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Serum Osteocalcin/Bone-Specific Alkaline Phosphatase Ratio Is a Predictor for the Presence of Vertebral Fractures in Men with Type 2 Diabetes

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Abstract We examined whether or not BMD or bone markers were useful for assessing the risk of vertebral fractures in 248 Japanese men with type 2 diabetes. We analyzed the relationships between bone markers (osteocalcin [OC], bone-specific alkaline phosphatase [BAP], urinary N-terminal cross-linked telopeptide of type-I collagen) or BMD and HbA_{1c}, urinary C-peptide, insulin-like growth factor-I (IGF-I), parathyroid hormone, $1,25(OH)_2$ vitamin D, and the presence of prevalent vertebral fractures. Multiple regression analysis adjusted for age, body height, weight, duration of diabetes, and serum creatinine showed that serum OC and OC/BAP ratio were correlated negatively with HbA_{1c} ($P < 0.01$) and positively with IGF-I ($P < 0.01$). Multivariate logistic regression analysis adjusted for the above parameters showed that serum OC/BAP ratio was inversely associated with the presence of vertebral fractures (odds ratio = 0.695, $P < 0.05$). This association was still significant after additional adjustment for lumbar or femoral neck BMD. Our results suggest that poor diabetic control and lower IGF-I level are linked to impaired bone formation and resultant reduction in OC/BAP ratio in men with type 2 diabetes. The OC/BAP ratio could be clinically useful for assessing the risk of vertebral fractures independent of BMD in diabetic men.

Keywords Osteocalcin · Bone-specific alkaline phosphatase · Type 2 diabetes mellitus · Vertebral fracture · Bone fragility

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The number of patients with diabetes mellitus and osteoporosis is rapidly increasing in industrialized countries, where Western-style aging societies are prevalent. A relationship between diabetes and osteoporotic fractures is becoming increasingly recognized [1]. Vertebral and hip fractures are the most important osteoporotic fractures because they frequently occur and increase the mortality of elderly people as high as six- to ninefold [2, 3]. Although patients with type 2 diabetes show no bone mineral density (BMD) reduction, fracture risks are known to increase approximately up to 1.5-fold at the hip, proximal humerus, forearm, and foot [4–6]. Moreover, our recent study revealed that Japanese patients with type 2 diabetes have an increased risk of vertebral fractures independent of BMD [7].

Bone fragility in patients with type 2 diabetes may be caused by low bone turnover [8]. Hyperglycemia in type 2 diabetes might be associated with factors that influence bone strength and quality independently of BMD [9–11]. Several studies have indicated that hyperglycemia induces a low turnover bone with osteoblast dysfunction [12, 13]. Hyperglycemia and advanced glycation end products (AGEs) promote the apoptosis of osteoblastic cells [14, 15] and restrain the differentiation of cells [16–19]. These findings suggest that hyperglycemia may cause diminished

bone formation. A previous clinical study has indicated that serum osteocalcin (OC) was low before treatments and elevated after treatments of diabetes, while bone-specific alkaline phosphatase (BAP) was reduced [20]. Previous in vitro studies have shown that chronic hyperglycemia increased the activity and expression of BAP and decreased OC expression and cellular calcium uptake [10]. It is well-known that BAP is expressed in the early period of osteoblastic differentiation, whereas OC is expressed in the later period [21]. Thus, hyperglycemia could cause impaired osteoblastic maturation, resulting in bone fragility in patients with type 2 diabetes.

It is thought that bone metabolism in type 2 diabetes is affected by abnormal hormonal actions. Patients with type 2 diabetes appear to have increased BMD, possibly due in part to an anabolic effect of hyperinsulinemia [22, 23] and in part to obesity [24]. In addition, patients with type 2 diabetes have reduced bone turnover and may have reduced levels of parathyroid hormone (PTH) [25]. These factors may protect patients from reduction of BMD and fracture risks. On the other hand, insulin-like growth factor-I (IGF-I), which is anabolic for bone, may also be reduced in patients with type 2 diabetes [26, 27]. However, it is still unclear how these factors are associated with BMD, bone markers, or bone fragility in patients with type 2 diabetes.

In this study, to examine these issues, we investigated the relationships between bone markers (OC, BAP, and urinary N-terminal cross-linked telopeptide of type-I collagen [uNTX]) or BMD and HbA_{1c}, urinary C-peptide (uC-peptide), IGF-I, PTH, $1,25(OH)_2$ vitamin D, and the presence of vertebral fractures in Japanese men with type 2 diabetes.

Subjects and Methods

Subjects

The subjects in this study were 248 Japanese men with type 2 diabetes aged 20–83 years (mean 59.0). We consecutively recruited subjects who visited Shimane University Hospital for education, evaluation, or treatment of diabetes. Subjects agreed to participate in this study and gave informed consent. This study was approved by the institutional review board of our institution. None had hepatic or renal dysfunction or nutritional derangements that might cause changes in bone metabolism. We excluded patients with histories of falls and traffic accidents in order to eliminate the possibility of injury-associated fractures. Forty-two patients had received insulin treatment, 95 patients had taken oral hypoglycemic agents (sulfonylurea, 82; metformin, 28; alpha-glucosidase inhibitor, 28), and 121 patients had not previously been under any medications for diabetes. All subjects were free of drugs known to influence bone and calcium metabolism like vitamin D and bisphosphonate as well as thiazolidinedione until the time of the present study.

Radiography

Lateral X-ray films of the thoracic and lumbar spine were taken in the same week as the serum collection. The anterior, central, and posterior heights of each of the 13 vertebral bodies from Th4 to L4 were measured. A vertebral fracture was diagnosed if at least one of three height measurements along the length of the same vertebrae had decreased by >20% compared to the height of the nearest uncompressed vertebral body [28]. None of the subjects had a history of serious trauma.

BMD and Biochemical Measurements

BMD values of the lumbar spine (L), femoral neck (F), and one-third of the radius (1/3R) were measured by dual-energy X-ray absorptiometry (QDR-4500; Hologic, Waltham, MA). The same operator tested all of the subjects during the study to eliminate operator discrepancies. The coefficients of variation (precision) of measurements of the lumbar spine, femoral neck, and mid-radius by our methods were 0.9, 1.7, and 1.9%, respectively. Values were also expressed relative to the standard deviation (SD) of age- and sex-matched normal Japanese mean values provided by the manufacturer (Z score).

After overnight fasting, serum and first void urine samples were collected. Biochemical markers were measured by standard biochemical methods, as previously described [29, 30]. Hemoglobin A_{1c} (HbA_{1c}) was determined by high-performance liquid chromatography (HPLC). BAP in serum and uC-peptide pooled for 24 h were measured by enzyme immunoassay and chemiluminescent enzyme immunoassay, respectively. Intact PTH was measured by electrochemiluminescent immunoassay. $1,25(OH)_2$ vitamin D, OC, and IGF-I were measured by radioimmunoassay. uNTX was measured by enzyme linked immunosorbent assay.

Statistical Analysis

Data were expressed as mean ± SD. Because uC-peptide and intact PTH showed a markedly skewed distribution, logarithmic (log) transformation of these values was carried out before performing correlation and regression analyses. Statistical significance between the groups was determined using Student's *t*-test. Simple, multiple, and logistic regression analyses were performed using the statistical computer program StatView (Abacus Concepts, Berkeley, CA). $P < 0.05$ was considered significant.

Results

Relationships between BMD or Bone Markers Versus HbA_{1c}, uC-Peptide, IGF-I, Intact PTH, and $1,25(OH)_2$ Vitamin D

Baseline characteristics of subjects are shown in Table 1. Since our simple regression analysis showed that HbA_{1c}, uC-peptide, IGF-I, intact PTH, and $1,25(OH)_2$ vitamin D were affected by age, body stature, and renal function (data not shown), multiple regression analyses were performed with each of these parameters adjusted for age, body height, weight, duration of diabetes, and serum creatinine as an independent variable versus BMD at each skeletal site or bone markers as a dependent variable (Table 2). OC and OC/BAP ratio were correlated significantly and negatively with HbA_{1c} ($P = 0.0057$ and $P < 0.0001$, respectively) and positively with IGF-I ($P = 0.0095$). BAP was correlated significantly and negatively with IGF-I ($P = 0.0304$) and positively with log(intact PTH) ($P = 0.0247$). Although L- and F-BMD were not significantly correlated with HbA_{1c} or any hormonal parameters, 1/3R-BMD was correlated positively with HbA_{1c} ($P = 0.0416$) and negatively with log(intact PTH) ($P = 0.0324$).

Table 1 Baseline characteristics of subjects

Characteristic	Normal range	
Number of subjects		248
Age (years)		59.0 ± 13.7
Duration of diabetes (years)		10.7 ± 9.1
Body height (cm)		165.4 ± 7.0
Body weight (kg)		64.9 ± 16.0
BMI (kg/m^2)		23.6 ± 4.7
Serum creatinine (mg/dl)	0.44–1.23	0.77 ± 0.15
Fasting plasma glucose (mg/dl)	60–110	171 ± 60
HbA_{1c} (%)	4.3–5.8	9.1 ± 2.5
uC-peptide (μg/day)	60–120	70.9 ± 49.6
IGF-I (ng/ml)	59–215	151 ± 60
Intact PTH (pg/ml)	10–65	38.4 ± 16.2
$1,25(OH)_2$ vitamin D (pg/ml)	20–60	49.2 ± 19.4
BAP (U/L)	9.6–35.4	26.3 ± 9.4
OC (ng/ml)	2.5–13.0	5.1 ± 2.4
uNTX (nMBCE/mM-Cr)	13.0–66.2	34.8 ± 24.3
L2–L4 BMD (g/cm^2)		1.042 ± 0.181
T score		−0.04 ± 1.152
Z score		0.47 ± 1.12
F-BMD (g/cm^2)		0.776 ± 0.132
T score		−0.69 ± 1.06
Z score		0.25 ± 1.05
1/3R-BMD (g/cm^2)		0.711 ± 0.070
T score		−1.62 ± 1.32
Z score		−0.66 ± 1.14
Vertebral fracture (yes/no)		76/172 (30.6%)

BMI body mass index, *PTH* parathyroid hormone, *NTX* N-terminal cross-linked telopeptide of type-I collagen, *L* lumbar, *F* femoral neck, *1/3R* one-third of the radius

Comparison of Demographic and Biochemical Parameters, Bone Markers, and BMD Between Patients with and Without Vertebral Fractures

Next, we compared various parameters including HbA_{1c}, uC-peptide, IGF-I, intact PTH, $1,25(OH)_2$ vitamin D, bone markers, and BMD values at each site between patients with and without vertebral fractures (Table 3). Patients with vertebral fractures were significantly older ($P = 0.0071$), were shorter ($P = 0.0203$), and had lower absolute L-BMD ($P = 0.0441$) than patients without vertebral fractures. IGF-I and OC/BAP ratio in patients with vertebral fractures tended to be lower than in patients without them ($P = 0.0620$ and $P = 0.0940$, respectively). On the other hand, no significant differences in the levels of HbA_{1c}, uC-peptide, IGF-I, intact PTH, $1,25(OH)_2$ vitamin D, or bone markers were observed between subjects with and without fractures.

When multivariate logistic regression analysis was performed with the presence of vertebral fractures as a dependent variable and levels of HbA_{1c}, uC-peptide, IGF-I, intact PTH, $1,25(OH)_2$ vitamin D, bone markers, and BMD adjusted for age, body weight, height, duration of diabetes,

Table 2 Correlations between bone markers or BMD versus HbA_{1c}, uC-peptide, IGF-I, intact PTH, and $1,25(OH)_2$ vitamin D

	HbA_{1c}		Log (uC-peptide)		IGF-I		Log (intact PTH)		$1,25(OH)_2D$	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
BAP	0.063	0.3365	0.011	0.8776	−0.154	0.0304	0.154	0.0247	−0.092	0.2267
OC	−0.184	0.0057	–	0.9984	0.180	0.0095	0.033	0.6379	−0.098	0.2241
OC/BAP ratio	−0.250	<0.0001	−0.135	0.0618	0.255	0.0002	−0.042	0.5385	−0.049	0.5289
uNTX	0.040	0.5437	0.088	0.2165	−0.042	0.5487	–	0.9954	−0.095	0.2133
L2–L4 BMD	−0.074	0.2650	−0.005	0.9409	−0.002	0.9757	−0.134	0.0513	0.005	0.9499
F-BMD	−0.075	0.1973	0.071	0.2498	−0.002	0.9798	−0.101	0.0877	−0.031	0.6316
1/3R-BMD	0.127	0.0416	0.032	0.6437	0.062	0.2392	−0.142	0.0324	0.072	0.3392

Multiple regression analysis adjusted for age, body height, weight, duration of diabetes, and serum creatinine

PTH parathyroid hormone, *NTX* N-terminal cross-linked telopeptide of type-I collagen, *L* lumber, *F* femoral neck, *1/3R* one-third of the radius

Table 3 Comparison of demographic and biochemical parameters, bone markers, and BMD between those with and without vertebral fractures

	Vertebral fractures		*P*
	Yes	No	
Number of subjects	76	172	
Age (years)	62.5 ± 13.0	57.5 ± 13.7	0.0071
Duration (years)	11.7 ± 8.4	10.2 ± 9.4	0.2585
Body height (cm)	163.8 ± 6.7	166.1 ± 7.0	0.0203
Body weight (kg)	62.1 ± 12.2	66.1 ± 17.3	0.0647
BMI (kg/m^2)	23.0 ± 3.7	23.8 ± 5.1	0.2230
Creatinine (mg/dl)	0.77 ± 0.16	0.77 ± 0.15	0.8471
Fasting plasma glucose (mg/dl)	169 ± 51	172 ± 65	0.6965
HbA_{1c} (%)	9.0 ± 2.0	9.1 ± 2.7	0.6404
uC-peptide (μg/day)	71.8 ± 44.4	70.5 ± 51.9	0.8562
IGF-I (ng/ml)	140.8 ± 52.3	156.3 ± 62.7	0.0620
Intact PTH (pg/ml)	38.7 ± 13.5	38.3 ± 17.3	0.8609
1,25$(OH)_2$ vitamin D (pg/ml)	46.8 ± 15.9	50.2 ± 20.7	0.2976
BAP (U/l)	27.2 ± 8.9	26.3 ± 9.7	0.3651
OC (ng/ml)	4.9 ± 2.4	5.1 ± 2.4	0.4369
OC/BAP ratio	0.19 ± 0.10	0.22 ± 0.11	0.0940
uNTX (nMBCE/mM-Cr)	34.8 ± 15.7	34.9 ± 27.4	0.9848
L2–L4 BMD (g/cm^2)	1.006 ± 0.150	1.057 ± 0.192	0.0441
Z score	0.31 ± 0.92	0.54 ± 1.19	0.1349
F-BMD (g/cm^2)	0.754 ± 0.121	0.786 ± 0.137	0.0898
Z score	0.16 ± 0.91	0.30 ± 1.11	0.3368
1/3R-BMD (g/cm^2)	0.707 ± 0.062	0.712 ± 0.074	0.6487
Z score	−0.63 ± 1.08	−0.67 ± 1.17	0.7990

BMI body mass index, *PTH* parathyroid hormone, *NTX* N-terminal cross-linked telopeptide of type-I collagen, *L* lumbar, *F* femoral neck, *1/3R* one-third of the radius

Table 4 Associations between the presence of vertebral fractures and HbA_{1c}, uC-peptide, IGF-I, intact PTH, 1,25 $(OH)_2$ vitamin D, bone markers, and BMD

	Presence of vertebral fractures, OR (95% CI)	*P*
HbA_{1c}	1.021 (0.755–1.382)	0.8917
uC-peptide	1.215 (0.833–1.673)	0.2321
IGF-I	0.892 (0.634–1.256)	0.5132
Intact PTH	1.052 (0.776–1.426)	0.7435
1,25$(OH)_2$ vitamin D	0.824 (0.563–1.206)	0.3186
BAP	1.217 (0.922–1.605)	0.1654
OC	0.868 (0.644–1.168)	0.3493
OC/BAP ratio	0.695 (0.496–0.974)	0.0345
uNTX	0.984 (0.714–1.357)	0.9219
L2–L4 BMD	0.744 (0.549–1.007)	0.0559
F-BMD	0.899 (0.635–1.245)	0.4943
1/3R-BMD	1.174 (0.833–1.655)	0.3602

Multivariate logistic regression analysis was performed with the presence of vertebral fractures as a dependent variable and HbA_{1c}, uC-peptide, IGF-I, intact PTH, 1,25$(OH)_2$ vitamin D, BMD at each site, and bone markers adjusted for age, body height, weight, duration of diabetes, and serum creatinine as independent variables

PTH parathyroid hormone, *NTX* N-terminal cross-linked telopeptide of type-I collagen, *L* lumbar, *F* femoral neck, *1/3R* one-third of the radius, *OR* odds ratio, *CI* confidence interval

Table 5 Associations between the presence of vertebral fractures and OC/BAP ratio

	Presence of vertebral fractures, OR (95% CI)	*P*
OC/BAP ratio	0.695 (0.496–0.974)	0.0345
OC/BAP ratio[a]	0.682 (0.481–0.966)	0.0310
OC/BAP ratio[b]	0.707 (0.502–0.995)	0.0465
OC/BAP ratio[c]	0.687 (0.485–0.974)	0.0346
OC/BAP ratio[d]	0.708 (0.501–0.999)	0.0493
OC/BAP ratio[e]	0.704 (0.493–1.005)	0.0533

Multivariate logistic regression analysis was performed with the presence of vertebral fractures as a dependent variable and OC/BAP ratio as an independent variable adjusted for age, body height, weight, duration of diabetes, and serum creatinine

[a] Additionally adjusted for L-BMD

[b] Additionally adjusted for F-BMD

[c] Additionally adjusted for HbA_{1c}

[d] Additionally adjusted for IGF-I

[e] Additionally adjusted for HbA_{1C} and IGF-I

OR odds ratio, *CI* confidence interval

and serum creatinine as independent variables (Table 4), OC/BAP ratio was selected as an index affecting the presence of vertebral fractures ($P = 0.0345$). L-BMD tended to affect the presence of vertebral fractures ($P = 0.0559$) but was not significant. In contrast, F-BMD, 1/3R-BMD, and any other bone markers or hormones were not associated with the presence of vertebral fractures. OC/BAP ratio was still significantly and inversely associated with the presence of vertebral fractures after additional adjustment for L- or F-BMD, HbA_{1c}, or IGF-I (Table 5).

Discussion

In this study, OC/BAP ratio was correlated negatively with HbA_{1c} and positively with IGF-I in men with type 2 diabetes. Moreover, OC/BAP ratio was significantly and inversely associated with the presence of vertebral fractures independently of BMD. These findings suggest that poor glycemic control and lower IGF-I level may cause impaired osteoblastic differentiation and resultant reduction in OC/BAP ratio, which in turn may cause bone fragility and vertebral fractures independently of BMD in diabetic men. Thus, our findings seem to support the previous observations that hyperglycemia and reduced IGF-I are involved in bone fragility in type 2 diabetes [8–19, 26, 27]. However, multivariate logistic regression analysis showed that OC/BAP ratio was associated with the presence of vertebral fractures independently of HbA_{1c} or IGF-I (Table 5). This result as well as no association of HbA_{1c} or IGF-I with the presence

of vertebral fractures (Table 4) suggest that hyerglycemia or reduced IGF-I themselves are not directly linked to bone fragility but indirectly related to it by causing osteoblast dysfunction.

A recent meta-analysis showed that patients with type 2 diabetes had higher hip BMD than nondiabetic controls, despite an increased risk of hip fracture [4], suggesting that BMD values may not reflect bone fragility in type 2 diabetes. Recently, we also reported that L-BMD was not associated with the presence of prevalent vertebral fractures in women with type 2 diabetes, suggesting that L-BMD was not sensitive enough to assess the risk of vertebral fractures in this group [31]. In this study, we found that BMD at any site was not associated with the presence of vertebral fractures in men with type 2 diabetes, although L-BMD showed a tendency ($P = 0.0559$). Therefore, BMD, which is considered the gold standard for evaluating fracture risk in primary osteoporosis, seems to be not useful for assessing the risk of vertebral fractures in both men and women with type 2 diabetes. In postmenopausal women with type 2 diabetes, we have recently shown that serum IGF-I and pentosidine levels were associated with the presence of vertebral fractures independently of BMD, suggesting that they become surrogate markers for assessing the risk of vertebral fractures [29, 32]. In this study, we have shown that serum OC/BAP ratio could predict the presence of vertebral fractures in men with type 2 diabetes and could compensate for the insensitivity of BMD in the population.

IGFs are thought to be linked to the pathogenesis of diabetes-related complications [33]. Impaired production of IGFs could also cause bone complication in diabetes because IGFs are among the most important regulators of bone cell function [34]. Indeed, we previously found that serum IGF-I level was inversely associated with the risk of vertebral fractures in nondiabetic postmenopausal women [35, 36] as well as in their type 2 diabetic counterparts [29]. However, in men with type 2 diabetes, the relationship between serum IGF-I level and bone metabolism has been little documented. In this study, serum IGF-I level was correlated negatively with OC and OC/BAP ratio and positively with BAP, while the hormone was not significantly associated with BMD or the presence of vertebral fractures. Thus, in patients with type 2 diabetes, serum IGF-I level could predict the presence of vertebral fractures in postmenopausal women but not in men, although the significant positive correlation between IGF-I and OC/BAP ratio (Table 2) suggests that its reduction in the circulation was associated with impaired osteoblast function in men.

Several studies have shown that hyperglycemia causes hypercalciuria [37], which might result in enhancement of PTH secretion, while hyperglycemia could also cause suppressed PTH secretion from the parathyroid [25, 38]. Thus, impaired PTH and vitamin D metabolism might be involved in diabetic bone fragility. However, our present findings show that intact PTH and $1,25(OH)_2$ vitamin D are not associated with any bone markers or the presence of vertebral fractures in men with type 2 diabetes.

Although circulating insulin is considered to stimulate osteoblastogenesis and enhance bone formation [22, 39], the present study shows that uC-peptide, as a surrogate marker for residual insulin secretion, was not significantly associated with BMD or bone markers in men with type 2 diabetes. We also found that its level was not different between patients with and those without vertebral fractures. These findings are consistent with our previous ones in patients with type 2 diabetes, in which there were no associations between serum fasting C-peptide and BMD, bone metabolic markers, or vertebral fractures [29, 30]. However, subjects in our studies had received several treatments including insulin administration. Therefore, we should be cautious about the relationship between the capacity of residual insulin secretion and bone metabolism.

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 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 with the disorders. Third, the subjects in this study were only Japanese. The capacity of insulin secretion and degree of obesity in Asians are known to be different compared to Western people [40]. Therefore, it needs to be clarified whether or not our findings are universal. Fourth, we did not measure the fraction of undercarboxylated OC in men with and without fractures compared with healthy age-matched men. Increased metabolic bioactivity of undercarboxylated OC increased pancreatic β-cell proliferation, energy expenditure, insulin sensitivity, and adiponectin production and decreased adiposity [41, 42]. Thus, the undercarboxylated form of OC appears to regulate glucose homeostasis and to be one of the important bone markers when diabetes is studied. Finally, the conclusions of this study are weakened by its cross-sectional design and absence of age-matched healthy controls. Moreover, several other important variables were missing, such as 25-hydroxyvitamin D, estradiol, sex hormone binding globulin, and free testosterone. More than 50% of subjects were treated.

In conclusion, we found that serum OC/BAP ratio was more potently associated with the presence of vertebral fractures than BMD or other bone markers in men with type 2 diabetes, and it could be used as a surrogate marker for assessing the risk of vertebral fractures in that population. Thus, our previous and current studies together suggest that serum IGF-I and pentosidine levels in postmenopausal women [29, 32] and serum OC/BAP ratio in men may

compensate for the ineffectiveness of BMD in evaluating the risk of vertebral fractures in type 2 diabetes. We need to determine their cut-off values that most effectively detect incident vertebral fractures by conducting a prospective study on larger populations in future.

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