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ORIGINAL RESEARCH

Associations of Obesity Indices with Bone Mineral Densities and Risk of Osteoporosis Stratified Across Diabetic Vascular Disease in T2DM Patients

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Objective: To evaluate associations of obesity indices with bone mineral densities (BMD) and risk of osteoporosis in T2DM patients totally and stratified across presence of any diabetic cardiovascular complications.

Methods: Cross-sectional analyses of baseline information on a cohort of 250 T2DM patients were conducted in Xiamen, China. Obesity indices included body weight, height, body mass index (BMI), waist and waist hip ratio (WHR). BMD was measured using dual-energy X-ray absorptiometry at three different sites, and osteoporosis was defined based on the minimum T-scores of BMD. Presence of any diabetic vascular complications was confirmed by checking their medical records histories.

Results: Among the 250 T2DM patients, 50 (20.0%) were defined as osteoporosis. Multivariable linear regression and multivariable logistic regression analyses showed that igher obesity indices, including body weight, BMI and waist, but neither body height nor waist hip ratio, were positively associated with the minimum T-scores of BMD and had significantly decreased risk of osteoporosis. Stratified analyses across presence of any of diabetic vascular complications showed similar results for those with any of diabetic vascular complications, while no significant association between obesity indices and minimum T-scores of BMD was found for those without. Postmenopausal women (vs men) and ever drinking were significantly associated with increased risk of osteoporosis, and the adjusted odds ratios (95% CIs) were 5.165 (1.762–15.138, p = 0.003) and 3.789 (1.087–13.214, p = 0.037), respectively. None of metabolic profiles, including systolic and diastolic blood pressure, triglyceride, total cholesterol, high-density lipoprotein cholesterol, HbA1c and blood uric acid, was significantly associated with either minimum T-scores of BMD or risk of osteoporosis.

Conclusion: Associations of obesity indices with either BMD or risk of osteoporosis in T2DM patients varied by presence of any diabetic vascular complication and should be not interpreted as causal without considering the often-unmeasured effect modification by health status.

Keywords: obesity, bone mineral density, osteoporosis, diabetic vascular complications, diabetes

Introduction

Diabetes mellitus is one of the major causes of death worldwide. The International Diabetes Federation (IDF) has estimated that about 537 million adults aged 20–79 years had diabetes mellitus in 2021, and this number is estimated to increase to 643 million by 2030 and 783 million by 2045. The complications of diabetes affect nearly every tissue of the body. Meanwhile, diabetes mellitus is also a leading cause of cardiovascular diseases, blindness, renal failure, and amputations.[1] Osteoporosis is another common metabolic disease that affects more than 200 million people globally, which is also a skeletal complication of type 2 diabetes mellitus (T2DM). Osteoporosis is characterized by reduced bone mass and damaged bone tissue microstructure, resulting in increased bone fragility and being prone to fracture.[2] Within 1 year after hip fracture, 20% of patients

Received: 29 July 2022
Accepted: 26 October 2022
Published: 3 November 2022

will die from complications such as venous thrombosis and pneumonia, approximately 50% will become disabled.[3] Hence, it is important for the treatment of osteoporosis in patients with T2DM in terms of prevention of fracture.

Both T2DM and osteoporosis are chronic disorders which are associated with severe morbidity and increased mortality.[4] Although there are a few previous studies which reported increased BMI declines the risk of osteoporosis in patients with diabetes mellitus,[5,6] it seems that available evidence on the association between obesity indices and bone mineral density (BMD) or risks of osteoporosis was controversial. A lot of previous studies showed a positive correlation between BMI and BMD,[6] while several other studies suggested that obesity was a risk factor for certain fractures.[7,8] More and more studies have shown that BMI and other measures of adiposity, such as waist circumference, body fat percentage, have different associations with various health conditions.[9–11] Furthermore, little is known about the different relationships between BMI and osteoporosis in T2DM patient stratified across with or without diabetic cardiovascular complications. Therefore, in the present research, we firstly aimed to investigate the associations of various obesity indices, including body weight, height, body mass index (BMI), waist and waist hip ratio (WHR), with BMD and risks of osteoporosis for T2DM patients in total and stratified across presence of any diabetic cardiovascular complications. Secondly, associations of metabolic profiles, such as systolic and diastolic blood pressure (BP), triglyceride, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), HbA1c, homeostasis model assessment - insulin resistance (HOMA-IR) and blood uric acid, and other life styles (menopause and regular drinking) with BMD and risks of osteoporosis were explored.

Methods

Ethics Statement

The study was approved by the Human Research Ethics Committee of the Zhongshan Hospital, Fudan University (Xiamen Branch) (B2019-015). All participants provided written informed consent.

Study Population

This study was designed as a cross-sectional analysis of this T2DM patient cohort. From January 2018 to April 2020, a total of 490 patients diagnosed as T2DM from the Department of Endocrinology, Zhongshan Hospital, Fudan University (Xiamen Branch) (Xiamen, China) had been recruited into the present ongoing cohort. Patients were diagnosed as diabetes based on American Diabetes Association (ADA) 2018 criteria: (1) a self-reported history of diabetes previously diagnosed by health-care professionals; (2) fasting plasma glucose (FGP) ≥126 mg/dL (7.0 mmol/L); (3) 2-hour plasma glucose (2-h PG, OGTT) ≥200 mg/dL (11.1 mmol/L); or (4) HbA1c ≥6.5% (48 mmol/mol).[12] T2DM was identified for diabetes cases with the age of 20 years or older who are overweight or obese and/or have a family history of diabetes. Finally, 240 patients without bone mineral density (BMD) measurement were excluded, and 250 (149 men and 101 postmenopausal women) T2DM patients were left for the present study.

Measurements

Face-to-face interview was conducted for each patient to collect socio-demographic status, lifestyle habits, present and previous history of health and medications, including histories of diabetic complications and treatment. Diabetic vascular complications, including diabetic retinopathy, diabetic kidney disease, diabetic peripheral neuropathy and diabetic peripheral arterial disease, were all confirmed by checking their medical records histories. Diabetic retinopathy, encompassing simple, non-proliferative or proliferative retinopathy, was diagnosed by an experienced ophthalmologist who evaluated the optical fundi by using ophthalmoscopy or retinal photography. Diabetic kidney disease was diagnosed based on the presence of albuminuria and/or reduced estimated glomerular filtration rate (eGFR) in the absence of other primary causes of kidney damage. Patients were asked for the symptoms or signs of motor, sensory, and autonomic nerves. Standard neurological examinations, including the foot sensation test using monofilament or vibration, the ankle reflex assessment and nerve conduction velocity (NCV) tests, were conducted by experienced clinicians. Diabetic peripheral neuropathy was diagnosed when at least two of the following symptoms presented: being insensible to 10-g Semmes-Weinstein monofilament at any of plantar sites on each foot, reduced vibration perception, absence of ankle reflex, or at least two abnormal NCV tests. Diabetic

peripheral arterial disease was defined as an ankle–brachial index (ABI) <0.9 calculated by the higher values of systolic blood pressure (BP) in either dorsalis pedis or posterior tibial arterial divided by the higher brachial systolic BP.

Subjects underwent weight and height measurements by using a calibrated scale after removing shoes and heavy clothes. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. Subjects were classified by WHO guidelines for the Asian Pacific population into five BMI categories: underweight (less than 18.5 kg/m^2), normal weight (18.5–22.9 kg/m^2), overweight (23.0–24.9 kg/m^2), obesity I (25.0–29.9 kg/m^2), and obesity II (equal to or more than 30.0 kg/m^2).[13,14] Since there were only 8 (3.2%) patients with underweight and 17 (6.8%) patients with obesity II, three BMI categories were used in the present study, including normal weight or below (less than 23.0 kg/m^2), overweight (23.0–24.9 kg/m^2) and obesity (25.0 kg/m^2 or over). Waist circumference (WC) was measured at the midpoint between the inferior costal margin and the superior border of the iliac crest on the midaxillary line. Hip circumference (HC) was measured at the widest part of the hip at the level of the greater trochanter. All measurements were in centimeters (cm) to the nearest 0.1 cm. Waist hip ratio (WHR) was calculated as the ratio of waist to hip circumference. Arterial blood pressure was measured with OMRON electronic sphygmomanometer after sitting for at least 15 minutes. Three readings were taken at 5-min intervals and the mean of them was recorded.

After a 12-h overnight fasting, blood samples were collected to measure fasting plasma glucose (FPG), glycosylated hemoglobin A1c (HbA1c), liver function, renal function and lipid profiles. All biochemical measurements were tested in the clinical laboratory of the Zhongshan Hospital, Fudan University (Xiamen Branch). Serum creatinine (CRE), uric acid (UA), Triglyceride (TG), total cholesterol (TC), and high-density lipoprotein cholesterol (HDL-C) were determined on an analyzer (Roche Elecsys Insulin Test, Roche Diagnostics). Low-density lipoprotein cholesterol (LDL-C) was calculated by fried Ewald's formula: LDL-C=(TC−HDL-C)−TG/5.[15] FPG concentration was measured by the hexokinase method and HbA1c by the Bio-Rad Variant Hemoglobin A1c assay. HOMA-IR was calculated using the formula: fasting serum insulin (mU/L) *fasting plasma glucose (mmol/L)/22.5.

BMD Measurement and Definition of Osteoporosis

BMD was measured using dual-energy X-ray absorptiometry (DXA) (QDR4500A, Hologic Inc., Waltham MA, USA) and operated by professional technicians at department of radiology, Zhongshan Hospital, Fudan University (Xiamen Branch). BMD of each patient at three different sites, including total lumbar, femur neck (FN), and total hip were checked. Osteoporosis was defined by the minimum T-score of BMD at total lumbar, femur neck, and total hip of −2.5 or below.[12,16]

Statistical Analyses

Data were presented as the mean ± standard deviation for continuous variables or number and percentage for categorical variables. Skewness and kurtosis tests for continuous variables were conducted and found all followed approximation of normal distributions. Differences between subjects categorized by osteoporosis (vs non-osteoporosis) were analyzed using one-way ANOVA for continuous variables and chi-square test for categorical variables.

Multivariable linear regression was conducted to explore associations between obesity indices (body weight, height, BMI (continuous and categorical values), WC and WHR) and metabolic profiles (systolic and diastolic blood pressure (BP), TG, TC, HDL-C, LDL-C, FPG, HbA1c, HOMA-IR and UA) with the minimum values of BMD. Multivariable logistic regression models were used to calculate the adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for osteoporosis. Both multivariable linear regression and multivariable logistic regression were adjusted for potential confounders, including age, sex, ever smoking and drinking habits, and diabetic vascular complications. Interactions between presence of any of diabetic vascular complications and indices of obesity on the minimum values of BMD and risk of osteoporosis were tested. Furthermore, multivariable linear regression and multivariable logistic regression analyses stratified across any of diabetic vascular complications were conducted separately with adjustment for the same potential confounding variables. All p-values were two-sided and p-value <0.05 was considered statistically significant. All statistical analyses were performed using Stata14.0 (StatCorp, College Station, TX).

Results

Demographic and Clinical Characteristics Stratified by Osteoporosis

Among the 250 T2DM patients, the means (±SDs) of age were 57.8 (±11.7) years, and 101 (40.4%) were postmenopausal women. There were 50 (20.0%) T2DM patients who were defined as osteoporosis. Table 1 shows differences of demographics, life style habits and clinical characteristics stratified by osteoporosis. Compared with T2DM subjects without osteoporosis, those with osteoporosis were more likely to be women, older and showed significantly lower levels

Table 1 Demographic and Clinical Characteristics of Subjects Stratified by Osteoporosis in 250 T2DM Patients

Variables	Osteoporosis			
	Total	No	Yes	P value
Demographics				
N (%)	250 (100.0%)	200 (80.0%)	50 (20.0%)	
Woman Sex (n, %)	101 (40.4%)	67 (33.5%)	34 (68.0%)	<0.001
Age (years)	57.8±11.7	56.5±12.0	62.8±9.1	<0.001
Ever smoking (n, %)	91 (36.4%)	80 (40.0%)	11 (22.0%)	0.018
Ever drinking (n, %)	64 (25.6%)	54 (27.0%)	10 (20.0%)	0.310
Clinical characteristics				
Weight (kg)	67.7±12.7	69.8±12.2	59.1±11.1	<0.001
Height (cm)	164.9±8.7	166.3±8.2	159.3±8.2	<0.001
BMI (kg/m^2)	24.8±3.5	25.2±3.5	23.2±3.3	<0.001
BMI category (kg/m^2, n (%))				0.005
Normal weight or below (<23.0)	84 (33.6%)	58 (29.0%)	26 (52.0%)	
Overweight (23.0–24.9)	53 (21.2%)	43 (21.5%)	10 (20.0%)	
Obesity I & II (≥25.0)	113 (45.2%)	99 (49.5%)	14 (28.0%)	
Waist (cm)	88.6±9.6	89.6±9.5	84.5±9.2	0.001
Waist hip ratio	0.94±0.06	0.95±0.06	0.92±0.06	0.017
Systolic blood pressure (mmHg)	131.3±16.9	131.1±16.9	132.0±16.7	0.741
Diastolic blood pressure (mmHg)	82.1±9.9	82.2±9.9	81.7±10.1	0.756
Triglyceride (mmol/L)	1.99±2.12	2.09±2.30	1.60±1.07	0.148
Total cholesterol (mmol/L)	4.57±1.55	4.57±1.12	4.58±2.66	0.943
HDL-cholesterol (mmol/L)	1.12±0.32	1.10±0.28	1.23±0.44	0.011
LDL-cholesterol (mmol/L)	2.55±1.00	2.60±1.00	2.37±0.98	0.135
Fasting plasma glucose (mmol/L)	8.36±3.08	8.51±3.09	7.77±2.99	0.127
HbA1c (%)	9.14±2.31	9.20±2.36	8.89±2.09	0.393
HOMA-IR (*10-6mol*IU*L^{-2})	5.26±1.93	5.19±2.06	5.52±1.23	0.915
History of T2DM (years)	7.85±6.79	7.42±6.79	9.59±8.57	0.057
Blood uric acid (μmol/L)	352.2±97.5	359.6±97.2	322.8±94.1	0.017
Diabetic vascular complications				
Diabetic retinopathy (n, %)	74 (29.6%)	58 (29.0%)	16 (32.0%)	0.678
Diabetic kidney disease (n, %)	41 (16.4%)	34 (17.0%)	7 (14.0%)	0.608
Diabetic peripheral neuropathy (n, %)	36 (14.4%)	28 (14.0%)	8 (16.0%)	0.719
Diabetic peripheral arterial disease (n, %)	172 (68.8%)	134 (67.0%)	38 (76.0%)	0.219
Any of diabetic vascular complications (n, %)	202 (80.8%)	160 (80.0%)	42 (84.0%)	0.521
T-score of bone mineral density (BMD)				
Lumbar vertebra	−1.17±1.31	−0.75±1.04	−2.83±0.90	<0.001
Femoral neck	−1.32±1.00	−1.02±0.82	−2.52±0.70	<0.001
Hip joint	−0.91±0.95	−0.62±0.76	−2.10±0.64	<0.001
Minimum T-score	−1.67±1.03	−1.29±0.73	−3.17±0.62	<0.001

Notes: All percentages are column percentage; except for percentages, all values are mean ± s.d.

Abbreviations: BMD, bone mineral density; BMI, body mass index; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment - insulin resistance; LDL, low-density lipoprotein cholesterol; T2DM, type 2 diabetes mellitus.

of body weight, height, BMI, waist, waist hip ratio, blood uric acid and T-score of BMD (including lumbar vertebra, femoral neck, hip joint and minimum of the T-score of these three parts). T2DM subjects with osteoporosis also showed significantly higher HDL-C level than their controls. But there was no statistically significant difference on other metabolic profiles between these two groups, including systolic and diastolic BP, TG, TC, LDL-C, FPG, HbA1c and HOMA-IR. As for diabetic vascular complications, such as diabetic retinopathy, diabetic kidney disease, diabetic peripheral neuropathy, and diabetic peripheral arterial disease, etc. subjects with osteoporosis reported similar prevalence as those without.

Associations of Obesity Indices with Minimum T-Score of BMD

Table 2 shows associations of clinical characteristics with minimum T-score of BMD by using the multivariable linear regression analyses. For obesity indices, body weight, BMI and waist, but neither height nor waist hip ratio, were significantly and positively associated with minimum T-score of BMD, and the corresponding regression coefficients ± SE were 0.332±0.007, 0.281±0.066 and 0.204±0.007 (all p-values <0.05). Compared to normal weight or below, obesity

Table 2 Multivariable Linear Regression for Minimum T-Score of BMD and Logistic Regression for Osteoporosis in 250 T2DM Subjects

Variables	Minimum T-Score of BMD			Osteoporosis		
	Standardized Beta	Standard Error (SE)	P-value	OR	95% CI	P-value
Sex (Postmenopausal women vs men)	−0.416	0.167	0.013	5.165	1.762–15.138	0.003
Age (years)	−0.156	0.006	0.034	1.043	0.999–1.090	0.058
Ever smoking	−0.006	0.154	0.938	0.973	0.321–2.950	0.962
Ever drinking	0.011	0.158	0.868	3.789	1.087–13.214	0.037
Weight (kg)	0.332	0.007	<0.001	0.938	0.894–0.984	0.008
Height (cm)	0.124	0.012	0.229	0.962	0.895–1.035	0.297
BMI (kg/m^2)†	0.281	0.066	<0.001	0.547	0.357–0.840	0.006
BMI category (kg/m^2)						
Normal weight or below (<23.0)	…			1.000		
Overweight (23.0–24.9)	0.126	0.175	0.071	0.874	0.331–2.310	0.786
Obesity I & II (≥25.0)	0.269	0.149	<0.001	0.350	0.151–0.812	0.014
Trend test			<0.001			0.014
Waist (cm)	0.204	0.007	0.003	0.954	0.912–0.998	0.040
Waist hip ratio	0.023	1.129	0.741	0.045	0.001–27.784	0.344
Systolic blood pressure (mmHg)	0.038	0.005	0.624	0.980	0.953–1.008	0.165
Diastolic blood pressure (mmHg)	−0.045	0.008	0.556	1.046	0.995–1.099	0.076
Triglyceride (mmol/L)	−0.078	0.034	0.266	0.846	0.532–1.346	0.481
Total cholesterol (mmol/L)	−0.087	0.055	0.299	1.157	0.810–1.651	0.423
HDL-cholesterol (mmol/L)	−0.024	0.217	0.729	0.931	0.264–3.276	0.911
LDL-cholesterol (mmol/L)	0.170	0.082	0.032	0.624	0.373–1.044	0.072
Fasting plasma glucose (mmol/L)	0.137	0.021	0.027	0.941	0.824–1.075	0.371
HbA1c (%)	0.030	0.030	0.652	0.956	0.805–1.135	0.609
HOMA-IR ($*10\text{-}6mol*IU*L^{-2}$)	−0.001	0.003	0.765	0.999	0.982–1.017	0.912
History of T2DM (years)	−0.014	0.009	0.160	1.019	0.964–1.078	0.495
Blood uric acid (μmol/L)	0.088	0.001	0.172	0.997	0.993–1.002	0.217
Diabetic vascular complications						
Diabetic retinopathy	0.138	0.136	0.818	0.947	0.439–2.043	0.890
Diabetic kidney disease	0.038	0.172	0.542	0.826	0.294–2.323	0.717
Diabetic peripheral neuropathy	0.014	0.177	0.820	0.922	0.355–2.391	0.867
Diabetic peripheral arterial disease (n, %)	−0.069	0.145	0.284	1.630	0.675–3.935	0.277
Any of diabetic vascular complications	−0.016	0.167	0.798	1.080	0.372–3.137	0.887

Notes: †BMI was impressed by per SD increase of BMI.

Abbreviations: BMD, bone mineral density; BMI, body mass index; CI, confidence interval; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment - insulin resistance; LDL, low-density lipoprotein cholesterol; OR, odds ratio; T2DM, type 2 diabetes mellitus.

was significantly associated with higher minimum T-score of BMD. As for metabolic profiles, higher LDL-cholesterol and fasting plasma glucose levels were significantly associated increased minimum T-scores of BMD and the corresponding regression coefficients ± SE were 0.170±0.082 and 0.137±0.021 (both p-values <0.05), while others (including systolic and diastolic BP, triglyceride, total cholesterol (TC), HDL-cholesterol, HbA1c, HOMA-IR and blood uric acid) were not significantly associated with minimum T-scores of BMD. Besides, female gender for postmenopausal women compared to male and older age were negatively associated with minimum T-scores of BMD (both p-values <0.05).

Associations of Obesity Indices with Osteoporosis

Associations between clinical characteristics and osteoporosis by using the multivariable logistic regression analyses are presented in Table 2. Similar to associations with minimum T-score of BMD, higher obesity indices, including body weight, BMI and waist, were significantly associated with lower risk of osteoporosis, and the corresponding ORs (95% CIs) were 0.938 (0.894–0.984), 0.547 (0.357–0.840) and 0.954 (0.912–0.998) (all p-values <0.05). Obesity, compared to normal weight or below, also showed decreased risk of osteoporosis with OR (95% CI) of 0.350 (0.151–0.812, p = 0.014). All the metabolic profiles (systolic and diastolic BP, TG, TC, HDL- or LDL-cholesterol, FPG, HbA1c, HOMA-IR and blood uric acid) were not significantly associated with risk of osteoporosis. Female gender for postmenopausal women compared to male and ever drinking were significantly associated with increased risk of osteoporosis, with the adjusted ORs and 95% CIs of 5.165 (1.762–15.138) and 3.789 (1.087–13.214) (both p-values <0.05), respectively.

Associations of obesity indices with minimum T-score of BMD and osteoporosis stratified by presence of any of diabetic cardiovascular disease.

None of the interactions between any of diabetic vascular complications and indices of obesity on the minimum values of BMD and risk of osteoporosis was statistically significant (all p-values >0.05). Multivariable linear regression on associations of obesity indices with minimum T-score of BMD and multivariable logistic regression analyses of obesity indices with osteoporosis stratified by presence of any of diabetic cardiovascular disease were further conducted and shown in Table 3. For those diabetes patients with any of diabetic vascular diseases, higher obesity indices, including body weight, BMI and waist, were significantly associated with lower minimum T-scores of BMD and decreased risk of osteoporosis. But for those patients without any of diabetic vascular diseases, none of the obesity indices was significantly associated with minimum T-scores of BMD, and results for obesity indices with osteoporosis could not be drawn since multivariable logistic regression models for these patients could not be converged.

Discussion

In the present study of 250 patients with T2DM, about 20.0% of them were diagnosed as osteoporosis. Multivariable regression analyses with adjustment for potential confounding factors showed that higher obesity indices, including body weight, BMI and waist, but neither body height nor waist hip ratio, were significantly and positively associated with the minimum T-score of BMD and had significantly decreased risk of osteoporosis. Stratified analyses showed similar results for those with any of diabetic vascular diseases but not for those without. Postmenopausal women (vs men) and regular drinking habits were significantly associated with increased risk of osteoporosis. As for metabolic profiles, systolic and diastolic BP, triglyceride, total cholesterol (TC), HDL-cholesterol, HbA1c, HOMA-IR and blood uric acid were not significantly associated with either minimum T-scores of BMD or risk of osteoporosis.

Osteoporotic fractures are among the "non-classical" complications of diabetes, although subjects with T2DM have increased risk of bone fragility fractures compared to nondiabetic subjects.[4,17] In this study, we found that the mean values of the minimum T-score were lower than the general adults and about 20% of them were diagnosed with osteoporosis. In the present study, we found that females for postmenopausal women compared to male were significantly associated with increased risk of osteoporosis. It is generally assumed that for women, the rapid decline in estrogen leads to an increase in bone conversion and an acceleration of bone loss after menopause.[18,19] Therefore, lower peak bone mass and postmenopausal estrogen deficiency lead to a higher risk of fractures and earlier fragility fractures in women compared to men.[18] Recent studies thought that may underestimate the fragility of male bone,[20–22] especially several risk factors and diseases have been shown to cause secondary osteoporosis in men.[22,23] Such as alcohol abuse, smoking and sedentary.[20,23] After adjusting the potential confounding factors, we consistently found that drinking was

Table 3 Multivariable Linear Regression for Minimum T-Score of BMD and Logistic Regression for Osteoporosis Stratified by Any of Diabetic Vascular Diseases in 250 T2DM Subjects

Variables	Minimum T-Score of BMD			Osteoporosis		
	Standardized Beta	Standard Error (SE)	P-value	OR	95% CI	P-value
No any of diabetic vascular disease						
Weight (kg)	0.076	0.017	0.763			
Height (cm)	0.508	0.030	0.076			
BMI (kg/m^2)†	0.186	0.184	0.322			
BMI category (kg/m^2)						
Normal weight or below (<23.0)						
Overweight (23.0–24.9)	0.298	0.475	0.150			
Obesity I & II (≥25.0)	0.327	0.452	0.146			
Trend test			0.182			
Waist (cm)	0.437	0.021	0.052			
Waist hip ratio	0.447	3.388	0.051			
Any of diabetic vascular diseases						
Weight (kg)	0.362	0.008	<0.001	0.937	0.889–0.988	0.015*
Height (cm)	0.052	0.014	0.652	0.978	0.902–1.061	0.596
BMI (kg/m^2)†	0.299	0.073	<0.001	0.546	0.341–0.877	0.012*
BMI category (kg/m^2)						
Normal weight or below (<23.0)				1.000		
Overweight (23.0–24.9)	0.108	0.199	0.166	0.681	0.224–2.074	0.499
Obesity I & II (≥25.0)	0.272	0.162	0.001	0.349	0.139–0.878	0.025*
Trend test			0.001			0.025*
Waist (cm)	0.177	0.008	0.019	0.959	0.913–1.006	0.087
Waist hip ratio	−0.029	1.239	0.695	0.127	0.001–129.751	0.560

Notes: †BMI was impressed by per SD increase of BMI. Both linear regression and logistic regression were adjusted for age, sex, ever smoking and drinking, systolic and diastolic BP, triglyceride, total cholesterol, HDL- and LDL-cholesterol, fasting plasma glucose, history of T2DM, blood uric acid and any of diabetic cardiovascular complications.

Abbreviations: BMD, bone mineral density; BMI, body mass index; CI, confidence interval; OR, odds ratio.

significantly associated with increased risk of osteoporosis. Therefore, our results implied that for T2DM patients who were postmenopausal women or had regular drinking habits, screening of osteoporosis and intervention of elevating their bone mineral density should be strengthened.

Available evidence on the association between obesity indices and BMD or osteoporosis was controversial. Although a lot of studies showed a positive correlation between BMI and BMD,[6] several recent studies have challenged the widespread belief that obesity was protective against fracture with results suggesting that obesity was a risk factor for certain fractures.[7,8] In the present study, we found that higher obesity indices, including body weight, BMI and waist, were significantly and positively associated with the minimum T-score of BMD and had significantly decreased risk of osteoporosis. Stratified analyses across presence of any diabetic vascular diseases also found similar results on the association of obesity indices with the minimum T-score of BMD and osteoporosis for those with any diabetic vascular diseases. Studies had showed that weight-bearing increases bone density by acting at the cellular level. Bone cells are particularly sensitive to biomechanical stress, the action of osteoclasts is inhibited and osteoblast differentiation is stimulated when coping with stress.[6,24] The reason why T2DM is associated with lower risk of osteoporosis may be due to some endocrine effects of diabetes itself that have a greater impact on bone health. T2DM is preceded by a period of insulin resistance that leads to hyperinsulinemia[16] and T2DM may protect individuals from age-related bone loss although hyperinsulinemia may also have a negative impact on sex hormone-binding globulins and leads to elevated free sex hormone levels.[14,25] For example, cohort studies found that newly diagnosed diabetes can significantly reduce fracture risk.[13] However, poor glycemic control and long-term exposure to hyperglycemia can lead to accumulation of

advanced glycation end products (AGEs) and the development of diabetic microvascular complications,[13] causing the vulnerability of bone.[26] When diabetes complications occur, the beneficial effect of obesity on bone may be faded/attenuated by the time. The reasons why weight and BMI play an advantage on bone density may be because obese individuals have sufficient nutritional intake and have a greater amount of lean tissue, since there is a direct relationship between the increase in lean tissue and bone density.[27]

There were a lot of studies have shown that BMI and other measures of adiposity, such as waist circumference, body fat percentage, have different associations with various health conditions.[9–11] For example, Schooling CM et al found that in the elderly, the relationship between obesity and mortality varied according to the underlying health status. In those with poor health status, obesity was associated with better outcome, whereas in those with initially good health status, obesity was associated with worse outcome.[8] We further conducted stratified analyses across presence of any diabetic vascular diseases and found that, for those without any diabetic vascular diseases, obesity indices were not significantly associated with minimum T-scores of BMD. We assumed that those without any diabetic vascular diseases were relatively healthier than those with any diabetic vascular diseases although all of them were T2DM patients. Therefore, our findings implied that relationships of higher obesity indices with either BMD or osteoporosis are far beyond of drawing a clear conclusion and should not be interpreted as causal without considering the often-unmeasured effect modification by health status. Future studies are needed to determine if and how visceral obesity and metabolic complications of obesity (type 2 diabetes mellitus, insulin resistance, chronic inflammation, etc) are causally associated with bone status and fragility fracture risk.[12]

We should be careful to generalize our findings due to the following limitations. Firstly, all subjects in the present study were sampled from only one hospital in China, and the selection bias was obvious. Secondly, our sample size was quite small, and only postmenopausal women were selected for females; therefore, we may not have enough power to determine the true associations of obesity indices with BMD and osteoporosis. Thirdly, the present analyses were based on the baseline information of our ongoing cohort study, therefore we cannot determine the temporal sequence among obesity and osteoporosis. On the other hand, we were probably the first, to the best of our knowledge, to test the associations of obesity indices with BMD and osteoporosis stratified across presence of any diabetic vascular diseases and found various results between obesity indices and BMD for those with and without any diabetic vascular diseases.

Conclusion

Generally, higher obesity indices (body weight, BMI and waist) were significantly and positively associated with the minimum T-score of BMD and had significantly decreased risk of osteoporosis. But for those without any diabetic vascular diseases, obesity was not significantly associated with BMD. Our findings implied that relationships of obesity indices with either BMD or osteoporosis varied by presence of any diabetic vascular complication and should be not interpreted as causal without considering the often-unmeasured effect modification by health status.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the Helsinki Declaration and its later amendments or comparable ethical standards.

Acknowledgments

We are grateful to all the patients for their participation.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was supported by the grants from Guiding Project on Medicine & Health in Xiamen, China (No. 3502Z20209048) and National Key R&D Program of China (No. 2017YFC0907100).

Disclosure

The authors declare that they have no conflicts of interest.

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