic and spinal radiographs in lateral and antero-posterior projections were obtained. Following the classification by Genant *et al.* (9), VFs were diagnosed if a reduction of 20 % or more was observed by two investigators who were

blinded to each other's readings. If judgment of VFs did not agree, the film was independently reassessed. If the re-evaluated findings were again different, we regarded that case as a non-fracture.

Statistical analysis

All data are expressed as the mean ± SD for each index. The Mann-Whitney *U*-test was used to compare parameters between subjects with and without VFs. P values < 0.05 were considered significant. To compare the strength of association between BMD values at each measurement point and the presence of VFs, we analyzed the areas under the receiver operating characteristic (ROC) curves (10). For each of the BMD measurements at the lumbar spine and for each of the VF groups, possible cut-off points for BMD were defined, and the proportion of subjects with fractures below these points (the sensitivity) and the proportion of subjects without fractures above these points (the specificity) were calculated. This calculation yields an ROC curve that illustrates the relationship between sensitivity and specificity for each BMD measurement as a discriminator between the normal and fracture groups. Statistical analyses were performed using the computer program StatView for Windows, version 5.0 (SAS Institute, Cary, NC).

Results

Background data

Background data for the control and GC-treated subjects are presented in Table 1. There were 11 (8.3%) subjects with VFs in the control group and 30 (34.5%) in the GC group. The prevalence of VFs in the GC group was significantly higher than that of controls (P < 0.001, chi-square test); however, there was no difference in L-BMD between the control and GC group. Multivariable logistic analysis adjusted for age, BMI, and L-BMD revealed that GC use was an independent risk factor for VFs (odds ratio (OR) 10.93, 95% confidence interval (CI) 4.36-27.40, P < 0.001).

Comparison of various parameters between subjects with and without vertebral fractures in the GC group

We compared various parameters of GC patients with and without VFs. As shown in Table 2, patients with VFs were significantly older than those without VFs. There was no difference in other parameters, including L-BMD, between those with and without VFs.

Distribution of BMD in subjects with and without vertebral fractures

Figure 1 shows the distribution of L-BMD in all subjects as a function of age. In control subjects, those with VFs (black dots) are clearly grouped in the region with higher age and lower BMD. In contrast, subjects with VFs in the GC group were not associated with age or BMD.

Cut-off values for vertebral fracture

The cut-off value of L-BMD for VFs in the GC group was higher than that of controls (GC group vs. control: 0.936 vs. 0.825 g/cm^2) (Table 3). The sensitivity and specificity of ROC analysis in the GC group were lower than those of the control group (53.5 vs. 74.0 %).

Multivariable logistic regression analysis with the presence of vertebral fractures

Finally, we performed multivariable logistic regression analysis with the presence of VFs as the dependent variable and L-BMD adjusted for age and BMI as the independent variable. L-BMD in the control group was significantly associated with the presence of VFs (OR = 0.26, 95 % CI 0.09 - 0.74 per SD increase, P = 0.012). In contrast, there was no significant association in the GC group between VFs and L-BMD, even after adding current or past maximum PSL dose or duration of GC treatment as independent variables (Table 4).

Discussion

This study revealed that the VF rate in the GC group was significantly higher than that of age-matched controls and that GC use was an independent risk factor for VFs when adjusted for age, BMI, and L-BMD. It has been established by meta-analysis that GC users have an increased risk of fractures compared to controls (1). Kanis *et al.* reported that exposure to corticosteroids was associated with a significantly increased risk of fractures in both genders (11), which is compatible with our findings that male GC users had a higher risk of fractures than control subjects.

We also showed that age-matched BMD (BMD Z score) did not differ between GC-treated patients with and without VFs. The cut-off value of L-BMD for VFs in the GC group was higher compared to that of the control group. In addition, the sensitivity and specificity of cut-off values for VFs in the GC group were lower than those of the control group. These results are in agreement with our previous report on female GC treated patients (3). However, the cut-off value of L-BMD T score for VFs in male GC users was higher than

that in female users (-1.03 vs. -1.88), and the sensitivity and specificity of the cut-off L-BMD value in men were lower than those of the cut-off L-BMD value in women (53.5% vs. 61.5%), suggesting that assessing bone fragility by measuring BMD is more difficult for male patients taking GCs than for female GC users.

Several reports have also noted that L-BMD is not sensitive enough to assess the risk of VFs. Orwoll *et al.* suggested that osteophytic calcification exerted an important influence on the measurement of L-BMD in men because the presence of osteophytes obscured the relationship of BMD to age (12). The prevalence of osteoporosis became lower when estimated by L-BMD instead of by FN-BMD in both genders (13), suggesting that L-BMD was less sensitive for the diagnosis of osteoporosis. Thus, FN- or R-BMD might be more suitable measures for evaluating the risk of VFs in GC users than L-BMD. We compared the FN-BMD values of 132 control subjects and 73 GC users, as well as the R-BMD of 132 controls and 58 GC subjects. Compared to normal subjects, cut-off values of FN- and R-BMD for VFs in the GC group were higher than those of the control group [FN: 0.724 vs. 0.644 g/cm^2; R: 0.726 vs. 0.621 g/cm^2], and the sensitivity and specificity in the GC group were both low [FN: 52.0 vs. 75.2%; R: 56.0 vs. 84.3%]. Thus, FN- and R-BMD seem to give results similar to those found by L-BMD. Taken together, these results indicate that it is difficult to assess bone fragility in male GC-treated patients by measurement of BMD at any site, suggesting that bone strength of GC users was associated with bone quality rather than BMD.

The pathophysiologic mechanisms of impaired bone quality in GC users are still unknown. Bone quality is determined by architecture, turnover, micro damage accumulation, mineralization, and bone matrix proteins, such as collagen (14). *In vivo* studies have shown that GC administration caused low bone turnover by the suppression of osteoblast function, the induction of apoptosis in osteoblasts (15), and by a major loss of trabecular connectivity (16). GC also affected bone geometry by reducing bone formation rate on the periosteal surface (17). These results demonstrated that GC administration led to deterioration in bone structural properties. A limited report about the effect of GC treatment on bone material properties indicated that steroid administration reduced bone mineralization and elastic modulus of bone surrounding osteocyte lacunae (18). These skeletal factors might have led to the observed bone fragility of GC users in this study.

In this study, the current and past maximum dose were not significantly different between subjects with and without VFs in the GC group. Van Staa TP *et al.* revealed that the increased risk of fractures in GC users was related to the daily dose of GC (19). This

discrepancy might partly be explained by insufficient statistical power due to the smaller number of patients in this study.

This study has some limitations. First, the study was not population-based and the sample size was not large enough to draw definite conclusions. Second, we only analyzed the control subjects who attended Shimane University Hospital, a tertiary care center, for evaluation or treatment of back pain or osteoporosis. Therefore, the control subjects enrolled in this study might have had a relatively severe case of the disorder and might not be representative of normal Japanese men. Third, we did not confirm that all of GC-treated men did not have VFs when GC was administrated. Several underlying autoimmune diseases would negatively affect bone health and compound the effect of GCs. Osteopenia and osteoporosis in systemic lupus erythematosus (SLE) are associated more closely with increased disease duration than cumulative GC use (20). Indeed, approximately 30% of patients enrolled into the Risedronate GIOP prevention study had VFs at baseline (21). These reports suggested that inflammatory diseases themselves are risk factors for osteoporosis and that all VFs in this study were not caused by GC use alone. Finally, hypogonadism is most common cause for osteoporosis, and low testosterone levels are associated with vertebral fractures in men (14, 22). However, we did not assess dysfunction of the hypothalamus-pituitary-gonadal axis in this study.

In conclusion, this report shows that the prevalent fracture rate and the cut-off value of BMD for VFs in male GC-treated subjects are higher than those in control subjects and that BMD values could not distinguish GC-treated subjects with fractures from those without fractures, suggesting that bone strength in male GC users would be defined by bone quality rather than bone density. Further studies are needed to clarify how GC administration influences bone quality.

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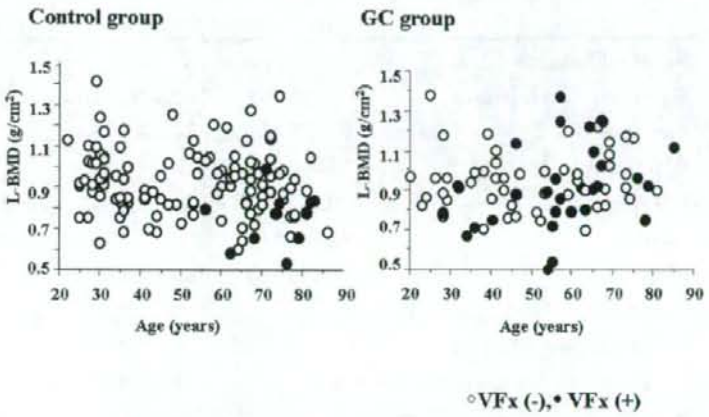
Figure Legends

Figure 1. Distribution of BMD in men with and without vertebral fracture. White dots represent subjects without vertebral fractures, and black dots represent subjects with vertebral fractures.

GC, glucocorticoids; VF, vertebral fracture

Figure 1.



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