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Serum leptin and adiponectin are positively associated with bone mineral density at the distal radius in patients with type 2 diabetes mellitus

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Abstract

There have been several reports about associations of serum leptin or adiponectin with bone mineral density and biochemical markers of bone turnover. However, the precise roles of adipocytokines in bone metabolism have not been fully elucidated. We investigated the associations of serum level of leptin or adiponectin with bone mineral density, serum osteocalcin, and urinary N-terminal telopeptide of type I collagen (NTX) in 40 Japanese patients with type 2 diabetes mellitus. Bone mineral density was measured by using dual-energy x-ray absorptiometry at different sites (distal radius, femoral neck, and lumbar spine) and was expressed as *z* score. Multiple regression analysis revealed that there were significant positive correlations between serum leptin or adiponectin level and *z* score at the distal radius, but not at the femoral neck or the lumbar spine. Although no correlation was observed between serum leptin and serum osteocalcin, there was a significant negative correlation between serum leptin and urinary NTX, a marker of bone resorption. No correlation was observed between serum adiponectin and serum osteocalcin or urinary NTX. These results indicate that leptin and adiponectin may have a protective effect on bone metabolism in patients with type 2 diabetes mellitus.

1. Introduction

Several reports have demonstrated that diabetic patients have an increased risk for bone fracture [1-6], and decreased bone mineral density (BMD) is known as a major determinant of fracture. The previous articles have shown osteopenia and osteoporosis in type 1 diabetes mellitus [7,8]. On the other hand, some studies reported lower BMD values in patients with type 2 diabetes mellitus [9-11], but the others showed similar [8,12,13] or higher [14-16] BMD values compared with healthy subjects.

Type 2 diabetes mellitus is strongly associated with obesity. Adipose tissues are considered to be endocrine tissues capable of secreting adipose-derived peptides known as adipocytokines. It has been reported that serum leptin concentrations are increased in obese subjects and correlate with the percentage of body fat [17]. To the contrary, plasma adiponectin concentrations are decreased under conditions of obesity, type 2 diabetes mellitus [18], and coronary artery disease [19]. Because body weight positively correlates with BMD, it is generally thought that obesity protects against osteoporosis [20-25]. The protective effect on BMD in obese subjects may be mediated through increased muscle mass, fat mass, hyperinsulinemia, and possibly higher leptin levels.

Some previous studies have shown that serum leptin level positively [26] or negatively [27-29] correlates with BMD, or does not correlate [30,31] after adjusting for body weight, body mass index (BMI), or body fat. Leptin seems to have at least 2 different effects on bone metabolism, an indirect inhibitory effect or a direct stimulatory effect on bone formation. Ducy et al [32] and Takeda et al [33] demonstrated that leptin inhibited bone formation through the hypothalamus via the sympathetic nervous system in leptin-deficient (ob/ob) and leptin receptor–deficient (db/db) mice. Steppan et al [34], to the contrary, reported that the stimulatory effect of leptin on osteoblastic activity could be direct in ob/ob mice. It was also reported that leptin and its receptor were expressed in normal human osteoblasts [35,36]. In addition, leptin was able to enhance osteoblast differentiation [37].

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Table 1
Clinical characteristics of study subjects

		Reference range
N (men/women)	40 (28/12)	
Age (y)	56.9 ± 14.9	
BMI (kg/m^2)	23.9 ± 3.8	18.5-25
Body fat (%)	23.5 ± 6.5	<30
Duration of diabetes (y)	14.3 ± 10.7	
HbA_{1c} (%)	8.9 ± 2.0	4.3-5.8
1,25-$(OH)_2D_3$ (pg/mL)	38.9 ± 9.5	20-60
Intact PTH (pg/mL)	35.1 ± 14.4	10-65
Leptin (ng/mL)	5.6 ± 3.3	Not determined
Adiponectin (μg/mL)	9.5 ± 7.1	3.8-18.9
Osteocalcin (ng/mL)	5.8 ± 1.7	2.5-13.0
Urinary NTX (nmol BCE/mmol creatinine)	36.8 ± 16.3	13.0-54.3

Data are expressed as mean ± SD. BCE indicates bone collagen equivalents.

So far there have been several reports concerning the association between adiponectin and BMD in human subjects. Lenchik et al [38] showed that serum adiponectin was inversely correlated with BMD value in 80 subjects containing 69 type 2 diabetic patients. Although subjects from other reports were perimenopausal healthy women [29] and nondiabetic female adolescents [30], there were no associations between adiponectin and BMD in either report. Therefore, relationships between adipocytokines and bone metabolism are still controversial.

In this study, we measured serum leptin and adiponectin concentrations, BMD values, and biochemical markers of bone turnover to investigate the possible role of adipocytokines on bone metabolism in patients with type 2 diabetes mellitus.

2. Materials and methods

2.1. Subjects

The study subjects were 40 Japanese patients with type 2 diabetes mellitus who consecutively visited our hospital. Subjects who were taking medicines such as corticosteroids, estrogens, bisphosphonates, calcium, vitamin D, vitamin K_2, ipriflavone, calcitonin, or selective estrogen receptor modulators were excluded beforehand, and those who had a previous history of bone fractures or renal dysfunction (serum creatinine >1.5 mg/dL) were excluded. This study was performed under a protocol for the use of human subjects in research approved by the ethics committee of Hiroshima University School of Medicine.

2.2. Biochemical measurements

Serum and urinary samples were taken early in the morning after an overnight fast and stored at −80°C before analysis. Serum 1,25-dihydroxyvitamin D_3 (1,25-$[OH]_2D_3$) was measured by radioimmunoassay (RIA; Immunodiagnostic Systems, Boldon, UK), intact parathyroid hormone (intact PTH) by immunoradiometric assay (IRMA; Nichols Institute Diagnostics, San Clemente, CA), leptin by RIA (Linco Research, St Charles, MO), and adiponectin by enzyme-linked immunosorbent assay (ELISA; Otsuka, Chiyoda, Tokyo, Japan). Serum osteocalcin as a marker of bone formation was measured by IRMA (Mitsubishi Kagaku Bio-clinical Laboratories, Chiyoda, Tokyo, Japan), and urinary N-terminal telopeptide of type I collagen (NTX) as a marker of bone resorption by ELISA (Mochida Pharmaceutical, Yotsuya, Tokyo, Japan). Glycosylated hemoglobin (HbA_{1c}) was measured by high-performance liquid chromatography (ARKRAY, Kyoto, Japan).

2.3. BMD measurements

Bone mineral density values were measured with dual-energy x-ray absorptiometry (DXA) by using the Hologic QDR-4500A instrument (Hologic, Waltham, MA) at the forearm (distal one third of radius), femoral neck, and lumbar spine (L2-L4). Total body fat (%) was also measured with the same instrument. BMD was expressed as a z score (SD from age- and sex-matched normal mean values of Japanese).

2.4. Statistical analysis

Data are expressed as mean ± SD. Statistical analyses were performed with StatView software (version 5.0, Abacus Concepts, Berkeley, CA). Multiple regression analyses were performed to evaluate (1) the relationship of BMD at each site (z score) with serum leptin or adiponectin, BMI, body fat, and HbA_{1c} as independent variables, and (2) the relationship of serum osteocalcin or urinary NTX with serum leptin or adiponectin, age, sex, BMI, body fat, and HbA_{1c} as independent variables. $P < .05$ was considered statistically significant.

3. Results

Clinical characteristics and BMD (z scores) at each site of the study subjects are shown in Table 1 and Table 2, respectively. There were 28 men and 12 women aged 18 to 84 years. The z score is the standard deviation from age- and sex-matched normal mean values. Serum levels of 1,25-$(OH)_2D_3$ and intact PTH were within reference range in all subjects. Eight (20%) subjects were treated by diet only, 18 (45%) with oral hypoglycemic agents, and 14 (35%) with insulin. One (2.5%) subject was treated with pioglitazone and 8 (20%) with statins. The z scores at the distal one third of the radius were negative, whereas those at the lumbar spine and femoral neck were positive.

Table 2
Bone mineral density (z score) of study subjects

Distal radius, 1/3 (right)	−0.24 (−0.65 to 0.17)
Distal radius, 1/3 (left)	−0.31 (−0.76 to 0.15)
Femoral neck (right)	0.46 (0.10 to 0.81)
Femoral neck (left)	0.52 (0.17 to 0.87)
Lumbar spine (L2-L4)	0.43 (0.16 to 0.71)

Data are expressed as mean (95% confidence interval).
The z score is the standard deviation from age- and sex-matched normal mean values.

Table 3
The relationship of BMD (z score) with leptin by multiple regression analyses

	β	SE	P
Distal radius, 1/3 (left)			
Not adjusted	2.205	0.822	.011
Adjusted for BMI	2.470	0.927	.011
Adjusted for body fat	1.711	1.376	.222
Adjusted for HbA_{1c}	2.154	0.828	.013
Adjusted for BMI and HbA_{1c}	2.351	0.951	.018
Adjusted for body fat and HbA_{1c}	1.567	1.392	.268
Femoral neck (left)			
Not adjusted	−0.340	0.691	.625
Adjusted for BMI	−0.822	0.763	.288
Adjusted for body fat	−0.180	1.159	.878
Adjusted for HbA_{1c}	−0.351	0.701	.619
Adjusted for BMI and HbA_{1c}	−0.912	0.783	.252
Adjusted for body fat and HbA_{1c}	−0.208	1.183	.861
Lumbar spine (L2-L4)			
Not adjusted	−0.330	0.546	.549
Adjusted for BMI	−0.886	0.584	.138
Adjusted for body fat	0.247	0.908	.787
Adjusted for HbA_{1c}	−0.273	0.541	.616
Adjusted for BMI and HbA_{1c}	−0.784	0.596	.197
Adjusted for body fat and HbA_{1c}	0.409	0.901	.653

β indicates population regression.

Relationships of z score with serum leptin and adiponectin level after adjusting for BMI or body fat and/or HbA_{1c} are shown by multiple regression analysis in Table 3 and Table 4, respectively. Only z scores of the left radius and femoral neck are used because the right-side results do not differ from their left-side counterparts. There was a significant positive correlation between serum leptin level and z score at the distal radius after adjusting for BMI and/or HbA_{1c}, but the significant relationship disappeared after adjusting for body fat. Correlations between serum leptin level and z score at the femoral neck or the lumbar spine were not significant. On the other hand, there was a significant positive correlation between serum adiponectin level and z score at the distal radius after adjusting for BMI or body fat and/or HbA_{1c}. Correlations between serum adiponectin level and z score at the femoral neck or the lumbar spine were not significant.

Table 4
The relationship of BMD (z score) with adiponectin by multiple regression analyses

	β	SE	P
Distal radius, 1/3 (left)			
Not adjusted	1.767	0.648	.010
Adjusted for BMI	2.284	0.682	.002
Adjusted for body fat	1.589	0.623	.015
Adjusted for HbA_{1c}	1.715	0.682	.016
Adjusted for BMI and HbA_{1c}	2.209	0.705	.003
Adjusted for body fat and HbA_{1c}	1.522	0.656	.026
Femoral neck (left)			
Not adjusted	−0.634	0.538	.246
Adjusted for BMI	−0.490	0.590	.412
Adjusted for body fat	−0.609	0.549	.274
Adjusted for HbA_{1c}	−0.715	0.565	.214
Adjusted for BMI and HbA_{1c}	−0.567	0.610	.358
Adjusted for body fat and HbA_{1c}	−0.689	0.577	.240
Lumbar spine (L2-L4)			
Not adjusted	−0.448	0.427	.301
Adjusted for BMI	−0.220	0.462	.637
Adjusted for body fat	−0.401	0.433	.360
Adjusted for HbA_{1c}	−0.304	0.442	.496
Adjusted for BMI and HbA_{1c}	−0.110	0.472	.817
Adjusted for body fat and HbA_{1c}	−0.250	0.447	.580

β indicates population regression.

Table 5
The relationship of biochemical markers of bone turnover with leptin by multiple regression analyses

	β	SE	P
Serum osteocalcin			
Not adjusted	−0.041	0.102	.693
Adjusted for age and sex	−0.137	0.123	.271
Adjusted for age, sex, and BMI	−0.075	0.149	.618
Adjusted for age, sex, and body fat	0.032	0.167	.850
Adjusted for age, sex, and HbA_{1c}	−0.140	0.123	.265
Adjusted for age, sex, BMI, and HbA_{1c}	−0.084	0.150	.582
Adjusted for age, sex, body fat, and HbA_{1c}	0.019	0.170	.911
Urinary NTX			
Not adjusted	−0.114	0.124	.363
Adjusted for age and sex	−0.392	0.131	.005
Adjusted for age, sex, and BMI	−0.320	0.158	.051
Adjusted for age, sex, and body fat	−0.589	0.177	.002
Adjusted for age, sex, and HbA_{1c}	−0.386	0.127	.004
Adjusted for age, sex, BMI, and HbA_{1c}	−0.296	0.153	.062
Adjusted for age, sex, body fat, and HbA_{1c}	−0.555	0.175	.003

β indicates population regression.

Relationships of biochemical markers of bone turnover with serum leptin and adiponectin after adjusting for age, sex, BMI, or body fat, and/or HbA_{1c} are shown by multiple regression analysis in Table 5 and Table 6, respectively. There was no correlation between serum leptin and osteocalcin levels. On the other hand, a significant negative correlation between serum leptin and urinary NTX after adjusting for age, sex, body fat, and/or HbA_{1c} was found. To

Table 6
The relationship of biochemical markers of bone turnover with adiponectin by multiple regression analyses

	β	SE	P
Serum osteocalcin			
Not adjusted	0.017	0.081	.834
Adjusted for age and sex	−0.041	0.099	.679
Adjusted for age, sex, and BMI	−0.084	0.102	.416
Adjusted for age, sex, and body fat	−0.068	0.096	.484
Adjusted for age, sex, and HbA_{1c}	−0.051	0.100	.615
Adjusted for age, sex, BMI, and HbA_{1c}	−0.092	0.103	.380
Adjusted for age, sex, body fat, and HbA_{1c}	−0.075	0.098	.446
Urinary NTX			
Not adjusted	0.106	0.098	.288
Adjusted for age and sex	0.047	0.116	.689
Adjusted for age, sex, and BMI	−0.027	0.115	.816
Adjusted for age, sex, and body fat	0.033	0.118	.780
Adjusted for age, sex, and HbA_{1c}	0.069	0.114	.545
Adjusted for age, sex, BMI, and HbA_{1c}	−0.006	0.112	.960
Adjusted for age, sex, body fat, and HbA_{1c}	0.055	0.115	.637

β indicates population regression.

the contrary, there were no correlations between serum adiponectin and serum osteocalcin or urinary NTX.

4. Discussion

Our study revealed that BMD at the distal radius, not at the femoral neck or the lumbar spine, was positively associated with leptin and adiponectin in patients with type 2 diabetes mellitus. These results suggest that leptin and adiponectin may have protective effects against bone loss at the distal radius in patients with type 2 diabetes mellitus.

Previous studies have shown lower [9-11], similar [8,12,13], or higher [14-16] BMD values in patients with type 2 diabetes mellitus compared with healthy subjects. Such controversial results among these studies could be attributable to the differences in the backgrounds of study subjects (age, sex, glycemic control, obese or nonobese, etc), sites, and differing methods for BMD measurements. We adopted a *z* score to express BMD because *z* score is a standard deviation calculated from age- and sex-matched normal mean values of Japanese. A recent study [39] of BMDs measured at the lumber spine, femoral neck, and distal radius by using DXA demonstrated that BMD at the distal radius was significantly lower in patients with type 2 diabetes mellitus than in control subjects, but not different at the femoral neck or the lumbar spine. Majima et al [39] also reported that the *z* score at the distal radius was the lowest among the 3 sites, as the cortical/cancellous bone ratio was different among the 3 sites and highest at the distal radius. Their results are compatible with our data, suggesting a loss of cortical bone rather than cancellous bone may occur in type 2 diabetes mellitus, and therefore the radius may be most susceptible to bone loss in type 2 diabetes mellitus.

There are still some controversies about the association of leptin with BMD [26-31]. Our study revealed that there was a significant positive association of leptin with BMD at the distal radius in patients with type 2 diabetes mellitus. This association remained significant after adjusting for BMI and/or HbA_{1c}, but disappeared after adjusting for body fat. These results indicate that the influence of leptin on BMD does not depend on glycemic control and BMI, but strongly depends on body fat, which reflects fat volume more directly.

Recently, several biochemical markers have been used in the evaluation of bone turnover [40,41], although there have been a few reports about the association between adipocytokines and biochemical markers of bone turnover [27,42,43]. Holloway et al [44] showed that leptin inhibited osteoclast generation and bone resorption in vitro. This report is consistent with our data demonstrating that urinary NTX inversely associated with serum leptin, which suggests that leptin may decrease bone resorption in patients with type 2 diabetes mellitus. On the other hand, we could not find a relationship between serum leptin and osteocalcin levels. A decrease in serum osteocalcin level among diabetic patients has been reported [45], and Okazaki et al [46] suggested that serum osteocalcin could be affected by hyperglycemia. It is possible that osteocalcin is largely affected by glycemic control rather than leptin.

There have been reports that statins have been demonstrated to have an impact on bone resorption [47,48]. Although 20% of the subjects were treated with statins in our study, NTX values of the patients treated with statins are not significantly different from those of the other patients without statins.

We demonstrated that there was a positive association of adiponectin with BMD at the distal radius in patients with type 2 diabetes mellitus. Berner et al [49] indicated that adiponectin and its receptors are expressed in vitro in human and murine osteoblasts. Oshima et al [50] showed that adiponectin could increase bone mass by suppressing osteoclastogenesis and bone-resorption activity of osteoclasts in vivo (in mice) and in vitro. Although no association was observed between adiponectin and biochemical markers of bone turnover, our results suggest that adiponectin could directly influence BMD independent of obesity and glycemic control and could be involved in other bone metabolic factors except bone turnover in type 2 diabetes mellitus.

In conclusion, our study revealed that BMD at the distal radius, not at the femoral neck or the lumbar spine, was positively associated with leptin and adiponectin in patients with type 2 diabetes mellitus. Furthermore, leptin concentrations were inversely associated with urinary NTX, a marker of bone resorption. These results indicate that leptin and adiponectin might interact protectively with BMD at the distal radius in patients with type 2 diabetes mellitus. However, the precise regulating effect of adipocytokines on bone metabolism is not largely understood yet. Further research is necessary to confirm these associations and to solve abnormalities of bone metabolism in patients with type 2 diabetes mellitus.

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