Osteoporos Int (2011) 22:1191–1198
DOI 10.1007/s00198-010-1310-6

ORIGINAL ARTICLE

Serum insulin-like growth factor-I is a marker for assessing the severity of vertebral fractures in postmenopausal women with type 2 diabetes mellitus

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Received: 18 February 2010 / Accepted: 3 May 2010 / Published online: 8 June 2010

Abstract
Summary Although previous studies indicated that serum insulin-like growth factor-I (IGF-I) was inversely associated with the presence of vertebral fractures (VFs), little is known whether serum IGF-I is associated with multiple VFs. We report that serum IGF-I could be clinically useful for assessing the severity of VFs in type 2 diabetic postmenopausal women.
Introduction The number of VFs is associated with the mobility and mortality of the elderly people. Although serum IGF-I is inversely associated with the presence of VFs, little is known about the relationship between serum IGF-I and multiple VFs.
Methods In this cross-sectional study, we recruited 479 men and 334 postmenopausal women with type 2 diabetes mellitus and measured serum IGF-I, bone mineral density, and bone turnover markers. Lateral X-ray films of the thoracic and lumbar spine were taken to diagnose the VF.
Results In postmenopausal women, serum IGF-I level was decreased when the number of VFs was increased [no VFs; 138±51 ng/ml (mean ± SD) vs. one VF; 119±42 (p=0.006), two VFs; 103±39 (p=0.002), and three and more VFs; 91±40 (p<0.001)]. Multiple logistic regression analysis adjusted for age, duration of diabetes, body mass index, serum creatinine, and HbA_{1c} showed that serum IGF-I level was inversely associated with the presence of one VF [odds ratio (OR)=0.67, p=0.029], two VFs (OR=0.40, p=0.017), as well as three and more VFs (OR=0.27, p=0.005). These associations were still significant after the additional adjustment for BMD at the lumbar spine. In contrast, no significant association of serum IGF-I level with VFs was found in men.
Conclusions Serum IGF-I level was inversely associated with the number of prevalent VFs in postmenopausal women with type 2 diabetes, suggesting that serum IGF-I could be clinically useful for assessing the severity of VFs in the population.

Keywords Insulin-like growth factor-I · Multiple vertebral fractures · Postmenopausal women · Type 2 diabetes mellitus · Vertebral fracture

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Introduction

Insulin-like growth factor-I (IGF-I) is known to have an anabolic effect in bone. Circulating IGF-I, mainly produced in the liver via regulation by growth hormone and diet, acts in an endocrine manner, which activates bone remodeling and exerts anabolic effects on bone tissues [1–3]. In osteoblast-specific knockout mice of IGF-I receptor, significant reduction in bone mass and deficient mineralization were observed [4]. Liver-specific IGF-I gene-null mice revealed a marked reduction in bone volume, periosteal circumference, and medial lateral width [5]. We have previously shown that serum IGF-I level was positively associated with bone mineral density (BMD) and inversely with the risk of vertebral fracture (VF) in postmenopausal women [6, 7]. Several studies reported that low circulating IGF-I was involved in male idiopathic osteoporosis through

decreased bone formation [8, 9]. These findings indicate that the circulating IGF-I has a pivotal role in bone metabolism.

Although a relationship between diabetes and osteoporotic fractures is recently becoming increasingly recognized [10], the etiology of diabetes-associated bone abnormality is still unclear. Patients with type 2 diabetes mellitus (T2DM) were reported to have higher BMD than that in non-diabetic controls, despite an increased risk of osteoporotic fractures [11, 12]. This finding suggests that BMD is not necessarily a good marker for the bone fragility in T2DM, and that BMD measurement, which has been considered as a golden standard for evaluating fracture risk in primary osteoporosis, seems to be less useful in patients with T2DM. It is therefore an urgent task to seek suitable surrogate markers for diabetes-related bone disease that supplement the insensitivity of BMD and assess fracture risk in T2DM.

IGFs are thought to be linked to the pathogenesis of diabetes-related complication [13]. An in vivo study has demonstrated that IGF-I levels in serum and cortical bone were significantly reduced in spontaneously diabetic Goto-Kakizaki rats, which displayed a significant decrease in BMD at long bone metaphyses and vertebrae [14]. Clinically, we have previously reported that serum IGF-I level was inversely associated with the presence of prevalent VFs independent of BMD in postmenopausal women with T2DM [15]. In contrast, we found no association between serum IGF-I and the presence of VFs in men with T2DM [16]. Thus, serum IGF-I level could be useful for assessing the risk of VFs in postmenopausal women with T2DM, but not in men, suggesting a gender difference in the effect of serum IGF-I on bone metabolism in T2DM.

VF is a serious problem because the occurrence of one incident VF frequently augments the risk of another one [17], resulting in the increased mobility and mortality of the elderly people [18, 19]. Moreover, it has been reported that patients' health-related quality of life was worse in osteoporotic women when the number of VFs increased [20], and that the mortality caused by cardiovascular disease was increased according to the number of VFs [21]. Therefore, it is important to assess the risk of multiple VFs and to evaluate the prognosis in patients with osteoporosis.

To our knowledge, however, there are no studies on the association of serum IGF-I with multiple VFs in patients with T2DM. In this report, we conducted a cross-sectional study to investigate the association between serum IGF-I and the number of prevalent VFs in men and in postmenopausal women with T2DM. In addition, we examined correlations of serum IGF-I with bone turnover markers and BMD in each gender.

Subjects and methods

Subjects

The subjects in this study were 479 male and 334 postmenopausal female patients of T2DM. We consecutively recruited subjects who visited Shimane University Hospital for treatments of diabetes. Subjects agreed to participate in this study and gave informed consent. This study was approved by the institutional review board of Shimane University Faculty of Medicine. Nobody had hepatic or renal dysfunction or nutritional derangements that might cause changes in bone metabolism and serum IGF-I concentration. We also excluded patients with primary hyperparathyroidism or with a history of falling or traffic accidents to eliminate the possibility of injury-associated fractures. The numbers of patients who had been taking insulin, sulfonylurea, metformin, and alpha-glucosidase inhibitors, respectively, were 89, 159, 59, and 56 men and 93, 103, 64, and 38 women. All subjects were free of drugs known to influence bone and calcium metabolism such as vitamin D, estrogen replacement, and bisphosphonate as well as thiazolidinedione.

Radiography

Lateral X-ray films of the thoracic and lumbar spine were taken in the same week of the serum and urine collection. The anterior, central, and posterior heights of each of the 13 vertebral bodies from Th4-L4 were measured. A patient was diagnosed as VF when at least one of the three height measurements of a vertebra decreased by >20% when compared to the height of the nearest uncompressed vertebral body [22].

BMD of the lumbar spine (L), femoral neck (FN), and one third of the radius (1/3R) were measured by the dual-energy X-ray absorptiometry (QDR-4500; Hologic, Waltham, MA, USA). The same operator tested all the subjects during the study to eliminate inter-observer error. The coefficients of variation (precision) of measurements of L-, FN-, and 1/3R-BMD by our methods were 0.9%, 1.7%, and 1.9%, respectively. Z-score indicates a deviation from the averaged BMD in normal age- and sex-matched subjects in the standardized normal distribution.

Biochemical measurements

After overnight fasting, serum and first void urine samples were collected. Biochemical markers were measured by standard methods as previously described [15, 16]. Serum osteocalcin was measured by radioimmunoassay (RIA) with the coefficient of variation (CV) of 5.48%. C-peptide and immunoreactive insulin (IRI) were measured by

enzyme immunoassay with CVs of 2.20% and 2.20%, respectively. Urinary N-terminal cross-linked telopeptide of type-I collagen (uNTX) were measured by enzyme-linked immunosorbent assay with CV of 5.66%.

Serum IGF-I was measured by RIA with [^{125}I]-IGF-I as a competitive radioligand and a polyclonal anti-human antibody. Bound radioactivity was measured using a gamma counter and concentrations were determined relative to a standard curve prepared with recombinant human IGF-I. The CV of IGF-I measurement was 2.28%.

Statistical analysis

Data were expressed as mean ± SD. Student's t test, χ^2 test and Pearson's correlation coefficient were used in univariate analyses. Statistical evaluations for differences among the groups were carried out using one-way analysis of variance followed by the Tukey-Kramer post-hoc test. Multiple logistic regression was used for multivariate analysis to adjust confounding factors. All analyses were performed using a statistical computer program StatView (Abacus Concepts, Berkeley, CA, USA). $P<0.05$ was considered to be significant.

Results

Baseline characteristics of subjects

Demographic and biochemical parameters as well as BMD were shown in Table 1, and these parameters were compared between the male and the female subjects. Age, duration of diabetes, osteocalcin, and Z-score at femoral neck and radius were significantly lower in men than those in postmenopausal women [$p<0.001$ except for duration of diabetes ($p<0.05$)]. In contrast, serum creatinine, IGF-I, and absolute BMD and T-score were significantly higher in men ($p<0.001$).

Association of serum IGF-I level with baseline characteristics, bone turnover markers, and BMD

Correlation of serum IGF-I with baseline characteristics was examined. Both in men and postmenopausal women, serum IGF-I level was significantly and negatively correlated with age (men; $r=-0.42$, $p<0.001$ and postmenopausal women; $r=-0.36$, $p<0.001$, respectively) and duration of diabetes (men; $r=-0.17$, $p<0.001$ and postmenopausal women; $r=-0.18$, $p=0.002$, respectively). Serum IGF-I level was

Table 1 Baseline characteristics of subjects

Number of subjects	Postmenopausal women 334	Men 479	p
Age (years)	67.6±9.4	60.3±12.8	<0.001
Duration of diabetes (years)	12.6±10.1	11.0±9.1	0.031
BMI (kg/m2)	24.2±4.4	23.8±4.4	0.279
FPG (mg/dL)	161±62	167±61	0.193
HbA_{1c} (%)	8.5±2.3	8.7±2.4	0.287
C-peptide (ng/mL)	1.7±0.8	1.8±1.2	0.136
IRI (μU/mL)	7.1±6.6	6.3±5.6	0.093
Creatinine (mg/dL)	0.66±0.25	0.81±0.23	<0.001
IGF-I (ng/mL)	129±50	148±54	<0.001
Osteocalcin (ng/mL)	7.2±3.4	5.0±2.4	<0.001
uNTX (nMBCE/mM-Cr)	51.9±31.6	33.6±17.7	0.707
L2-4 BMD (g/cm2)	0.857±0.181	1.038±0.187	<0.001
T-score	−1.39±1.62	−0.08±1.57	<0.001
Z-score	0.48±1.18	0.45±1.13	0.158
FN neck BMD (g/cm2)	0.629±0.127	0.770±0.126	<0.001
T-score	−1.46±1.16	−0.72±1.00	<0.001
Z-score	0.38±1.21	0.25±1.02	<0.001
1/3R BMD (g/cm2)	0.522±0.087	0.707±0.073	<0.001
T-score	−2.70±1.68	−1.44±1.49	<0.001
Z-score	0.51±1.47	−0.42±1.38	<0.001
Number of vertebral fracture			
0	223 (66.8%)	313 (65.3%)	0.730
1	72 (21.6%)	101 (21.1%)	0.941
2	20 (6.0%)	51 (10.6%)	0.029
3 and more	19 (5.7%)	14 (2.9%)	<0.001

BMI body mass index, *FPG* fasting plasma glucose, *HbA_{1c}* hemoglobin A_{1c}, *IRI* immunoreactive insulin, *IGF-I* insulin-like growth factor-I, *uNTX* urinary N-terminal cross-linked telopeptide of type-I collagen, *BMD* bone mineral density, *L* lumbar, *FN* femoral neck, *1/3R* one third of the radius

significantly and positively correlated with body mass index (BMI) in men (r=0.21, p<0.001), but not in postmenopausal women (r=0.10, p=0.068).

Serum IGF-I level was significantly and positively correlated with serum C-peptide (men; r=0.21, p<0.001 and postmenopausal women; r=0.18, p<0.001, respectively), while no significant correlation was found between serum IGF-I versus fasting plasma glucose, HbA_{1c}, or IRI in either sex (data not shown).

Correlations of serum IGF-I with bone turnover markers were shown in Fig. 1. Osteocalcin was significantly and positively correlated with serum IGF-I level in postmenopausal women (r=0.18, p=0.004), but not in men (r=0.07, p=0.192). No significant correlations were found between serum IGF-I and uNTX in postmenopausal women or men.

Serum IGF-I level was significantly and positively correlated with absolute BMD in postmenopausal women (L-BMD: r=0.17, p=0.002; F-BMD: r=0.15, p=0.012; and 1/3R-BMD: r=0.17, p=0.007, respectively) and in men (F-BMD: r=0.19, p<0.001; and 1/3R-BMD: r=0.24, p<0.001, respectively), while serum IGF-I showed no significant correlations with L-BMD in men or Z-score at any of the three sites in either sex (data not shown).

Multiple regression analyses were then performed on the association of serum IGF-I level with BMD as well as with bone turnover markers after being adjusted for age, duration of diabetes, BMI, serum creatinine, and HbA_{1c}. Although serum IGF-I level was not significantly associated with absolute BMD at any skeletal site in postmenopausal women and men (data not shown), serum IGF-I was significantly and positively correlated with serum osteocalcin in postmenopausal women (r=0.19, p=0.007).

Association between serum IGF-I level and the presence of vertebral fractures

We compared the parameters between the subjects with and without prevalent VFs (Tables 2 and 3). In either sex, Z-scores at each site were not different between patients with and without VFs except for that at the lumbar spine in men, although subjects with VFs were significantly older than those without VFs (p<0.01).

Serum IGF-I levels in postmenopausal women with one VF (119.4±42.1 ng/ml), two VFs (103.0±38.9 ng/ml), as well as three and more VFs (91.4±40.3 ng/ml) were significantly lower than in those without VFs (137.5±50.9 ng/ml; Fig. 2). In contrast, there were no significant differences in serum IGF-I levels between those with and without VFs in men.

Multiple logistic regression analyses were then performed to evaluate the associations of serum IGF-I level with the presence of prevalent VFs after the adjustment for age, duration of diabetes, BMI, serum creatinine, and HbA_{1c} (Table 4). Serum IGF-I level was significantly and inversely associated with the presence of one VF (p=0.029), two VFs (p=0.017), as well as three and more VFs (p=0.005) in postmenopausal women, while no significant

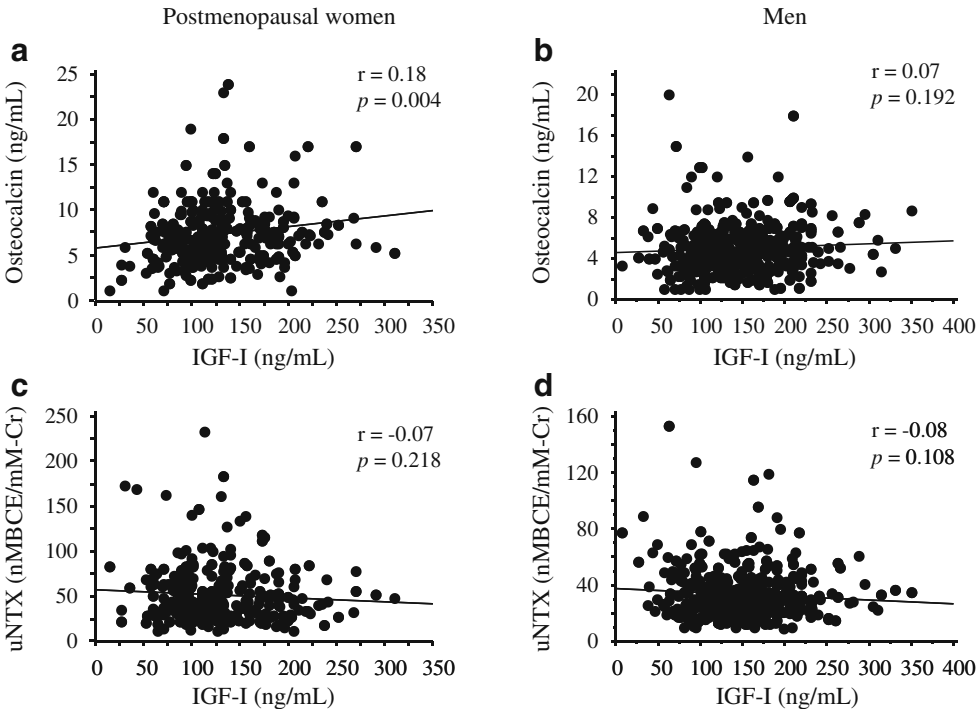

Fig. 1 Correlations of serum IGF-I level with serum osteocalcin and uNTX. Serum IGF-I level was significantly and positively correlated with serum osteocalcin in postmenopausal women (**a**), but not in men (**b**), while serum IGF-I level was not correlated with uNTX (**c** and **d**)

Table 2 Comparison of demographic and biochemical parameters between subjects with and without vertebral fractures in postmenopausal women with type 2 diabetes

Postmenopausal women				
Number of vertebral fracture	None	1	2	3 and more
Number of patients	223	72	20	19
Age	65.6±9.0	70.5±9.1***	70.8±8.9*	76.9±5.3***
Duration of diabetes	11.2±9.5	14.3±10.6*	19.0±11.2**	15.4±11.1
BMI	24.4±4.1	24.1±4.7	24.2±6.2	22.4±3.7
FPG	160±64	171±59	141±50	153±69
HbA_{1c}	8.6±2.3	8.7±2.5	7.7±2.0	8.3±2.7
C-peptide	1.7±0.8	1.7±0.8	1.7±1.0	1.4±1.0
IRI	6.8±6.5	6.8±5.1	10.0±10.1	8.8±7.6
Creatinine	0.63±0.22	0.73±0.35**	0.64±0.21	0.74±0.20
Osteocalcin	7.4±3.3	7.4±3.8	6.6±2.9	5.1±2.6*
uNTX	49.4±25.3	55.8±38.5	59.2±39.4	54.8±48.0
L2-4 BMD	0.885±0.169	0.810±0.169**	0.803±0.215	0.744±0.235**
Z-score	0.59±1.15	0.31±1.07	0.28±1.46	0.10±1.49
FN BMD	0.649±0.125	0.600±0.120**	0.603±0.120	0.548±0.138**
Z-score	0.46±1.19	0.24±1.17	0.29±1.19	0.10±1.63
1/3R BMD	0.535±0.087	0.496±0.089**	0.524±0.063	0.482±0.066*
Z-score	0.54±1.53	0.28±1.40	0.84±1.07	0.81±1.51

BMI body mass index, *FPG* fasting plasma glucose, *HbA_{1c}* hemoglobin A_{1c}, *IRI* immunoreactive insulin, *uNTX* urinary N-terminal cross-linked telopeptide of type-I collagen, *BMD* bone mineral density, *L* lumbar, *FN* femoral neck, *1/3R*, one third of the radius

*$p<0.05$, **$p<0.01$, ***$p<0.001$ vs. non-vertebral fracture

association was found between serum IGF-I and VFs in men. After the additional adjustment for L-BMD, these associations of IGF-I with the presence of VFs were still significant in postmenopausal women ($p=0.049$, $p=0.025$, and $p=0.005$, respectively). When FN-BMD or 1/3R-BMD was substituted for L-BMD, serum IGF-I level was significantly and inversely associated with the presence of three and more VFs [odds ratio (OR)=0.26, 95% confidential interval (CI) 0.09-0.79 per SD increase, $p=0.018$ and OR=0.30, 95%CI 0.10-0.93, p=0.038, respectively], but not significantly with the presence of one VF (FN-BMD; OR=0.77, 95%CI 0.52-1.12, $p=0.167$ and 1/3R-BMD; OR=0.73, 95%CI 0.48-1.11, $p=0.139$, respectively) or two VFs (FN-BMD; OR=0.52, 95%CI 0.24-1.13, p=0.099 and 1/3R-BMD; OR=0.54, 95%CI 0.24-1.21, $p=0.132$, respectively).

Table 3 Comparison of demographic and biochemical parameters between subjects with and without vertebral fractures in men with type 2 diabetes

Men				
Number of vertebral fracture	none	1	2	3 and more
Number of patients	313	101	51	14
Age	58.2±13.2	64.5±10.9***	61.9±14.1	66.5±8.3*
Duration of diabetes	10.3±9.0	12.4±9.4*	11.9±8.9	13.9±10.1
BMI	24.0±4.7	23.6±3.6	23.6±4.2	23.0±1.9
FPG	172±62	154±48*	161±58	171±111
HbA_{1c}	8.8±2.5	8.5±2.0	8.4±2.1	8.4±2.9
C-peptide	1.9±1.2	1.8±1.2	1.7±0.7	1.4±1.1
IRI	6.1±4.8	7.3±7.9	5.9±5.4	5.6±3.5
Creatinine	0.79±0.20	0.83±0.27	0.81±0.26	0.85±0.40
Osteocalcin	5.0±2.4	5.0±2.4	5.0±2.7	5.6±3.5
uNTX	33.4±23.5	36.1±19.8	33.6±15.7	41.3±27.1
L2-4 BMD	1.054±0.191	1.034±0.165	0.983±0.170*	0.919±0.248*
Z-score	0.52±1.17	0.47±0.97	0.18±1.05	−0.20±1.44*
FN BMD	0.783±0.131	0.749±0.108*	0.762±0.128	0.708±0.129*
Z-score	0.30±1.07	0.19±0.92	0.22±0.85	−0.08±1.22
1/3R BMD	0.715±0.071	0.690±0.073**	0.701±0.079	0.700±0.075
Z-score	−0.37±1.34	−0.46±1.38	−0.62±1.44	−0.35±1.99

BMI body mass index, *FPG* fasting plasma glucose, *HbA_{1c}* hemoglobin A_{1c}, *IRI* immunoreactive insulin, *uNTX* urinary N-terminal cross-linked telopeptide of type-I collagen, *BMD* bone mineral density, *L* lumbar, *FN* femoral neck, *1/3R* one third of the radius

*$p<0.05$, **$p<0.01$, ***$p<0.001$ vs. non-vertebral fracture

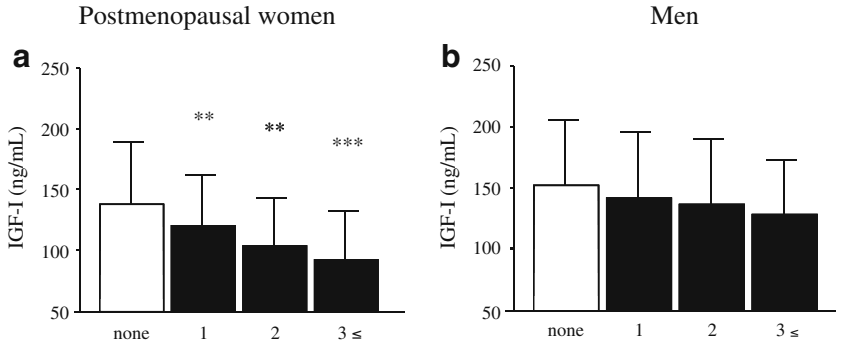

Fig. 2 Association of serum IGF-I level with the number of vertebral fractures. Serum IGF-I levels in postmenopausal women with one VF, two VFs, as well as three and more VFs were significantly lower than in those without VFs (**a**), while serum IGF-I levels were not significantly different between with and without VFs in men (**b**)

Discussion

We have previously shown that lower serum IGF-I level was associated with the presence of prevalent VFs in postmenopausal women with T2DM [15], but not in men [16]. In the present study, we examined larger number of subjects and found that serum IGF-I level was significantly and inversely associated with the number of prevalent VFs in postmenopausal women (Table 4). The present findings basically support our previous observations and suggest that serum IGF-I might be involved in the etiology of diabetes-related bone abnormality and could be clinically useful for assessing not only the presence of VFs but also their severity in postmenopausal women.

IGFs are known to be crucial in osteoblastogenesis [23, 24]. Numerous studies showed that IGF-I stimulated the proliferation, differentiation, and mineralization of osteoblastic cells [4, 25]. In this study, we found the significant association of serum IGF-I with osteocalcin, a bone formation marker, in postmenopausal women (see "Results" section), confirming that serum IGF-I links to osteoblastic function. As diabetic patients have bone fragility associated with low turnover of bone with osteoblastic dysfunction [26], the reduction of serum IGF-I might induce the diabetes-related bone fragility.

As a decline in serum IGF-I level occur with normal aging, it is thought that the hormonal level is associated with poor physical function or disability in elderly people. Cappola et al. reported that low serum IGF-I level was associated with decreased muscle strength and mobility in older women [27]. On the other hand, although the number of VFs is also associated with the mobility [20], it is poorly understood whether or not serum IGF-I level is associated with multiple VFs. In this study, we found that serum IGF-I was inversely associated with the number of VFs independent of age in postmenopausal women (Table 4 and Fig. 2). This finding suggests that low serum IGF-I level may be linked to the increased mobility not only through decreased muscle strength but also through increased VFs in postmenopausal women.

In this study, we found no association of serum IGF-I level with the presence of VFs in men (Table 4 and Fig. 2), suggesting that there is a sex-dependency in the effects of IGF-I on bone metabolism in diabetic patients. Other studies also indicated no association of serum IGF-I with VFs or non-VFs in male subjects [28–30]. The present data

Table 4 Associations between the presence of vertebral fractures and serum IGF-I

	Postmenopausal women		Postmenopausal women[a]		Men	
Number of vertebral fracture	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
1	0.67 (0.46–0.96)	0.029	0.69 (0.47–0.99)	0.049	0.93 (0.74–1.17)	0.534
2	0.40 (0.18–0.85)	0.017	0.42 (0.19–0.90)	0.025	0.84 (0.60–1.18)	0.315
3 and more	0.27 (0.11–0.67)	0.005	0.24 (0.09–0.65)	0.005	0.81 (0.40–1.63)	0.554

Multivariate logistic regression analysis was performed with the presence of vertebral fractures as a dependent variable and serum IGF-I adjusted for age, duration of diabetes, BMI, creatinine, and HbA1c as an independent variable.

OR odds ratio, *CI* confidential intervals, *unit of change* standard deviation per increase

[a] Additionally adjusted for L-BMD

is consistent with other studies and our previous observations [16], suggesting that serum IGF-I may be less important as a risk factor for VFs in men than in women.

Previous studies using genetic mutant mouse showed that IGF-I deficiency in the whole body or in the liver induced the reduction of cortical bone, while trabecular bone was not changed or increased [5, 31, 32]. These studies indicated that IGF-I is more important in cortical bone than in trabecular bone. Although a few studies reported no significant association of serum IGF-I and non-vertebral fractures in non-diabetic subjects [29, 30], there are no studies investigating these associations in diabetic patients. In this study, we examined only vertebrae, which contain a relatively higher proportion of trabecular bone, but not other bones such as hip and forearm. Previous studies demonstrated that IGF-I might have a crucial role especially in cortical bone of diabetic animals [14]. Further studies are thus needed to investigate the association of IGF-I with other osteoporotic fractures mainly involving cortical bone in T2DM.

To clarify which factor affects serum IGF-I level in T2DM, we examined the correlation of baseline parameters with serum IGF-I level (see "Results" section). It is of interest that serum IGF-I was positively associated with C-peptide, which is a surrogate marker of residual insulin secretion from pancreatic β cells, while the hormonal level was not associated with IRI, which indicates the peripheral insulin concentration. This association suggests that endogenous insulin secreted from pancreatic β cells is important to promote serum IGF-I secretion. Since residual insulin secretion is known to be needed for hepatic expression and generation of IGF-I [33, 34], it may be more important for the prevention of diabetes-related bone fragility to maintain the capacity of endogenous insulin secretion rather than circulating insulin level.

This study has some limitations. First, we analyzed only subjects who visited Shimane University Hospital, a tertiary center, for treatment of diabetes mellitus. Therefore, the participants enrolled in this study might have relatively severe states of the disorder and might not be representative of Japanese patients with the disorder. Second, more than 50% of subjects were treated. Therefore, we cannot exclude the possibility that the treatment of diabetes affected serum IGF-I level and the occurrence of VF. Third, the subjects in this study were only Japanese. Capacity of insulin secretion and degree of obesity in Asian are known to be different from Western people [35]. Therefore, it needs to be clarified whether or not our findings are universal. Finally, the conclusions of this study are weakened by its cross-sectional design. It is necessary to pay attention to that, in a cross-sectional study, causal relationships cannot generally be referred. Since it is reported that estrogen and corticosteroid interact growth hormone/IGF-I axis [36, 37], serum IGF-I level might be just an intermediary and not the cause of the fractures.

In conclusion, we found that serum IGF-I level was inversely associated with the number of VFs independent of age, duration of diabetes, BMI, serum creatinine, and HbA_{1c} as well as BMD in postmenopausal women with T2DM. Thus, serum IGF-I may compensate for the ineffectiveness of BMD and may be useful for evaluating the risk and severity of VFs in postmenopausal women with T2DM.

Conflicts of interest None.

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