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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Adiponectin Is Associated with Changes in Bone Markers during Glycemic Control in Type 2 Diabetes Mellitus

Ippei Kanazawa, Toru Yamaguchi, Mika Yamauchi, Masahiro Yamamoto, Soichi Kurioka, Shozo Yano and Toshitsugu Sugimoto

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Adiponectin Is Associated with Changes in Bone Markers during Glycemic Control in Type 2 Diabetes Mellitus

Ippei Kanazawa, Toru Yamaguchi, Mika Yamauchi, Masahiro Yamamoto, Soichi Kurioka, Shozo Yano, and Toshitsugu Sugimoto

Department of Internal Medicine 1, Shimane University Faculty of Medicine, Izumo, Shimane 693-8501, Japan

Objective: Although several experiments show that adiponectin is associated with bone metabolism, a relationship between adiponectin and bone markers is still unclear. We monitored chronological changes in hyperglycemia, serum adiponectin, and bone markers during glycemic control in type 2 diabetes and analyzed relationships among these parameters.

Subjects and Results: A total of 50 Japanese patients with poorly controlled type 2 diabetes [initial hemoglobin A_{1c} (HbA_{1c}) = 10.0 ± 2.5%] were recruited, and biochemical data were collected before and after glycemic control for a month. Of bone formation markers, bone-specific alkaline phosphatase was decreased with a mean change of −3.11 [95% confidence interval (CI), −5.03 to −1.20; $P < 0.01$], whereas osteocalcin (OC) was increased with a mean change of 1.94 (95% CI, 1.45–2.42; $P < 0.001$) and undercarboxylated OC (ucOC)/OC ratio was decreased with a mean change of −0.15 (95% CI, −0.27 to −0.03; $P < 0.01$). Although adiponectin level was not significantly different before and after glycemic control, baseline adiponectin level, but not HbA_{1c}, was positively correlated with changes in OC, ucOC, and urinary N-terminal cross-linked telopeptide of type I collagen (uNTX) ($r = 0.30$, $P = 0.04$; $r = 0.32$, $P = 0.03$; and $r = 0.36$, $P = 0.01$, respectively). Changes in adiponectin were also negatively correlated with changes in OC and uNTX ($r = -0.42$, $P < 0.01$; and $r = -0.38$, $P < 0.01$, respectively). Changes in HbA_{1c} were negatively correlated with changes in OC ($r = -0.30$, $P = 0.03$).

Conclusion: These findings show that treatments for hyperglycemia enhance OC level and suggest that serum adiponectin level before starting to compensate poorly controlled diabetics could predict the subsequent improvement of bone remodeling markers during glycemic control. ***(J Clin Endocrinol Metab* 94: 3031–3037, 2009)**

The number of patients with diabetes mellitus and osteoporosis is rapidly increasing in industrialized countries where Western-style aging societies are prevalent. Recently, a relationship between diabetes and osteoporotic fractures is becoming increasingly recognized (1). Previous studies have shown that type 1 diabetes is associated with a decrease in bone mineral density (BMD) and an increased risk of osteoporotic hip and other fractures (2, 3). In contrast, although patients with type 2 diabetes show no BMD reduction, fracture risks are known to increase approximately up to 1.5-fold at the hip, proximal humerus, forearm, and foot (3–5), suggesting that they might have bone fragility that is not defined by BMD. However, it is still unclear why patients with type 2 diabetes have an increased risk of fracture despite normal BMD.

Bone mass is determined by a long-term net balance between bone formation and bone resorption. Bone fragility in patients with type 2 diabetes, if any, may be caused by low bone turnover (6, 7). Several studies indicated that hyperglycemia induced a low turnover of bone with osteoblast dysfunction and caused suppression of serum osteocalcin (OC) level (7, 8). Hyperglycemia and advanced glycation endproducts promote the apoptosis of osteoblastic cells (9, 10) and restrain the differentiation of the

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Abbreviations: BAP, Bone-specific alkaline phosphatase; BCE, bone collagen equivalents; BMD, bone mineral density; BMI, body mass index; CI, confidence interval; Cr, creatinine; FPG, fasting plasma glucose; HbA_{1c}, hemoglobin A_{1c}; OC, osteocalcin; ucOC, undercarboxylated OC; uNTX, urinary N-terminal cross-linked telopeptide of type I collagen.

cells (11–14). These findings suggest that hyperglycemia may cause diminished bone formation.

OC is a bone-specific protein of 49 amino acids that is synthesized by osteoblasts. Because a fraction of newly synthesized OC is released into the circulation, its serum concentration generally reflects mature osteoblastic activity and bone formation. OC contains three γ-carboxyglutamic acid residues derived from the vitamin K-dependent posttranslational modification of glutamic acid residues (15, 16). Serum undercarboxylated OC (ucOC) level has been reported to be increased in elderly women (17), particularly those with hip fracture (18), and to be negatively correlated with BMD (19). Although total OC level increases after improved glycemic control in type 2 diabetes (20, 21), it is still unknown how glycemic control affects serum ucOC level.

Adiponectin is one of the adipocytokines specifically and highly expressed in visceral, sc, and bone marrow fat depots (22). We and other researchers have shown that osteoblasts have an adiponectin receptor and that the proliferation, differentiation, and mineralization of osteoblastic cells are enhanced by adiponectin, suggesting that adiponectin could also influence bone metabolism (23, 24). Luo *et al.* (25) 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), although osteoclasts were not directly influenced by adiponectin. Thus, serum adiponectin could improve not only osteoblastic dysfunction but also low bone turnover, which is typically seen in diabetic patients and may cause bone fragility. However, only a few cross-sectional studies were performed on an association between serum adiponectin and bone markers in humans (26–28).

In this study, to clarify these issues, we investigated longitudinal changes in bone markers and serum adiponectin level before and after glycemic control in patients with type 2 diabetes for a month and statistically analyzed their relationships. We found that glycemic control might improve impaired bone formation and that serum adiponectin level could be clinically useful for predicting the beneficial bone reaction ahead of treatments.

Subjects and Methods

Subjects

From November 1, 2006, to April 30, 2008, type 2 diabetes patients with hemoglobin A_{1c} (HbA_{1c}) above 6.5% were enrolled and admitted to Shimane University Hospital. The subjects in this study were 50 Japanese patients with type 2 diabetes (31 men and 19 women) aged 28–87 yr (mean 63.6). Of the 19 female patients, 18 were postmenopausal. Nobody had hepatic or renal dysfunction or nutritional derangements that might cause changes in bone metabolism. All subjects were free of drugs known to influence bone and calcium metabolism like sex steroids, corticosteroids, vitamin D, vitamin K, calcitonin, or bisphosphonate as well as thiazolidinedione until the time of the present study. On admission, all subjects were put on a diet program; the calcium, vitamin D, and vitamin K content of the diet was 650 mg, 12 μg, and 242 μg/d depending on the caloric intake, which was 25–30 kcal/kg ideal body weight. At admission, 24 patients had previously not been under any medications for diabetes. Among the remaining 26 patients, 16 were on sulfonylurea agents (including four combined with metformin, two with α-glucosidase inhibitor, and two with insulin), 10 were on insulin (including one combined with metformin, two with sulfonylurea, and one with α-glucosidase inhibitor). At discharge, five patients were on diet alone, nine on sulfonylurea agents (including two combined with metformin, two with α-glucosidase inhibitor, two with both metformin and α-glucosidase inhibitor, and one with insulin), one on α-glucosidase inhibitors, three on metformin, and 32 on insulin (including one combined with α-glucosidase inhibitors and four with metformin). This study was approved by the ethical review board of our institution and complied with the Helsinki Declaration. All patients agreed to participate in the study and provided informed consent.

Biochemical measurements

On the second day after admission and the day before discharge, serum was collected after overnight fasting. The interval between the two determinations was 27.9 ± 6.3 d. Biochemical markers were measured by standard biochemical methods. HbA_{1c} was determined by HPLC. Bone-specific alkaline phosphatase (BAP) and serum OC were measured by enzyme immunoassay and RIA, respectively, as previously described (29, 30). ucOC was measured by electrochemiluminescence immunoassay, as previously described (31). Serum C-peptide and urinary N-terminal cross-linked telopeptide of type-I collagen (uNTX) were measured by ELISA, as previously described (29, 30). Total adiponectin was measured by an ELISA kit (Otsuka Pharmaceuticals, Tokyo, Japan) as indicated by the manufacturer. The coefficients of variation of measurements of total adiponectin by the ELISA kit was 3.1%.

Statistical analysis

Data are expressed as mean ± SD. We calculated changes in parameters by subtracting the baseline measurement from the second measurement. Statistical significance before and after glycemic control was determined using the Wilcoxon signed rank test, because serum adiponectin and bone markers showed a markedly skewed distribution [serum adiponectin: median value (med) = 5.7 μg/ml, minimum value (min) = 2.1 μg/ml, and maximum value (max) = 30.8 μg/ml; BAP: med = 26.6 U/liter, min = 9.1 U/liter, and max = 64.7 U/liter; OC: med = 4.4 ng/ml, min = 1.0 ng/ml, and max = 12.0 ng/ml; ucOC: med = 2.00 ng/ml, min = 0.39 ng/ml, and max = 10.10 ng/ml; uNTX: med = 32.6 nM bone collagen equivalents (BCE)/mM creatinine (Cr), min = 9.9 nM BCE/mM Cr, and max = 172.9 nM BCE/mM Cr]. Logarithmic (log) transformation of these values was carried out before performing correlation and regression analysis. Multiple regression analysis was performed after being adjusted for age, gender, duration of diabetes, body mass index (BMI), and serum Cr. Correlation analysis and multiple regression analysis were performed using the statistical computer program StatView (Abacus Concepts, Berkeley, CA). $P < 0.05$ was considered to be significant.

Results

Changes in markers for glucose and bone metabolism before and after glycemic control

Changes in markers for glucose and bone metabolism are summarized in Table 1. Diabetic control of the enrolled patients was poor on admission (HbA_{1c} = 10.0 ± 2.5%). Both fasting plasma glucose (FPG) and HbA_{1c} were significantly decreased after treatments with mean changes of −50.10 [95% confidential interval (CI), −74.65 to −25.55, $P < 0.001$] and −1.23 (95% CI, −1.56 to −0.89, $P < 0.001$), respectively, showing that hyperglycemia was markedly improved. Although body

TABLE 1. Changes in markers for glucose and bone metabolism

	Before	After	Mean change	95% CI	P
Subjects (male/female)	50 (31/19)				
Age (yr)	63.6 ± 13.7				
Duration of diabetes (yr)	12.2 ± 9.7				
Body height (cm)	160.0 ± 10.1				
Body weight (kg)	62.0 ± 19.1	61.0 ± 17.8	−1.75	−2.67 to −0.83	<0.001
BMI (kg/m^2)	24.0 ± 5.3	23.5 ± 4.9	−0.66	−1.00 to −0.32	<0.001
Serum Cr (mg/dl)	0.71 ± 0.25				
Serum C-peptide (ng/ml)	1.8 ± 1.0				
FPG (mg/dl)	197 ± 71	147 ± 53	−50.10	−74.65 to −25.55	<0.001
HbA_{1c} (%)	10.0 ± 2.5	8.8 ± 1.9	−1.23	−1.56 to −0.89	<0.001
Adiponectin (μg/ml)	8.5 ± 6.9	8.6 ± 6.5	0.05	−1.21 − 1.12	0.81
BAP (U/liter)	29.6 ± 12.5	26.6 ± 10.2	−3.11	−5.03 to −1.20	<0.01
OC (ng/ml)	4.8 ± 2.7	6.7 ± 3.4	1.94	1.45 − 2.42	<0.001
ucOC (ng/ml)	2.86 ± 2.44	3.37 ± 3.12	0.43	−0.26 − 1.13	0.42
ucOC/OC ratio	0.58 ± 0.38	0.44 ± 0.25	−0.15	−0.27 to −0.03	<0.01
uNTX (nM BCE/mM Cr)	39.9 ± 29.8	43.5 ± 33.8	3.59	−1.21 − 8.40	0.10
No medications [n (%)]	24 (48%)	5 (10%)			
Insulin [n (%)]	10 (20%)	32 (64%)			
Sulfonylurea [n (%)]	16 (32%)	9 (18%)			
Metformin [n (%)]	5 (10%)	11 (22%)			
α-Glucosidase inhibitor [n (%)]	3 (6%)	6 (12%)			

Statistical significance was determined using the Wilcoxon signed rank test. Normal range for serum Cr is 0.44–1.23 mg/dl; serum C-peptide, 0.6–28 ng/ml; FPG, 60–110 mg/dl; HbA_{1c}, 4.3–5.8%; adiponectin, 4.1–18.9 μg/ml; BAP, 9.6–35.4 U/liter; OC, 2.5–13.0 ng/ml; ucOC, <4.5 ng/ml; uNTX male, 13.0–66.2 nM BCE/mM Cr; and uNTX female, 14.3–89.0 nM BCE/mM Cr.

weight and BMI were significantly decreased with mean changes of −1.75 (95% CI, −2.67 to −0.83, $P < 0.001$) and −0.66 (95% CI, −1.00 to −0.32, $P < 0.001$), respectively, serum adiponectin level was not significantly different. BAP was decreased with a mean change of −3.11 (95% CI, −5.03 to −1.20, $P < 0.01$), whereas serum OC was increased with a mean change of 1.94 (95% CI, 1.45–2.42, $P < 0.001$). Although serum ucOC was not significantly changed, ucOC/OC ratio was decreased after treatments with a mean change of −0.15 (95% CI, −0.27 to −0.03, $P < 0.01$). On the other hand, uNTX was not significantly changed.

We have analyzed the difference in baseline data between the insulin treatment group and the noninsulin treatment group. However, we could not find any statistically significant difference in any variable except for serum C-peptide (insulin treatment, 1.29 ± 0.86 ng/ml, *vs.* noninsulin treatment, 1.94 ± 0.96 ng/ml, $P = 0.0498$). We have also reanalyzed changes in serum adiponectin and bone markers after separating between the insulin treatment group and the noninsulin treatment group. We found that BAP decreased and OC increased after treatments for diabetes regardless of insulin or noninsulin treatments (the data not shown).

Relationships between baseline values of demographic and biochemical markers *vs.* changes in bone markers during glycemic control

Next, we investigated whether or not baseline values of demographic and biochemical markers could be useful for predicting changes in bone markers during glycemic control (Table 2). Age was significantly and positively correlated with changes in BAP and ucOC/OC ratio ($r = 0.32$, $P = 0.03$; and $r = 0.42$, $P < 0.01$, respectively). Duration of diabetes was significantly and positively correlated with changes in OC ($r = 0.33$, $P = 0.02$). Changes in ucOC/OC ratio were significantly and negatively correlated with baseline body height, body weight, and BMI ($r = -0.30$, $P = 0.04$; $r = -0.38$, $P = 0.01$; and $r = -0.31$, $P = 0.04$, respectively). Baseline log(adiponectin) was significantly and positively correlated with changes in OC, ucOC, and uNTX ($r = 0.30$, $P = 0.04$; $r = 0.32$, $P = 0.03$; and $r = 0.36$, $P = 0.01$, respectively). Baseline log(BAP), log(OC), log(ucOC), and ucOC/OC ratio were significantly and negatively correlated with changes in BAP ($r = -0.58$, $P < 0.001$; $r = -0.28$, $P = 0.04$; $r = -0.40$, $P < 0.01$; and $r = -0.29$, $P = 0.04$, respectively). Baseline ucOC/OC ratio was significantly and negatively correlated with changes in ucOC ($r = -0.30$, $P = 0.04$). Baseline log(OC) was significantly and positively correlated with changes in ucOC/OC ratio ($r = 0.31$, $P = 0.04$), and baseline ucOC/OC ratio was significantly and negatively correlated with changes in ucOC/OC ratio ($r = -0.81$, $P < 0.001$). However, baseline serum C-peptide, FPG, or HbA_{1c} were not correlated with changes in any bone markers.

Next, to investigate whether baseline adiponectin or HbA_{1c} were related to changes in bone markers independent of age, gender, duration of diabetes, BMI, and serum Cr, multiple regression analysis was performed between baseline adiponectin and HbA_{1c} *vs.* changes in bone markers adjusted for these confounders. Baseline adiponectin was still significantly and positively correlated with changes in OC and uNTX ($r = 0.40$, $P = 0.04$; and $r = 0.48$, $P = 0.02$, respectively). On the other hand, baseline HbA_{1c} was not significantly correlated with changes in any bone markers.

TABLE 2. Correlations between changes in bone markers *vs.* baseline values of demographic and biochemical parameters

	ΔBAP		ΔOC		ΔucOC		ΔucOC/OC		ΔuNTX	
	r	*P*	r	*P*	r	*P*	r	*P*	r	*P*
Age	0.32	0.03	−0.04	0.77	0.23	0.14	0.42	<0.01	0.12	0.42
Duration of diabetes	0.01	0.94	0.33	0.02	0.24	0.11	0.00	0.99	0.24	0.09
Body height	−0.24	0.10	0.10	0.48	−0.13	0.40	−0.30	0.04	−0.25	0.08
Body weight	−0.10	0.49	0.10	0.81	−0.23	0.13	−0.38	0.01	−0.21	0.15
BMI	0.04	0.79	−0.02	0.91	−0.23	0.13	−0.31	0.04	−0.13	0.38
Serum Cr	0.07	0.61	−0.14	0.35	−0.19	0.22	−0.06	0.69	−0.04	0.80
Serum C−peptide	0.08	0.58	0.13	0.35	−0.11	0.49	−0.11	0.46	0.01	0.96
FPG	−0.14	0.35	0.19	0.18	0.17	0.28	0.19	0.21	−0.04	0.79
HbA_{1c}	−0.15	0.30	0.15	0.30	0.30	0.05	0.28	0.06	0.03	0.86
Log (adiponectin)	0.04	0.77	0.30	0.04	0.32	0.03	0.21	0.17	0.36	0.01
Log (BAP)	−0.58	<0.001	0.14	0.33	−0.09	0.58	−0.20	0.18	0.07	0.63
Log (OC)	−0.28	0.04	0.05	0.74	0.11	0.49	0.31	0.04	0.01	0.94
Log (ucOC)	−0.40	<0.01	0.11	0.45	−0.10	0.51	−0.24	0.11	−0.04	0.81
ucOC/OC ratio	−0.29	0.04	0.10	0.50	−0.30	0.04	−0.81	<0.001	−0.15	0.31
Log (uNTX)	−0.24	0.10	0.23	0.11	0.13	0.38	0.04	0.80	−0.04	0.81

Numbers in each cell describe a correlation coefficient. Logarithmic (log) transformation of adiponectin, BAP, OC, ucOC, and uNTX was carried out. Δ, Differences between after and before treatments.

Relationships between changes in body weight, hyperglycemia, and serum adiponectin *vs.* changes in bone markers during glycemic control

Next, we investigated relationships between changes in body weight, BMI, FPG, HbA_{1c}, and serum adiponectin level *vs.* changes in bone markers during glycemic control (Table 3). Changes in serum adiponectin were significantly and negatively correlated with changes in OC and uNTX ($r = -0.42$, $P < 0.01$; and $r = -0.38$, $P < 0.01$, respectively). Changes in HbA_{1c} were significantly and negatively correlated with changes in OC ($r = -0.30$, $P = 0.03$). Changes in body weight and BMI were significantly and positively correlated with changes in ucOC/OC ratio ($r = 0.41$, $P < 0.01$; and $r = 0.39$, $P = 0.01$, respectively). Changes in serum adiponectin were still significantly and negatively correlated with changes in OC and uNTX after being adjusted for changes in HbA_{1c} ($r = -0.42$, $P < 0.01$; and $r = -0.38$, $P < 0.01$, respectively). Changes in HbA_{1c} were also still significantly and negatively correlated with changes in OC after being adjusted for changes in serum adiponectin ($r = -0.30$, $P = 0.02$). These results suggest that serum adiponectin and HbA_{1c} were independently associated with bone markers.

Discussion

In this study, improvement of hyperglycemia in patients with type 2 diabetes was associated with a decrease in BAP as well as an increase in OC. Changes in HbA_{1c} were also significantly and inversely associated with changes in OC. Although ucOC was not significantly changed during treatments, the ucOC/OC ratio was decreased. It is known that OC reflects mature osteoblast function, whereas BAP and ucOC reflect an immature one (32, 33). Thus, these findings suggest that glycemic control may stimulate osteoblastic differentiation and enhance bone formation. On the other hand, baseline serum adiponectin level was positively associated with changes in bone markers during glycemic control. Changes in adiponectin were also negatively associated with changes in bone markers. These findings suggest that serum adiponectin could predict the degree of subsequent changes in bone markers during glycemic control and that bone metabolism could be linked to fat metabolism.

Several studies indicated that hyperglycemia induced a low-turnover bone with osteoblast dysfunction and caused suppression of serum OC level (7, 8, 21). Gerdhem *et al.* (7) have shown that serum OC, but not BAP, was lower in the diabetic women after correction for covariance of body weight and serum Cr. Okazaki *et al.* (20) have shown that serum OC was low before treatments and was elevated after treatments of diabetes, whereas BAP was reduced. On the other hand, Gregorio *et al.* (28) reported that improvement of metabolic control in non-insulin-dependent diabetes reduced serum OC level and increased bone mineral content. Our present findings seem to accord well with these former two studies. Previous *in vitro* studies have shown that chronic hyperglycemia increased the activity

TABLE 3. Correlations between changes in bone markers *vs.* changes in body weight, BMI, FPG, HbA_{1c}, and serum adiponectin

	ΔBAP		ΔOC		ΔucOC		ΔucOC/OC		ΔuNTX	
	r	*P*	r	*P*	r	*P*	r	*P*	r	*P*
ΔBody weight	−0.03	0.86	0.01	0.94	0.23	0.14	0.41	<0.01	0.20	0.17
ΔBMI	−0.09	0.53	0.05	0.76	0.25	0.11	0.39	0.01	0.19	0.21
ΔFPG	0.20	0.17	−0.26	0.07	−0.15	0.32	−0.09	0.55	−0.04	0.80
ΔHbA_{1c}	0.11	0.44	−0.30	0.03	−0.28	0.07	0.00	0.99	0.00	0.99
ΔAdiponectin	−0.07	0.61	−0.42	<0.01	−0.21	0.16	−0.01	0.97	−0.38	<0.01

Numbers in each cell describe a correlation coefficient. Δ, Differences between after and before treatments.

and expression of alkaline phosphatase, whereas it decreased OC expression and cellular calcium uptake (34). These findings explain the discrepancy in serum levels of OC and BAP in the clinical studies and suggest that hyperglycemia may directly impair osteoblastic maturation, which might result in impairment of bone quality as well as higher fracture rates in patients with type 2 diabetes despite no reduction in BMD.

Circulating ucOC is a valuable nutrition marker reflecting skeletal provision with vitamins K and D (35, 36). Vergnaud *et al.* (36) have shown that ucOC, but not total OC, predicted hip fracture risk independent of femoral neck BMD in elderly women, suggesting that ucOC could be clinically useful for assessing the risk of hip fracture independent of BMD. Although the levels of ucOC and ucOC/OC ratio are thought to be surrogate markers for bone quality as well as bone fragility (18, 37, 38), it was unclear how glycemic control affected ucOC and ucOC/OC ratio in patients with type 2 diabetes. Our present findings showed that OC was increased, whereas ucOC/OC ratio was decreased after glycemic control, suggesting that impaired bone formation in diabetes could be improved by treatments.

Studies on bone resorption status in diabetes are limited, and the results are conflicting. Some previous studies showed that hyperglycemia might activate osteoclasts, resulting in enhancement in bone resorption in diabetes (39). However, histomorphometric analysis of BB rats, which had long-term diabetes, showed that bone resorption was depressed (40). Clinically, alteration of bone resorption markers during glycemic control in type 2 diabetes seems to be controversial as well. Rosato *et al.* (21) indicated that pyridinoline (PYD) and deoxypyridinoline were increased after improved glycemic control, whereas Okazaki *et al.* (20) showed that deoxypyridinoline and type I collagen carboxy-terminal telopeptide were decreased. In this study, uNTX was not significantly changed during glycemic control, whereas serum OC and BAP were significantly changed. Changes in HbA_{1c} were also not significantly correlated with changes in uNTX, although they were significantly and negatively correlated with changes in OC. These findings indicate that glycemic control strongly affects bone formation markers, but not a bone resorption marker, and suggest that processes of bone formation and resorption might be uncoupled in type 2 diabetes and that treatments for hyperglycemia could improve impaired bone formation and bone remodeling.

Several recent experiments have shown that adiponectin could stimulate bone formation (23, 41) and regulate bone turnover (25). Several studies also documented a significant positive relationship between serum adiponectin and bone markers (26–28). Thus, adiponectin appears to mediate bone formation and bone remodeling, and serum hypoadiponectinemia may cause low turnover and lead to bone fragility in patients with type 2 diabetes (42), although the relationship between serum adiponectin level and BMD was still controversial (43–46). In this study, we observed that baseline serum adiponectin level was positively correlated with changes in OC, ucOC, and uNTX during glycemic control. We also found that changes in adiponectin were negatively associated with changes in OC and uNTX, which is independent of changes in HbA_{1c}. These findings indicate that baseline serum adiponectin value could be useful for predicting augmentation in bone markers during glycemic control and confirm the previous observations that serum adiponectin was clinically associated with bone markers in humans.

Fat mass is known to influence bone metabolism through adipocytokines, which are secreted from adipocytes (47). On the other hand, two recent animal studies have shown that OC derived from osteoblasts functions as a hormone regulating glucose metabolism and fat mass (48, 49). Moreover, it has been reported that bone marrow-derived circulating progenitor cells might transdifferentiate into adipocytes (50). Recently, we have shown that serum OC level is associated with glucose metabolism and atherosclerosis parameters in patients with type 2 diabetes (51). These findings suggest that bone metabolism and glucose/fat metabolism might be associated with each other. The association between bone markers *vs.* serum adiponectin and hyperglycemia found in this study might also suggest the interaction between bone metabolism and fat/glucose metabolism in a clinical setting.

This study has some limitations. First, the sample size was not large enough to make definite conclusions. Second, the subjects in this study were only Japanese, and BMIs in the present populations (mean, 24.0 kg/m^2) were lower than those observed in Caucasians. Capacity of insulin secretion and degree of obesity in Asians are known to be different from Western people (52), and thus our findings might not be applicable to Caucasians. Third, our study group was heterogeneous in treatments for diabetes. All diabetic medications may not be expected to have similar effects on bone turnover or adiponectin levels in the circulation. Although we found that changes in adiponectin or bone markers were not significantly different between the insulin treatment group and the non-insulin treatment group in the current study, we need to investigate this issue in future studies. Fourth, we should note the influence of caloric restriction on bone markers, although changes in body weight and BMI were not significantly associated with changes in bone markers except for that in ucOC/OC. Finally, a previous genetic study has shown that low serum adiponectin level might be influenced by genetic factors (53), 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.

In conclusion, we found decreases in BAP and ucOC/OC ratio as well as an increase in OC after treatments for hyperglycemia in type 2 diabetes. Serum adiponectin level could predict these beneficial bone reactions ahead of glycemic control. These clinical observations might support the concept that fat/glucose metabolism and bone metabolism interact with each other.

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Address all correspondence and requests for reprints to: Toru Yamaguchi, M.D., Ph.D., Department of Internal Medicine 1, Shimane University Faculty of Medicine, 89-1 Enya-cho, Izumo 693-8501, Japan. E-mail: yamaguch@med.shimane-u.ac.jp.

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8

骨質マーカーとしてのペントシジンと骨折リスク

山本 昌弘*

要旨 骨強度は「骨密度」と「骨質」の要因から構成され，骨質は構造特性と材質特性から成る．骨コラーゲン内ペントシジン含有量が増加すると骨強度が低下することから，ペントシジンは骨の材質特性を変化させ骨脆弱性を招く．この骨内のペントシジン含有量は血液中の濃度と正相関し，その血液や尿中濃度の増加がそれぞれ2型糖尿病および原発性骨粗鬆症患者において，椎体骨折の増加と関係することが明らかにされた．これらの結果から血液および尿中ペントシジン濃度が骨質を反映した椎体骨折予測マーカーとして有用であることが示唆された．

〈Key point〉

はじめに

2000年の米国国立衛生研究所（NIH）のコンセンサス会議において，骨粗鬆症は「骨強度の低下を特徴とし，骨折のリスクが増大しやすくなる骨格疾患」と定義され，骨強度は「骨密度」と「骨質」の要因から構成されると報告された[1]．骨密度は骨強度の約70%を説明する因子である[1]．しかし続発性骨粗鬆症であるステロイド骨粗鬆症や2型糖尿病では，骨密度が保たれているにもかかわらず脆弱性骨折が増加し，その骨強度の低下は骨密度では説明できないことが明らかとなった．このことより骨質の低下は骨強度に対し強い影響を与えていると考えられ，骨質を評価することが重要視されるようになった．

骨質の低下

本稿では2型糖尿病の骨密度非依存性脆弱性骨折とペントシジンの関連性に着目し，骨質を反映する生化学マーカーとしてのペントシジンの可能性について概説する．

Key words : 骨質，ペントシジン，2型糖尿病，椎体骨折，骨密度

* 島根大学医学部内科学講座内科学第一（〒693-8501 島根県出雲市塩冶町89-1）

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Ⅰ．骨質評価の重要性

骨密度と骨強度

Dual energy X-ray absorptiometry（DXA）法による骨密度測定は本邦においてもっとも多用される骨強度評価のツールと考えられるが，骨密度は必ずしも骨強度を正確に反映しているわけではない．閉経後原発性骨粗鬆症女性においてラロキシフェンによる骨粗鬆症治療は，腰椎骨密度の増加は2.5%前後と軽微であるにもかかわらず，対照群に比較して椎体骨折の相対危険度は40%減少し[2]，骨密度増加以上に骨折防止作用があることが知られている．続発性骨粗鬆症であるステロイド骨粗鬆症では，骨密度で予測される以上に椎体骨折が発生し[3]，骨密度では椎体骨折は予期できないことが明らかにされた[4]．2型糖尿病では，メタ解析により骨密度が対照群よりも高値であるにもかかわらず大腿骨頸部骨折が増加することが示されている[5),6]．2型糖尿病患者の椎体骨折においても，われわれの検討により対照群より骨密度が高いにもかかわらず既存骨折率が高いことが明らかとなった[7]．

骨質を評価

これらの結果は，骨密度では表せない骨脆弱性の存在，すなわち骨質の低下により骨強度が低下している場合があり，骨質を評価することが重要であることを示唆している．

Ⅱ．骨の材質特性とペントシジン

構造特性
材質特性

骨質は構造特性と材質特性によって構成され，前者には骨の大きさ，骨形態，微細骨構造が，後者にはコラーゲン，石灰化度および微小骨折（micro-damage）が含まれる[8]．このうちコラーゲンは骨基質の有機成分の90%を占めることから，骨の材質特性に大きな影響を及ぼしている．コラーゲン線維は，骨芽細胞内で3本螺旋を形成したプロコラーゲンが細胞外に分泌され，プロペプチドが切断された後，リジン酸化酵素により遺伝的に規定された部位でプロコラーゲン同士が架橋形成して形成される．

コラーゲン

ペントシジン

一方ペントシジンは，高齢者のヒト細胞外基質から発見された，ペントースとアルギニンおよびリジンが反応した構造を有する終末糖化物質（advanced glycation end-products；AGEs）[9]の一つで，高血糖状態や酸化ストレスの増加により非酵素的に生成され，蛋白間の架橋形成能を有すると考えられている物質である．近年骨内に存在するAGEsが骨代謝に影響を及ぼすことが見出されている．

AGEs

ペントシジンと骨強度

ペントシジンと骨強度に関するいくつかの知見が得られている．高齢者では皮質骨内のペントシジン含有量が増加し，生体力学的試験により骨内ペントシジン含有量の増加が骨強度の低下と関連することが知られている[10]．実際に

Saitoらは，大腿骨頸部骨折患者では対照群より骨内ペントシジン含有量が増加していることを見出している[11),12)]．

さらにSaitoらは，自然糖尿病発症ラットにおいて，骨コラーゲン内ペントシジン含有量が骨質と関連しうる可能性を提示した[13)]．このラットでは糖尿病発症後から骨内ペントシジン含有量が増加し，骨密度の低下がないにもかかわらず3点曲げ試験において骨強度が低下することを明らかにした[13)]．この結果は，骨コラーゲン内ペントシジン含有量が骨密度とは独立した骨強度に影響する因子であること，すなわち骨質のうち材質特性を反映する因子であることを示唆している．

材質特性を反映

ペントシジンがどのように骨強度に影響を及ぼしているかは明らかではない．その骨脆弱性を招く機序として，ペントシジンの架橋形成性の特性から，遺伝的に規定された特定の部位以外でプロコラーゲン間を連結して過剰架橋状態を招き，骨はしなやかさを失い脆弱性が増す可能性が考えられている[14)]（図1）．その他の機序として，ペントシジン生成にはリジンを必要とすることから，正常なコラーゲン架橋形成に必要なリジン残基がペントシジン形成で消費されることにより，架橋数が少なく全長が短いコラーゲン線維が形成され[15)]骨強度

骨脆弱性の機序

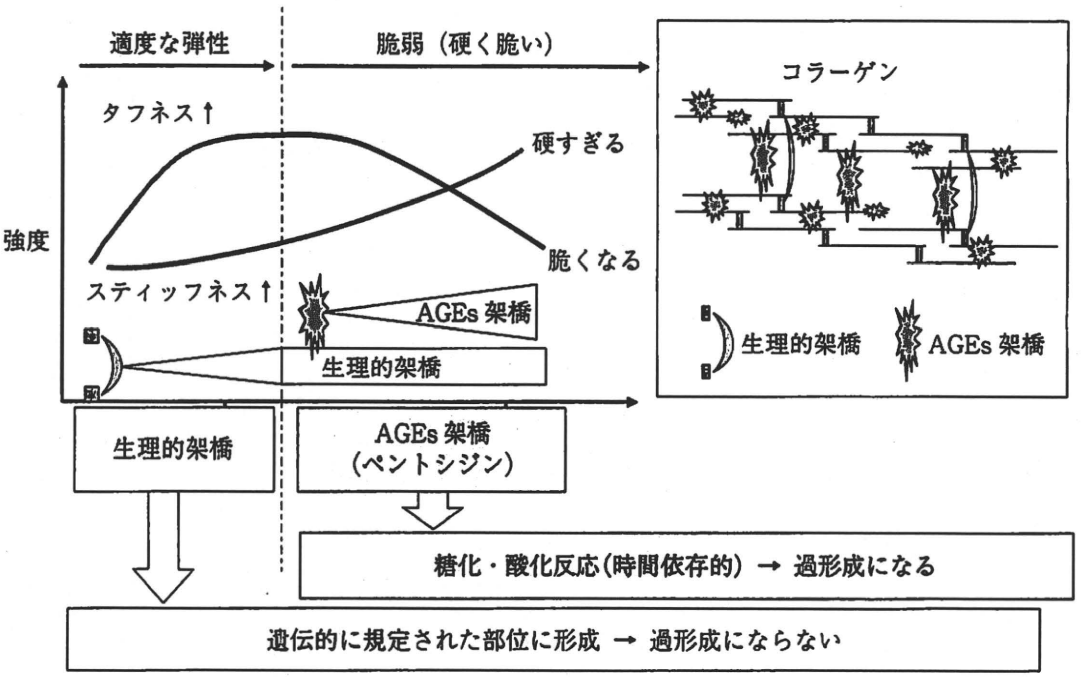

図1　コラーゲンの架橋形成と材質特性

コラーゲンの分子間架橋は，遺伝的に規定された部位で細胞外に分泌されたプロコラーゲン同士が架橋形成して形成される（生理的架橋）．これに加えて，それ以外の部位でAGEs（ペントシジン）がプロコラーゲン間に結合して過剰架橋状態になると，骨はしなやかさを失い脆弱性が増す可能性がある．

〔斎藤　充：Clin Calcium　18：364-372, 2008[14)] より改変〕

が低下することが想定されている．

Ⅲ．骨折危険予測マーカーとしてのペントシジン

血液中のペントシジン濃度
骨折の予測マーカー

このようにペントシジンはコラーゲンの材質特性を反映する骨折予測因子となりうる可能性が示されたが，骨内ペントシジン含有量を測定するには骨生検などの侵襲的検査を必要とするため，日常臨床での利用は困難と考えられていた．しかし近年，血液中のペントシジン濃度が骨内含有量と正相関することが明らかとなり[16]，その血中濃度が骨折の予測マーカーとして応用できる可能性がある．

2型糖尿病

2型糖尿病は椎体骨折の相対危険度が高いにもかかわらずその骨折危険度は骨密度には反映されないことから[7]，骨質低下に基づく骨強度の低下が予想されていた．一方，2型糖尿病の血液中のペントシジン濃度は対照群より高いことが知られている[17]．そこでわれわれは血液中のペントシジン濃度が骨質低下を反映して高値を呈していることを想定し臨床的検討を行った．閉経後2型糖尿病女性では，HbA1cや腎機能，糖尿病合併症の有無などの調整後において血清ペントシジン濃度が増加すると椎体骨折の相対危険度が高まることを見出した〔odds ratio 2.50（95％信頼区間 1.09～5.73），p＝0.030〕[18]．一方 Shirakiらは未治療閉経後女性において，ペントシジン尿中排泄量の多い群では新規椎体骨折の相対危険度が高いことを見出し〔hazard ratio 1.33（95％信頼区間 1.01～1.76），p＝0.04〕[19]，原発性骨粗鬆症においてもペントシジンが椎体骨折

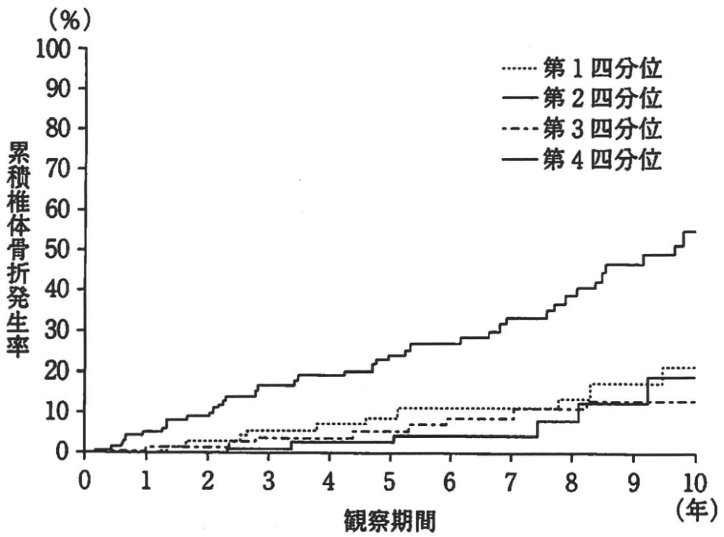

図2　尿中ペントシジン排泄量と累積椎体骨折発生率
尿中ペントシジン排泄量がもっとも高い第4四分位では，他の四分位よりも累積椎体骨折発生率が有意に早く高くなる．
〔Shiraki M, et al : J Bone Miner Metab　26 : 93-100, 2008[19] より改変〕

の予測因子として利用できることを明らかにした（図2）.

これらの臨床的検討により，ペントシジンの血液または尿中濃度は椎体骨折と関連する因子であることが示され，前項の検討からその値は骨質低下を反映した指標であると考えられた.

Ⅳ．骨・血管連関の説明因子としてのペントシジン

骨・血管連関

以前より骨粗鬆症の有病率が高い地域では，動脈硬化が多いことが観察されており，骨粗鬆症と動脈硬化・血管石灰化が密接に関係する「骨・血管連関」という概念が提唱されている．ペントシジンは骨脆弱性のみならず，動脈硬化・動脈石灰化と関係することが報告されている．2型糖尿病において動脈硬化指標である内頸動脈の内膜中膜複合体厚（intima-media thickness；IMT）は，腎機能で調整後において血清ペントシジン濃度と正相関[17]し，一方末期腎疾患患者の大動脈壁中膜の石灰化沈着はペントシジン沈着部位と一致する[20]ことが報告されている．このようにペントシジンは動脈硬化の成立機序として骨代謝との関わりを示唆する「骨・血管連関」を説明しうる因子である可能性が考えられる.

内膜中膜複合体厚

おわりに

骨密度で骨脆弱性の評価が困難である2型糖尿病の動物実験モデルおよび臨床検討により，ペントシジンが骨折と関係することから，その値は骨質低下を表していると考えられる．血液中のペントシジン濃度は骨コラーゲン内含有量と正相関することから，その血液濃度は骨質を反映したマーカーになることが示唆された．骨強度は骨密度と骨質から構成されることから，骨密度測定とペントシジン測定を組み合わせることにより，より精度の高い骨折予測が可能となることが考えられ，今後の検討が望まれる.

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Summary

Pentosidine as candidate for bone quality marker associated with fracture risk

Masahiro Yamamoto*

Bone strength reflects the integration of bone mineral density and bone quality, the latter of which consists of both structural properties and material properties. Increases in quantities of pentosidine in bone collagen deteriorate bone strength, suggesting that high levels of pentosidine in bone lead to fragility. Blood levels of pentosidine are correlated with bone content. Blood and urinary levels of pentosidine are associated with increased risk of vertebral fractures in patients with postmenopausal type 2 diabetes and primary osteoporosis. These results suggested that blood or urinary levels of pentosidine are useful markers for predicting the risk of vertebral fractures.

Key words : bone quality, pentosidine, type 2 diabetes mellitus, vertebral fractures, bone mineral density

* *Internal Medicine 1, Shimane University Faculty of Medicine*

トピックス

糖尿病患者の骨粗鬆症・骨折をめぐる話題

Topics on osteoporosis and bone fractures in patients with type 2 diabetes

特集

山本 昌弘　杉本 利嗣*
YAMAMOTO Masahiro　SUGIMOTO Toshitsugu

経口糖尿病治療薬のすべて

Key words 2型糖尿病　骨折　骨質　ベントシジン　チアゾリジン

1948年 Albright により，糖尿病と骨粗鬆症の関係が報告され，近年のメタ解析により1型糖尿病(T1DM)および2型糖尿病(T2DM)のいずれも骨折の相対危険度が高いことが明らかとなった．また一部の糖尿病治療薬では骨折が増加すると報告され，糖尿病と骨代謝の関連が注目されている．そこで本稿では主に2型糖尿病の骨脆弱性の特徴ついて，著者らのデータも交えて概説する．

糖尿病と骨折

メタ解析により1型糖尿病(T1DM)では，対照群より dual-energy X-ray absorptiometry(DXA)法による骨密度(bone mineral density；BMD)が低値で，相対骨折危険度が高いことから[1)2)]，T1DM における骨脆弱性には BMD 低下が関わっていると考えられる．インスリンは骨同化作用を有していることから[3)]，若年に発症した T1DM は最大骨量(peak bone mass)に対し負に影響し[4)]，骨粗鬆症を招いている可能性がある．また T1DM では，血清インスリン様成長因子-1濃度やオステオカルシンに代表される骨形成マーカーが低値であり[5)]，骨量減少症との関連が示唆されている[6)]．

一方，2型糖尿病(T2DM)のメタ解析では，T1DM と異なり，大腿骨頸部および椎体の BMD Z 値(年齢を考慮した BMD の標準偏差値)は非糖尿病者よりも高値であるにも関わらず，大腿骨頸部骨折の相対危険度が1.38～1.7倍増加していることが明らかとなった[1)2)]．一方，T2DM の椎体骨折に対しては十分な報告が存在しないことから，筆者らは50歳以上の男性および閉経後女性の椎体骨折に対して検討を行った．年齢，BMI，腰椎 BMD の調整後において T2DM の存在が独立した椎体骨折の危険因子であること，また対照群と異なり BMD が椎体骨折と関連しないことを明らかにした[7)]．これらの結果は，T2DM において BMD 非依存性の骨脆弱性が存在することを示唆している．

2000年の米国国立衛生研究所(NIH)のコンセンサス会議によると，骨粗鬆症は「骨強度の低下を特徴とし，骨折のリスクが増大しやすくなる骨格疾患」と定義され，骨強度は「骨密度」と「骨質」の要因から構成されると報告された[8)]．T2DM 患者の骨強度は BMD に依存しないことから，骨質低下により骨脆弱性が亢進していると考えられる．

上述したように骨質は構造特性と材質特性から

島根大学医学部内科学第一　*教授

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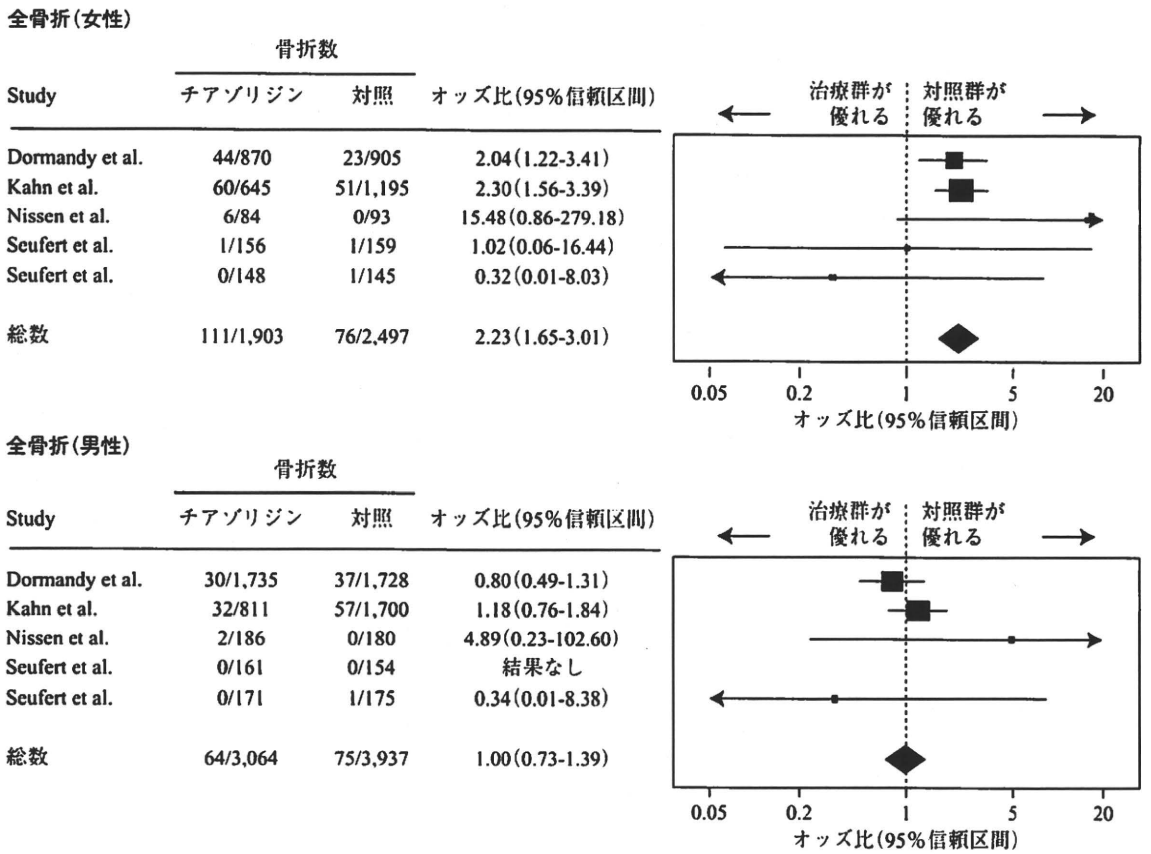

図1 全骨折に対するチアゾリジン治療の影響
(Loke YK, et al：CMAJ 180：32-39, 2009より改変)

構成されるが，現在日常診療で利用できる有用な骨質評価法は骨代謝マーカー測定による骨代謝回転のみである．近年，糖尿病と関連が深い終末糖化物質(advanced glycation end-products；AGEs)のひとつであるペントシジンが，大腿骨頸部骨折患者において骨基質のコラーゲン架橋に影響を及ぼし，その結果骨の材質特性が変化して骨強度が低下することが示された．筆者らは血清ペントシジン濃度と椎体骨折の関係を検討し，閉経後T2DM女性においてペントシジンが増加すると椎体骨折の相対危険度が有意に増加することを見い出した[9]．筆者らの報告に続き前向き観察研究において，対照群とは異なり閉経後T2DM女性群では，観察開始時の尿中ペントシジン濃度が高いほど観察期間中に骨折を生じる相対危険度が高いことが確認された[10]．これらの報告は，閉経後T2DM女性においてペントシジンがBMDとは独立した骨質を反映する有用な骨折予測マーカーになりうる可能性を示唆している．

糖尿病治療薬と骨代謝

このように糖尿病では骨折の相対危険度が増加しているが，その骨脆弱性亢進に一部の糖尿病治療薬の関与が指摘されている．スウェーデンや英国の住民ベースのデータを用いた検討により，インスリン分泌刺激薬やメトホルミンは，骨折危険度の増加と関連がない，あるいは低下させうることが報告されている[11][12]．インスリン治療と骨折の関係は，交絡因子の調整の有無で一貫した結論が得られておらず，その解釈には注意が必要である．