

Decreased Serum Insulin-like Growth Factor-I is a Risk Factor for Non-vertebral Fractures in Diabetic Postmenopausal Women

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Abstract

Objective Previous studies have shown that serum insulin-like growth factor-I (IGF-I) is involved in diabetes-related bone fragility. Although lower serum levels of IGF-I are reported to be associated with a higher risk of vertebral fractures in patients with type 2 diabetes, it is unknown whether or not the serum level of IGF-I is associated with the incidence of non-vertebral fractures.

Methods We investigated the relationships between the serum levels of IGF-I and the incidence of non-vertebral osteoporotic fractures in 188 men and 168 postmenopausal women with type 2 diabetes.

Results A multiple logistic regression analysis adjusted for age, duration of diabetes, observation period, body mass index, HbA1c, serum creatinine, and the bone mineral density at the lumbar spine showed that the serum IGF-I level was significantly and inversely associated with the incidence of non-vertebral osteoporotic fractures in postmenopausal women (odds ratio =0.48, 95% confidential interval [CI] 0.23-0.99 per SD increase; $p=0.047$), but not in men. Moreover, the inverse association between the serum IGF-I level and the incidence of non-vertebral fractures remained significant after additional adjustment for insulin use, and the serum calcium and phosphate levels (odds ratio =0.48, 95% CI 0.23-0.99 per SD increase; $p=0.046$).

Conclusion This is the first study to show that decreased serum IGF-I levels are associated with a higher risk of non-vertebral osteoporotic fractures in postmenopausal women with type 2 diabetes. Serum IGF-I could be a useful marker for assessing the incidence of osteoporotic fractures.

Key words: insulin-like growth factor-I, type 2 diabetes mellitus, fracture, non-vertebral fractures

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Introduction

Osteoporosis is a skeletal disorder that is characterized by compromised bone strength, which predisposes patients to an increased risk of fracture. Bone strength reflects the integration of two main features: bone mass and bone quality. Accumulating evidence shows that the risk of osteoporotic fractures is increased in patients with type 2 diabetes mellitus despite them having a normal or slightly elevated bone mineral density (BMD) (1, 2). These findings suggest that the risk of fracture is not related to BMD and that the measurement of BMD, which is a gold standard in the detection of primary osteoporosis, is not useful for screening patients

for diabetes-related bone fragility. It is therefore important to find other tools that are appropriate for assessing the risk of future osteoporotic fracture in patients with type 2 diabetes.

The insulin-like growth factor-I (IGF-I) in the circulation is mainly produced in the liver; its production is regulated by growth hormone and diet. It acts in an endocrine manner (3), activates bone remodeling and exerts anabolic effects on bone tissues (4, 5). A previous study showed that a marked reduction in bone volume, periosteal circumference, and medial lateral width developed in liver-specific IGF-I gene-null mice, which suggests that the serum IGF-I levels directly regulate bone growth and density (6). We previously reported that the serum IGF-I levels were inversely associ-

ated with the prevalence and severity of vertebral fractures, independent of BMD in postmenopausal women with type 2 diabetes (7, 8). Furthermore, Ardawi et al. reported that the serum IGF-I level is inversely associated with the presence of vertebral fractures in postmenopausal women with type 2 diabetes (9). Thus, it is suggested that serum IGF-I is involved in the etiology of diabetes-related bone fragility and that the serum level of IGF-I might be a clinically useful marker for assessing the future risk of fracture in patients with type 2 diabetes mellitus.

However, little is known about the association between the serum IGF-I level and non-vertebral fractures in patients with type 2 diabetes because, in previous studies, vertebral fractures were evaluated by X-ray examinations (7-9). Thus, in the present study, we examined whether the serum IGF-I level is associated with future non-vertebral fractures in men and postmenopausal women with type 2 diabetes.

Materials and Methods

Subjects

The patients who visited Shimane University hospital for education and treatment in relation to type 2 diabetes mellitus from 1997-2009 were screened. According to the records of our hospital, 453 men and 358 postmenopausal women with type 2 diabetes mellitus visited the hospital during the study period whose serum IGF-I and L-BMD levels were examined. We excluded 58 men and 18 postmenopausal women with hepatic dysfunction, pancreatic disease, hormonal therapy for breast cancer, primary hyperthyroidism, steroid therapy, and premenopausal women, because these conditions might influence bone metabolism and the serum IGF-I levels. We also excluded 207 men and 147 postmenopausal women who could not be followed up. Finally, 188 men and 168 postmenopausal women with type 2 diabetes mellitus were included in this analysis. The average observational period was 6.4 ± 0.7 years. The numbers of patients who had been taking insulin administration and oral hypoglycemic agents were 33 and 84 men as well as 51 and 61 women, respectively. Eleven, 10 and 4 women were taking active vitamin D, bisphosphonates, and selective estrogen receptor modulators, respectively. None of the male subjects had ever taken drugs for osteoporosis. In 2013, medical doctors reviewed the history of the subjects, with special attention paid to osteoporotic fractures. The incidence of all clinical non-vertebral fractures (other than traumatic fractures) was included in this analysis. The primary end-point of this study was to examine the association between the serum IGF-I level and the incidence of non-vertebral fractures in this population.

All of the subjects agreed to participate in this study and gave their informed consent. The present study was approved by the institutional review board of the Shimane University Faculty of Medicine.

Biochemical measurements

Blood samples were collected after overnight fasting. Biochemical markers were measured by the standard methods, as previously described (7, 8, 10). The serum level of IGF-I was measured by a radioimmunoassay with [¹²⁵I]-IGF-I as a competitive radioligand and a polyclonal anti-human antibody. The bound radioactivity was measured using a gamma counter and the concentrations were determined relative to a standard curve that was prepared with recombinant human IGF-I. The coefficients of variation (CV) of the IGF-I measurement was 2.28%.

Radiography

The BMD of the lumbar spine (L) was measured by dual-energy X-ray absorptiometry (QDR-4500; Hologic, Waltham, MA, USA). The CV of the measurements of the L-BMD by our method was 0.9%. The z-score indicated a deviation from the average BMD in normal age and sex matched subjects in the standardized normal distribution.

The ascertainment of non-vertebral fractures

On the basis of clinical interviews, non-vertebral fractures that were caused by low-trauma fractures (i.e., those occurring with falls from standing height or less) were taken into account. We included all of the fractures that occurred in the study subjects except for fractures of the hand, toes, metacarpals, face and skull, as well as pathological and post-procedural fractures (11, 12).

Statistical analysis

The data were expressed as the mean \pm SD. Before performing the statistical analysis, we checked that all of the variables were normally distributed by histogram and Shapiro-Wilk tests. The statistical significance of differences between two groups was determined using Student's *t*-test and the χ^2 test. A multiple logistic regression analysis was used to adjust for the confounding factors in the multivariate analysis. All of the analyses were performed using the Stat-View software program (Abacus Concepts, Berkeley, CA, USA). *p* values of <0.05 were considered to indicate statistical significance.

Results

The baseline characteristics of subjects and the comparison of various parameters between patients with and without osteoporotic fractures

Background characteristics such as the biochemical and demographic parameters as well as the BMD were collected when the serum IGF-I levels were measured. We then compared various parameters between the subjects with and without osteoporotic fractures (Table 1). In postmenopausal women, the serum creatinine levels were significantly higher in patients with fractures than in those without ($p=0.026$).

Table 1. Comparison of Background Data between Patients with and without the Incident of Osteoporotic Fractures.

Osteoporotic fractures	Men			Postmenopausal women		
	no	yes	p	no	yes	p
The number of subjects	181	7		144	24	
Age (years)	62.8 ± 9.6	63.9 ± 3.8	0.780	65.7 ± 9.0	69.3 ± 7.3	0.073
Duration of diabetes (years)	9.6 ± 9.2	16.9 ± 16.3	0.049	10.9 ± 9.3	13.1 ± 8.9	0.288
BMI (kg/m ²)	23.7 ± 4.2	22.1 ± 3.1	0.312	24.7 ± 4.5	25.1 ± 2.5	0.636
HbA1c (%)	8.7 ± 2.0	8.0 ± 2.2	0.363	8.6 ± 2.2	8.2 ± 2.2	0.403
Serum albumin (g/dL)	4.3 ± 0.4	4.1 ± 0.4	0.250	4.1 ± 0.5	4.2 ± 0.5	0.334
Serum calcium (mg/dL)	9.3 ± 0.4	9.0 ± 0.3	0.115	9.2 ± 0.3	9.2 ± 0.3	0.918
Serum phosphate (mg/dL)	3.3 ± 0.5	3.5 ± 0.7	0.531	3.7 ± 0.5	3.7 ± 0.5	0.904
Serum creatinine (mg/dL)	0.80 ± 0.21	0.83 ± 0.18	0.719	0.63 ± 0.25	0.76 ± 0.36	0.026
Serum IGF-I (ng/mL)	153 ± 51	128 ± 37	0.191	138 ± 52	125 ± 38	0.068
L-BMD (g/cm ²)	1.042 ± 0.176	1.032 ± 0.396	0.896	0.887 ± 0.187	0.874 ± 0.203	0.758
L-Z score	0.47 ± 1.06	0.30 ± 2.21	0.706	0.62 ± 1.23	0.75 ± 1.37	0.646
Insulin treatment	30	3	0.094	42	9	0.390
Oral hypoglycemic agents	81	3	0.911	54	7	0.439

BMI: body mass index, HbA1c: hemoglobin A1c, IGF-I: insulin-like growth factor-I, L: lumbar, BMD: bone mineral density

Table 2. Associations between the Incidence of Osteoporotic Fractures Versus Serum IGF-I, BMD, and HbA1c.

	Men		Postmenopausal women	
	OR (95% CI)	p	OR (95% CI)	p
Serum IGF-I	0.52 (0.19-1.40)	0.193	0.48 (0.23-0.99)	0.047
L-BMD	1.38 (0.60-3.18)	0.448	0.87 (0.45-1.66)	0.670
HbA1c	0.41 (0.12-1.40)	0.157	0.89 (0.50-1.59)	0.691

Multivariate logistic regression analysis was performed with the incidence of osteoporotic fractures as a dependent variable and serum IGF-I, L-BMD, HbA1c, age, duration of diabetes, observation period, BMI, serum albumin, and serum creatinine as independent variables.

OR: odds ratio, CI: confidential intervals

Unit of change; Standard deviation per increase.

The postmenopausal women with fractures were marginally older than those without ($p=0.073$), and the serum IGF-I levels were marginally lower in postmenopausal women with fractures than in those without ($p=0.068$). In men, the duration of diabetes was significantly longer in men with fractures than in those without ($p=0.049$), and the serum IGF-I levels tended to be lower in men with fractures than in those without ($p=0.191$).

The association between serum IGF-I levels and the incidence of osteoporotic fractures

Multiple logistic regression analyses adjusted for age, duration of diabetes, body mass index, HbA1c, serum albumin, serum creatinine, the observation period, and the L-BMD were performed to examine the association between serum IGF-I and the incidence of osteoporotic fractures (Table 2). In postmenopausal women, the serum IGF-I levels were significantly and inversely associated with the incidence of fracture ($p=0.047$). In addition, the association remained significant after additional adjustment for pioglitazone usage (odds ratio 0.48, 95% confidence interval [CI] 0.23-0.99, $p=0.046$). Moreover, the inverse association between the serum IGF-I level and the incidence of non-vertebral fractures remained significant even after additional adjustment for insu-

lin use, serum calcium and phosphate levels (odds ratio = 0.48, 95%CI 0.23-0.99 per SD increase, $p=0.046$). In contrast, there was not significant association between the serum IGF-I level and the incidence of fractures in men.

Discussion

We previously reported the results of two cross-sectional studies showing that low serum IGF-I levels were inversely associated with the presence of vertebral fractures, independent of the BMD in postmenopausal women with type 2 diabetes (7, 8). Moreover, in the present study, we showed, for the first time, that low serum IGF-I levels predict the incidence of osteoporotic non-vertebral fractures, even after adjustment for confounding factors including BMD. Previous studies showed the inverse association between the serum IGF-I level and the risk of vertebral fractures in type 2 diabetes; moreover, we firstly demonstrated the association between the serum IGF-I level and the incidence of non-vertebral fractures. Taken together, these findings indicate that low serum IGF-I levels may be involved in the etiology of the bone fragility that is observed in type 2 diabetes, and that the measurement of serum IGF-I, rather than the measurement of the BMD, may be clinically useful in assessing

the risk of osteoporotic fractures in patients with type 2 diabetes.

Interestingly, the association between serum IGF-I and the incidence of fractures in postmenopausal women with type 2 diabetes was independent of the BMD. Previous studies also showed a significant association between serum IGF-I and the prevalence of vertebral fractures after adjustment for the BMD (7-9). These findings indicate that serum IGF-I plays an important role for maintaining the bone quality in patients with type 2 diabetes. Furthermore, neither L-BMD nor HbA1c was associated with the incidence of osteoporotic fractures in men or postmenopausal women. Previous studies have shown that the risk of fractures is increased in patients with type 2 diabetes, regardless of their BMD and HbA1c levels (2, 3). The present findings were consistent with the findings of previous studies and suggest that the measurement of the BMD and the conditions of diabetic control are not good markers for assessing the risk of future osteoporotic fractures in patients with type 2 diabetes.

A decreased IGF-I function is thought to be linked to the pathogenesis of diabetic complications such as neuropathy, nephropathy and retinopathy (13). Moreover, the present findings suggest that the action of IGF-I is also important for bone strength in patients with type 2 diabetes. It is known that the serum level of IGF-I is decreased in patients with poorly controlled diabetes (9), and that the decreased serum levels of IGF-I improve after the achievement of glycemic control (14). Thus, further studies are necessary to examine whether or not glycemic control along with increased serum IGF-I decreases the risk of osteoporotic fractures in addition to improving the prognosis of patients with type 2 diabetes.

In the present study, there was no significant association between the serum IGF-I level and the incidence of osteoporotic fractures in men with type 2 diabetes. The conflict results between men and women might be caused by the limited number of male subjects with osteoporotic fractures (n=7). However, previous studies (including our own) showed that there was no association between the serum IGF-I level and the incidence of vertebral and non-vertebral fractures in men (8, 14-16). Thus, serum IGF-I may be less important as a risk factor for osteoporotic fractures in men than it is in women.

The present study is associated with several limitations. First, the sample size was not large enough to make definite conclusions due to the study design. Second, we only analyzed subjects who visited Shimane University Hospital, a tertiary center for the evaluation or treatment of diabetes mellitus and osteoporosis. Thus, the state of the disorders of the patients enrolled in this study might have been relatively severe. Third, we cannot exclude the possibility that the treatment of diabetes affected the serum IGF-I levels or the incidence of fractures. In addition, the study population included 18 men and 15 women who had taken pioglitazone. Previous studies have shown that thiazolidinediones increase the risk of osteoporotic fractures in postmenopausal women

with type 2 diabetes. Thus, we performed a further adjustment for treatment with pioglitazone and found the association between the serum IGF-I level and the incidence of osteoporotic fractures remained significant. However, we could not exclude the patients who were treated with pioglitazone due to the limited size of our study population and because the information about whether the patients continued pioglitazone treatment or whether the treatment was added was unavailable.

In conclusion, we found that the serum IGF-I level was inversely associated with the incidence of non-vertebral fractures, independently of the BMD and the HbA1c levels in postmenopausal women with type 2 diabetes. Thus, the serum IGF-I level may be a useful marker for assessing the risk of osteoporotic fractures. Thus, further large scale prospective studies will be necessary to confirm the present findings.

The authors state that they have no Conflict of Interest (COI).

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HM and IK conceived the study and participated in the design of the study and in the coordination and acquisition of data, performed the statistical analysis and wrote the manuscript. TS participated in the design of the study, interpreted the findings and revised the manuscript critically. All of the authors read and approved the final manuscript.

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