Journal of Bone and Mineral Metabolism (2019) 37:703–710
https://doi.org/10.1007/s00774-018-0960-x

ORIGINAL ARTICLE

Overweight and underweight are risk factors for vertebral fractures in patients with type 2 diabetes mellitus

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Received: 22 May 2018 / Accepted: 9 September 2018 / Published online: 20 September 2018

Abstract

The aim of this cross-sectional study was to examine the association between body mass index (BMI) and the prevalence of vertebral fracture (VF) in Japanese patients with type 2 diabetes (T2DM). A total of 798 patients with T2DM were enrolled. VF was determined semi-quantitatively using lateral X-ray films. The association between BMI quartiles (Q1: ≤ 21.2 kg/m^2, Q2: 21.3–23.4 kg/m^2, Q3: 23.5–25.8 kg/m^2, Q4: 25.9≤ kg/m^2) and the presence of VF was examined. Multiple logistic regression analyses adjusted for age, sex, diabetes duration, hemoglobin A1c (HbA1c), estimated glomerular filtration rate, and albumin showed that Q1, Q3, and Q4 were significantly associated with an increased VF risk compared to Q2, which served as a reference [Q1; odds ratio (OR) = 1.91, 95% confidence interval (CI) 1.24–2.95, $p = 0.004$, Q3; OR = 1.65, 95% CI 1.07–2.55, $p = 0.023$, and Q4; OR = 2.18, 95% CI 1.39–3.41, $p < 0.001$]. Moreover, these associations remained significant after additional adjustment for femoral neck T-score, a bone resorption marker, urinary N-terminal cross-linked telopeptide of type-I collagen, and use of insulin and thiazolidinedione. Our study shows for the first time that both overweight and underweight were associated with the bone mineral density (BMD)-independent risk of VF in patients with T2DM. Therefore, body weight control should be considered as a protective measure against diabetes-related bone fragility.

Keywords Body mass index · Bone mineral density · Vertebral fracture · Type 2 diabetes mellitus

Introduction

In the general population, hip and vertebral fractures are the most important osteoporotic fractures, because they frequently occur in and enhance mortality of elderly people six- to ninefold [1, 2]. Because hip fracture usually causes loss of function, many patients with hip fracture require long-term rehabilitation and institutionalization at a nursing home. Furthermore, vertebral fracture (VF) causes chronic back pain, loss of function, and multiple-organ dysfunction, including chronic obstructive pulmonary disease, myocardial infarction, congestive heart failure, and gastroesophageal reflux disease [3–5]. Moreover, accumulating evidence has shown that patients with diabetes mellitus have an increased risk of osteoporotic fractures [6–9]. A recent meta-analysis showed that VF risk is increased up to twofold in patients with diabetes compared to those without diabetes [9]. We also previously reported that patients with type 2 diabetes mellitus (T2DM) had an increased risk of VF independent of bone mineral density (BMD), although patients had higher BMD than controls [7]. Moreover, we recently reported a cohort study showing that the presence of severe VF increased all-cause mortality up to three- to eightfold in patients with T2DM [10]. Furthermore, we conducted a survey using activities of daily living (ADL) and quality of life (QOL) questionnaires in patients with T2DM and found that osteoporosis and severe VF were significantly associated with decreased ADL and QOL, even after adjusting for patients' background and other diabetic complications [11].

A low body mass index (BMI) is well known to be a significant risk factor for BMD reduction and osteoporotic fracture [12, 13]; thus, obesity is traditionally believed to be a protective factor against fracture. However, recent evidence suggests that obesity may be a risk factor for site-specific fragility fracture [14–17]. Despite this evidence, there are still conflicting views on the association between BMI and fracture. Numerous studies have shown that obesity is associated with decreased risk of hip fracture [14, 15]. However,

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a few studies have examined the association between BMI and VF risk. Pirro et al. showed that BMI was positively correlated with BMD at the lumbar spine and the presence of VF in postmenopausal women [16]. In addition, Laslett et al. demonstrated that body weight, BMI, and fat mass were associated with an increased number of VFs in an elderly adult cohort study [18]. However, several studies reported no association between BMI and VF incidence [13, 19, 20]. In contrast, T2DM is caused by obesity-induced insulin resistance and is therefore strongly associated with obesity. Thus, the contribution of obesity to fracture risk may be different between individuals with or without diabetes. However, no studies, so far, have focused on the association between BMI and fracture risk in patients with T2DM.

Based on our previous studies [21, 22], BMI was not linearly associated with fracture risk in patients with T2DM. Therefore, we hypothesized that both obesity and leanness were associated with fracture risk. In this study, we thus investigated the association of quartiles according to BMI with the prevalence of VF in patients with T2DM.

Materials and methods

Participants

In this cross-sectional study, we consecutively enrolled 798 Japanese patients with T2DM (500 men over 50 years old and 298 postmenopausal women) who visited the Shimane University hospital for T2DM-related education and treatment. No patients had renal dysfunction [estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2] or nutritional derangements that might have caused changes in bone metabolism and fracture-risk. We excluded patients with diseases including malignant disorders, hyperthyroidism, hyperparathyroidism, hepatic dysfunction, growth hormone deficiency, and acromegaly as well as patients treated with glucocorticoids, hormonal therapy, and anti-osteoporosis drugs, such as bisphosphonates, denosumab, and selective estrogen receptor modulators, because these diseases and medications influence bone metabolism. We also excluded patients with a history of falling or traffic accidents to eliminate the possibility of injury-associated fractures.

Demographic and biochemical parameters and BMD are shown in Table 1. The number of patients who had been administered insulin, sulfonylurea, metformin, thiazolidinedione, alpha-glucosidase inhibitor, dipeptidyl peptidase-4 inhibitor, and glucagon-like peptide-1 receptor agonist was 206, 297, 160, 63, 107, 42, and 1, respectively.

Biochemical measurements

After overnight fasting, serum and first-void urine samples were collected. Biochemical markers were measured with standard methods as previously described [21, 22]. Hemoglobin A1c (HbA1c) was determined with high-performance liquid chromatography. HbA1c values were estimated as National Glycohemoglobin Standardization Program (NGSP)-equivalent values. Serum total osteocalcin and urinary N-terminal cross-linked telopeptide of type-I collagen (uNTX) were measured with radioimmunoassay and enzyme-linked immunosorbent assay with the coefficients of variation (CV) of 5.5% and 5.7%, respectively.

Radiography

Lateral X-ray films of the thoracic and lumbar spine were taken in the same week of serum and urine collection. The anterior, central, and posterior heights of each of the 13 vertebral bodies from Th4 to L4 were measured. A patient was diagnosed with VF when at least one of the three vertebral height measurements was decreased by > 20% compared to the height of the nearest uncompressed vertebral body [23].

BMD of the lumbar spine (LS) and the femoral neck (FN) was measured with dual-energy X-ray absorptiometry (QDR-4500; Hologic, Waltham, MA). The CV of measurements of LS- and FN-BMD according to our methods were 0.9 and 1.7%, respectively. *T*-Scores indicate a deviation from the average BMD in sex-matched young Japanese normal reference's mean, and *Z*-scores indicate a deviation from the average BMD in normal age- and sex-matched Japanese individuals in the standardized normal distribution.

Statistical analysis

Data were expressed as mean ± standard deviation (SD). The Jonckheere–Terpstra test was performed to investigate whether there were linear trends in various parameters according to the quartiles of BMI. Multiple logistic regression analyses were used for multivariate analysis to adjust for confounding factors. Statistical analyses were performed using a statistical computer program StatView (Abacus Concepts, Berkeley, CA) and IBM SPSS version 19 (SPSS Japan Inc., Tokyo, Japan). A $p < 0.05$ was considered to be significant.

Table 1 Baseline characteristics of subjects

	Total	Men	Women
Number of subjects	798	500	298
Age (years)	66.7 ± 9.1	66.0 ± 8.7	68.0 ± 9.6
Duration of diabetes (years)	12.4 ± 9.7	12.3 ± 9.6	12.5 ± 10.0
BMI (kg/m^2)	23.8 ± 4.1	23.4 ± 3.3	24.6 ± 5.1
HbAlc (%)	8.9 ± 2.1	8.8 ± 2.1	9.0 ± 2.2
eGFR (mL/min/1.73 m^2)	77.1 ± 21.1	77.8 ± 21.1	76.0 ± 21.1
Albumin (g/dL)	4.1 ± 0.5	4.1 ± 0.5	4.0 ± 0.5
Osteocalcin (ng/mL)	5.7 ± 2.8	5.2 ± 2.7	6.5 ± 2.8
Urinary NTX (nMBCE/mM-Cr)	41.6 ± 30.0	35.6 ± 26.7	51.8 ± 32.4
LS-BMD (g/cm^2)	0.978 ± 0.221	1.041 ± 0.216	0.873 ± 0.185
T-score	− 0.48 ± 1.83	− 0.02 ± 1.76	− 1.27 ± 1.67
Z-score	0.60 ± 1.26	0.56 ± 1.21	0.66 ± 1.32
FN-BMD (g/cm^2)	0.700 ± 0.139	0.745 ± 0.127	0.624 ± 0.125
T-score	− 1.14 ± 1.09	− 0.93 ± 0.99	− 1.50 ± 1.14
Z-score	0.26 ± 1.12	0.20 ± 1.07	0.36 ± 1.18
Insulin *n* (%)	206 (25.8%)	114 (22.8%)	92 (30.9%)
Sulfonylurea *n* (%)	297 (37.2%)	191 (38.2%)	106 (35.6%)
Metformin *n* (%)	160 (20.1%)	88 (17.6%)	72 (24.2%)
Thiazolidinedione *n* (%)	63 (7.9%)	42 (8.4%)	21 (7.0%)
Alpha-glucosidase inhibitor *n* (%)	107 (13.4%)	63 (12.6%)	44 (14.8%)
DPP-4 inhibitor *n* (%)	42 (5.3%)	31 (6.2%)	11(3.7%)
GLP-1 receptor agonist *n* (%)	1 (0.1%)	1 (0.2%)	0 (0.0%)
Vertebral fracture n (%)	304 (38.1%)	203 (40.6%)	101 (33.9%)
Grade 1	145 (18.2%)	98 (19.6%)	47 (15.8%)
Grade 2	120 (15.0%)	80 (16.0%)	40 (13.4%)
Grade 3	39 (4.9%)	25 (5.0%)	14 (4.7%)

BMI body mass index, *HbA$_{1c}$* hemoglobin A$_{1c}$, *eGFR* estimated glomerular filtration rate, *NTX* N-terminal cross-linked telopeptide of type-I collagen, *LS* lumbar spine, *FN* femoral neck, *BMD* bone mineral density, *DPP-4* dipeptidyl peptidase-4, *GLP-1* glucagon-like peptide-1

Results

Association of BMI quartiles with various parameters including the presence of VF

First, we examined the association between BMI and various background parameters including the presence of VF. Participants were divided into four groups according to BMI (Q1: ≤ 21.2 kg/m^2, Q2: 21.3–23.4 kg/m^2, Q3: 23.5–25.8 kg/m^2, Q4: 25.9≤ kg/m^2), and linear trends in various background parameters were examined (Table 2). According to BMI increase, the ratio of male participants, eGFR, and uNTX showed significant trends to be decreasing (p trend = 0.001, < 0.001, and 0.001, respectively), whereas serum albumin, LS-BMD, FN-BMD, FN-T score, and FN-Z score showed significant trends to be increasing (p trend = 0.013, 0.047, < 0.001, < 0.001 and < 0.001, respectively). There was no significant trend for VF. However, the Q2 group showed lower VF prevalence (29.4%) compared to Q1 (43.1%), Q3 (28.6%), and Q4 (41.5%) groups.

Association of BMI quartiles with the presence of VF

Multiple logistic regression analyses were then performed to evaluate the association of BMI with the presence of VF (Table 3). In the unadjusted model, Q1 and Q4 were significantly associated with increased risk of VF compared to Q2 for all participants [Q1; odds ratio (OR) = 1.82, 95% confidence interval (CI) 1.21–2.75, p = 0.004 and Q4; OR = 1.71, 95% CI 1.13–2.58, p = 0.012]. After adjustment for age, sex, duration of diabetes, HbA1c, eGFR, and albumin (Model 1), Q1, Q3, and Q4 were significantly associated with increased risk of VF compared to Q2 (Q1; OR = 1.91, 95% CI 1.24–2.95, p = 0.004, Q3; OR = 1.65, 95% CI 1.07–2.55, p = 0.023, and Q4; OR = 2.18, 95% CI 1.39–3.41, p < 0.001). These associations were still significant even after adjustment for FN-T score (Model 2), FN-T score and uNTX (Model 3) and FN-T score, uNTX, and use of insulin and thiazolidinedione (Model 4 and Fig. 1). When FN-T score was replaced with LS-BMD, the association was still significant for all models; model 2 (Q1; OR = 1.76, 95% CI 1.13–2.75,

Table 2 Comparison of background characteristics among subjects stratified by BMI

BMI category	Q1 ≤ 21.2 kg/m^2	Q2 21.3–23.4 kg/m^2	Q3 23.5–25.8 kg/m^2	Q4 25.9< kg/m^2	*p* trend
Number of subjects	197	204	202	195	
Age (years)	66.9 ± 9.0	67.0 ± 8.9	67.2 ± 9.5	65.8 ± 9.0	0.339
Male [*n* (%)]	126 (64.0%)	147 (72.1%)	130 (64.4%)	97 (49.7%)	0.001
Duration of diabetes (years)	12.0 ± 9.5	14.4 ± 10.5	12.8 ± 10.1	10.3 ± 8.1	0.054
BMI (kg/m^2)	19.2 ± 1.7	22.4 ± 0.6	24.6 ± 0.7	29.2 ± 3.4	< 0.001
HbAlc (%)	9.1 ±2.5	8.7 ±2.1	8.9 ± 2.0	8.7 ± 1.9	0.645
eGFR(mL/min/1.73 m^2)	82.6 ± 22.1	77.3 ± 20.5	75.7 ±21.2	73.0 ± 19.7	< 0.001
Albumin (g/dL)	4.0 ± 0.6	4.1 ±0.6	4.1 ± 0.5	4.1 ± 0.5	0.013
Osteocalcin (ng/mL)	5.6 ± 2.7	5.8 ±2.6	5.8 ±3.1	5.6 ±2.8	0.907
Urinary NTX (nMBCE/mM-Cr)	49.6 ± 43.1	41.5 ±24.3	36.0 ± 20.5	40.0 ± 25.5	0.001
LS-BMD (g/cm^2)	0.909 ± 0.204	1.000 ±0.235	0.984 ±0.215	1.020 ± 0.213	0.047
T-score	− 1.11 ± 1.74	− 0.30 ± 1.90	− 0.41 ± 1.74	− 0.12 ± 1.79	0.040
Z-score	0.17 ± 1.18	0.61 ± 1.20	0.63 ± 1.12	1.00 ± 1.38	< 0.001
FN-BMD (g/cm^2)	0.647 ±0.134	0.706 ±0.131	0.723 ±0.132	0.724 ± 0.145	< 0.001
T-score	− 1.58 ± 1.08	− 1.15 ±1.02	− 0.95 ± 1.02	− 0.89 ± 1.10	< 0.001
Z-score	− 0.25 ± 1.08	0.22 ± 1.07	0.49 ± 1.02	0.59 ± 1.12	< 0.001
Vertebral fracture [*n* (%)]	85 (43.1%)	60 (29.4%)	78 (38.6%)	81 (41.5%)	0.766
Grade 1	39 (19.8%)	28 (13.7%)	37(18.3%)	41 (21.0%)	0.497
Grade 2	35 (17.8%)	21 (10.3%)	32(15.8%)	32 (16.4%)	0.885
Grade 3	11(5.6%)	11(5.4%)	9 (4.5%)	8(4.1%)	0.433

BMI body mass index, *HbA$_{1c}$* hemoglobin A$_{1c}$, *eGFR* estimated glomerular filtration rate, *uNTX* urinary N-terminal cross-linked telopeptide of type-I collagen, *LS* lumbar spine, *FN* femoral neck, *BMD* bone mineral density

$p = 0.013$, Q3; OR = 1.74, 95% CI 1.12–2.69, $p = 0.012$, and Q4; OR = 2.49, 95% CI 1.58–3.94, $p < 0.001$), model 3 (Q1; OR = 1.74, 95% CI 1.10–2.74, $p = 0.018$, Q3; OR = 1.69, 95% CI 1.08–2.65, $p = 0.023$, and Q4; OR = 2.37, 95% CI 1.48–3.79, $p < 0.001$), and model 4 (Q1; OR = 1.72, 95% CI 1.09–2.72, $p = 0.019$, Q3; OR = 1.68, 95% CI 1.07–2.64, $p = 0.024$, and Q4; OR = 2.35, 95% CI 1.46–3.77, $p < 0.001$).

Subsequently, associations were examined separately for men and women. In the unadjusted model, Q1 and Q4 were significantly associated with increased risk of VF compared to Q2 in male individuals (Q1; OR = 1.81, 95% CI 1.10–2.98, $p = 0.019$ and Q4; OR = 1.73, 95% CI 1.02–2.95, $p = 0.044$). In the adjusted model 1, Q1 and Q4 were still significantly associated with increased risk of VF compared to Q2 (Q1; OR = 1.86, 95% CI 1.10–3.12, $p = 0.020$ and Q4; OR = 1.89, 95% CI 1.08–3.31, $p = 0.026$). In the adjusted models 2, 3, and 4, the association of Q4 with VF risk remained significant ($p = 0.007$, 0.034, and 0.037, respectively), whereas that of Q1 with VF risk became marginal ($p = 0.056$, 0.078, and 0.082, respectively). In women, in the unadjusted model, Q1 and Q4 were marginally, but not significantly, associated with increased risk of VF compared to Q2 ($p = 0.087$ and $p = 0.092$, respectively). In the adjusted models 1, 2, 3, and 4, Q4 was significantly associated with increased risk of VF compared to Q2 ($p = 0.023$, 0.012, 0.007, and 0.009, respectively). In these separate analyses for men and women, although some associations became insignificant because the number of the participants was reduced, similar tendencies to the results for all participants were observed. These findings suggest that there is probably no sex-specific difference in the association between BMI and VF risk in patients with T2DM.

Discussion

This is the first study to show that not only underweight, but also overweight was a risk factor for VF in patients with T2DM. Previous meta-analyses showed that the association between BMI and fracture risk may be mediated through BMD [14, 15]. Johansson et al. showed that individuals with obesity showed a decreased risk of osteoporotic fractures compared to individuals with normal weight; however, adjustment for BMD demonstrated that individuals with obesity showed an increased risk of fracture [15]. Chan et al. also reported that BMI was inversely associated with risk of fracture in an unadjusted model, although BMI was positively associated with the fracture risk in a BMD-adjusted model [14]. Furthermore, Kaze et al. recently showed that there was no association between BMI and VF risk in

Table 3 Association between BMI category and the risk of vertebral fracture

BMI category	Crude		Model 1		Model 2		Model 3		Model 4	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	v	OR (95% CI)	*p*	OR (95% CI)	*p*
Total subjects ($n = 798$)										
Ql (≤ 21.2 kg/m^2)	1.82 (1.21–2.75)	0.004	1.91 (1.24–2.95)	0.004	1.68 (1.08–2.62)	0.022	1.65 (1.05–2.60)	0.030	1.63 (1.03–2.56)	0.036
Q2 (21.3–23.4 kg/m^2)	Reference		Reference		Reference		Reference		Reference	
Q3 (23.5–25.8 kg/m^2)	1.51 (0.99–2.28)	0.051	1.65 (1.07–2.55)	0.023	1.81 (1.17–2.81)	0.008	1.75 (1.12–2.75)	0.015	1.74 (1.11–2.74)	0.016
Q4 (25.9≤kg/m^2)	1.71 (1.13–2.58)	0.012	2.18 (1.39–3.41)	< 0.001	2.48 (1.57–3.92)	< 0.001	2.35 (1.47–3.75)	< 0.001	2.31 (1.44–3.71)	< 0.001
Men ($n = 500$)										
Ql (≤ 21.2 kg/m^2)	1.81 (1.10–2.98)	0.019	1.86 (1.10–3.12)	0.020	1.68 (0.99–2.84)	0.056	1.63 (0.95–2.79)	0.078	1.62 (0.94–2.78)	0.082
Q2 (21.3–23.4 kg/m^2)	Reference		Reference		Reference		Reference		Reference	
Q3 (23.5–25.8 kg/m^2)	1.46 (0.89–2.41)	0.133	1.55 (0.93–2.59)	0.096	1.68 (1.00–2.84)	0.051	1.54 (0.90–2.63)	0.115	1.54 (0.90–2.63)	0.116
Q4 (25.9≤ kg/m^2)	1.73 (1.02–2.95)	0.044	1.89 (1.08–3.31)	0.026	2.20 (1.24–3.90)	0.007	1.89 (1.05–3.41)	0.034	1.88 (1.04–3.40)	0.037
Women ($n = 298$)										
Ql (≤ 21.2 kg/m^2)	1.93 (0.91–4.12)	0.087	1.92 (0.84–4.42)	0.124	1.68 (0.72–3.91)	0.230	1.87 (0.78–4.52)	0.163	1.76 (0.72–4.28)	0.215
Q2 (21.3–23.4 kg/m^2)	Reference		Reference		Reference		Reference		Reference	
Q3 (23.5–25.8 kg/m^2)	1.68 (0.79–3.59)	0.180	1.69 (0.73–3.90)	0.218	1.90 (0.82–4.43)	0.135	2.19 (0.90–5.31)	0.084	2.08 (0.85–5.06)	0.108
Q4 (25.9≤ kg/m^2)	1.85 (0.91–3.78)	0.092	2.57 (1.14–5.79)	0.023	2.87 (1.26–6.55)	0.012	3.28 (1.38–7.77)	0.007	3.20(1.34–7.66)	0.009

Model 1: adjusted for age, gender, duration of diabetes, HbA1c, eGFR, and albumin

Model 2: model 1 plus FN-T score

Model 3: model 2 plus urinary NTX

Model 4: model 3 plus insulin and thiazolidinedione use

OR odds ratio, *CI* confidence interval

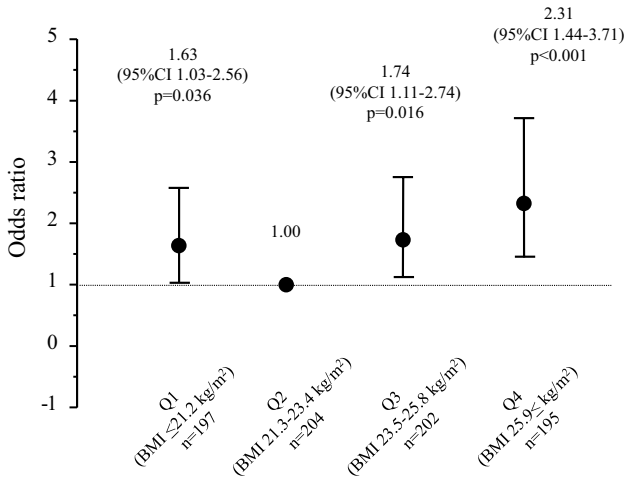

Fig. 1 Association between BMI quartile and the risk of VF in patients with T2DM. Multiple logistic regression analysis adjusted for age, gender, duration of diabetes, HbA1c, eGFR, albumin, FN-T score, uNTX, and use of insulin and thiazolidinedione was performed with the presence of VF as a dependent variable and BMI quartile as an independent variable

women in an unadjusted model, while increased BMI was significantly associated with the VF risk after adjustment for BMD [24]. In the present study, when FN-T score was adjusted for in the logistic analysis (Table 3), the associations seemed to be weak in Q1 (decreased OR and increased *p* value), while they were enhanced in Q3 and Q4 (increased OR and decreased *p* value), suggesting that the associations were partly mediated via BMD. Of note, in this study, these associations were significant in both the unadjusted and the adjusted models for BMD. Taken together, these findings suggest that BMI may be linked to the VF risk by altering bone quality in T2DM patients.

The mechanisms involved in the association of overweight with VF risk in patients with T2DM are unclear. It has been shown that patients with T2DM have low bone turnover [25], which leads to accumulation of advanced glycation end products in the bones and may be associated with deterioration of bone quality [26]. Body weight is known to impact bone turnover, which is positively correlated with BMD. Previous studies have shown that individuals with a higher BMI have lower bone turnover markers and higher BMD [27], and that weight loss results in increases in bone resorption markers [28]. These findings suggest that body weight directly influences bone resorption and bone turnover. In fact, in this study, BMI quartile was inversely associated with uNTX and positively correlated with FN-BMD. Therefore, overweight-induced suppression of bone resorption may partly contribute to bone fragility in patients with T2DM. In addition, previous studies have shown that adipokines secreted from adipose tissue are important for bone metabolism [29, 30]. Adiponectin is reported to be decreased in patients with diabetes and obesity [31] and was inversely associated with BMI [31, 32]. Several studies showed that adiponectin stimulates osteoblast differentiation and enhances bone turnover [33, 34]. We previously reported that serum adiponectin levels were positively associated with bone turnover markers [35, 36]. In addition, insulin resistance may also contribute significantly to the association between overweight and VF risk. A previous in vivo study showed that high-fat diet-induced obese mice had decreased bone turnover due to local insulin resistance in the bones [37]. Although we had no data related to insulin resistance in this study, previous clinical studies reported that insulin resistance might have a negative impact on bone mass [38]. Therefore, further studies are required to clarify the contribution of adipokines and insulin resistance to the association between BMI and fracture risk in T2DM.

On the other hand, the present study showed that underweight is also a BMD-independent risk factor for VF in patients with T2DM. The mechanisms involved in underweight-related VF are probably different from those involved in overweight-induced bone fragility. Although further studies are necessary, sarcopenia may be involved in the BMD-independent fracture risk in underweight individuals. Previous studies have shown that sarcopenia, which is characterized by reduction in the muscle mass and function, is associated with fall-fracture risks [39, 40], and that the risk of sarcopenia is increased in patients with T2DM compared to healthy individuals [41].

Our study focused on the effects of BMI on fracture risk in Japanese patients with T2DM. However, it is known that the degree of obesity is different between Asian and Western populations. Furthermore, the capacity of insulin secretion is different between Asian and Western populations [42]. Therefore, it needs to be clarified whether our findings are universal. However, our findings may provide insights into how diabetes-related osteoporosis should be treated in clinical settings. Body weight control is thus strongly recommended to improve not only blood glucose levels and reduce the risk of cardiovascular disease, but also diabetes-related bone fragility in patients with T2DM.

This study has some limitations. First, we analyzed only individuals who visited the Shimane University hospital, a tertiary center for treatment of diabetes mellitus. Therefore, participants enrolled in this study might have a relatively severe state of the disorder and may not be a representative of Japanese patients with the disorder. Second, more than half of the patients were treated. Therefore, we cannot exclude the possibility that treatment of diabetes affected BMI and the occurrence of VF. Third, healthy individuals were not examined in this study. Therefore, we cannot compare the contribution of BMI to the presence of VF between patients with T2DM and healthy individuals. Fourth, although Vitamin D status and parathyroid hormone levels

might be associated with the risk of VF in T2DM, these data were not examined in this study. Finally, the conclusions of this study are limited due to its cross-sectional design. It is necessary to conduct longitudinal studies to confirm the present findings in the future.

In conclusion, this is the first study to show the significant association between BMI and the prevalence of VF in patients with T2DM. Both overweight and underweight were associated with the BMD-independent risk of VF in patients with T2DM. Therefore, body weight control should be considered as a protective measure for diabetes-related bone fragility.

Acknowledgements This study was partly supported by research grant from Eli Lilly Japan.

Funding This study was partly supported by research grant from Eli Lilly Japan.

Compliance with ethical standards

Conflict of interest Ippei Kanazawa, Masakazu Notsu, Ayumu Takeno, Ken-ichiro Tanaka, Toshitsugu Sugimoto declare that they have no conflicts of interest.

Statement of human rights This study was approved by the institutional review board of Shimane University Faculty of Medicine. Procedures have been performed according to the 1964 Declaration of Helsinki.

Informed consent Informed consent was obtained from all individual participants included in the study.

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