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Association between muscle mass, bone mineral density and osteoporosis in type 2 diabetes

Youjin Pan, Jing Xu*

Department of Endocrinology, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou, China

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***Correspondence**
Jing Xu
Tel.: +86-150-6825-6508
Fax: +86-150-6825-6508
E-mail address:
47914057@qq.com

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ABSTRACT

Aims/Introduction: Type 2 diabetes mellitus is associated with an increased incidence of osteoporosis and sarcopenia. However, the relationship between osteoporosis and sarcopenia in patients with type 2 diabetes mellitus remains to be unclear. Appendicular skeletal muscle was adjusted by height (appendicular skeletal muscle mass [ASM]/height^2) as a marker of sarcopenia. This study aimed to explore the relationship between ASM/height^2, osteoporosis and bone mineral density (BMD) in this population.

Materials and Methods: A total of 192 women and 225 men with type 2 diabetes mellitus were recruited. General information, laboratory and BMD data were collected. Spearman's correlation, multiple regression analyses and receiver operating characteristic curve analysis were used to explore the correlation between ASM/height^2, BMD and bone metabolism markers.

Results: Spearman's correlation analysis showed that ASM/height^2 had a positive correlation with serum calcium and BMD (r = 0.209–0.404, P < 0.01). In multivariate regression analysis, we found significant correlations between ASM/height^2 and total lumbar spine, hip and femur neck BMD. According to the receiver operating characteristic curve, ASM/height^2 was the best marker of osteoporosis, with a cut-off value of 7.87 kg/m^2 for men and 5.94 kg/m^2 for women. When these cut-off values were used to identify sarcopenia, the risk of osteoporosis increased 6.036-fold in men and 4.079-fold in women, respectively.

Conclusions: In patients with type 2 diabetes mellitus, ASM/height^2 was positively correlated with BMD, and negatively correlated with osteoporosis.

INTRODUCTION

Osteoporosis and low-energy fractures are on the rise in the elderly, which can lead to poor quality of life, disability and even death[1]. Patients with type 2 diabetes mellitus are generally more prone to fracture than the general population[2,3]. The risk of fracture remains different even after adjusting diabetes duration, age and body mass index (BMI)[4,5]. Previous studies have reported and analyzed the risk factors related to osteoporosis in the general population[6]. However, it is important to discuss the risk factors of osteoporosis that might differ in people with type 2 diabetes mellitus due to metabolic disorders.

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Aging can lead to osteoporosis, but it can also result in a loss of muscle mass. This low muscle mass is named sarcopenia. The term sarcopenia is more than 20 years old.[7] Kwon *et al.*[8] reported that sarcopenia was 19.5% in women aged in their 50s, but increased to 22.1% in older women. Furthermore, Lima *et al.*[9] found the prevalence of osteoporosis to be 19.2% in pre-sarcopenia, and 35.3% in sarcopenia. Therefore, the mass of muscle loss showing a relationship to aging increases the risks regarding sarcopenia and osteoporosis[10].

The prevalence of sarcopenia in patients with type 2 diabetes mellitus is increased as a result of impaired insulin sensitivity[11], ranging from 7% to 29.3%. The relationship between osteoporosis and sarcopenia in type 2 diabetes mellitus patients remains to be unclear. The present study investigated the

relationship between lean mass (as a surrogate measure of mass of muscle), BMD and osteoporosis in patients with type 2 diabetes mellitus.

MATERIALS AND METHODS

Study population

The present study included 447 Chinese patients with type 2 diabetes mellitus (age >50 years). Participants underwent type 2 diabetes mellitus evaluation or treatment at the Second Affiliated Hospital of Wenzhou Medical University and Yuying Children's Hospital (Wenzhou, China) from January 2017 to December 2017. Exclusion criteria included: (i) malignant tumor and severe liver, kidney or heart disease (n = 35); (ii) diagnosis of parathyroid, pituitary, thyroid, gonadal and adrenal disease (n = 10); (iii) long use of vitamin D, calcium or other drugs that affect bone metabolism (n = 27); (iv) long-term bedridden patients (n = 14); and (v) patients with a lack of available information (n = 55). The present study was approved by the ethics committee of the Second Affiliated Hospital of Wenzhou Medical University (No. LCKY2017-21, date: July 2017), and written informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

Clinical assessment and health history

Their weight and height were measured with light clothing and no shoes. We calculated BMI by dividing weight (kg) by the square of height (m^2). Blood pressure (mmHg) was measured with a mercury sphygmomanometer after supine resting for 5 min. The duration of diabetes was calculated in years from the time of diagnosis of type 2 diabetes mellitus in the patient's medical records to our blood tests and BMD measurements. A history of smoking and alcohol consumption was defined as never or ever. The use history of oral hypoglycemic drugs, insulin, calcium channel blockers and statins were record.

Biochemical parameters

Serum samples were collected at 06.00 hours after overnight fasting (at least 8 h). Standard laboratory methods were used to measure markers of glucose metabolism, including fasting blood glucose (FBG) and glycosylated hemoglobin (HbA1c); serum lipid metabolism indices, including triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) levels; bone metabolism markers, including PINP, β-CTX, parathyroid hormone and 25-hydroxy-vitamin. In addition, other laboratory markers, such as serum creatinine, calcium, albumin and uric acid, were recorded.

BMD measurement

The BMD of each patient was measured using a dual-energy X-ray absorptiometry at three sites (Hologic-Discovery, Boston, MA, USA): total lumbar spine, total hip and femur neck. The World Health Organization standard for osteoporosis is a T score of <2.5 standard deviations of BMD[12].

Body composition measurements

The lean body mass of the arms and legs, and the ASM was carried out by dual bioelectrical impedance analyzer (InBody 720; Biospace, Seoul, Korea). Bioelectrical impedance analyzer is now considered an accurate method for assessing body composition[11]. As total skeletal muscle mass has an effect on body size, the measured skeletal muscle mass needs to be corrected for the individual's body size. The correction methods included dividing the skeletal muscle mass by the bodyweight (ASM / weight), body mass index (ASM / BMI) or height square (ASM / height^2). Most of the current studies, including those published by the Asian Working Group of Sarcopenia, International Working Group on Sarcopenia and European Working Group on Sarcopenia in Older People, use ASM/height^2 evaluated by DXA[13].

Statistical analysis

Men and women were analyzed separately. We used mean ± standard deviation to describe continuous variables, and used proportion to describe categorical variables. One-way ANOVA analysis and Pearson's χ^2-test were used to compare the mean and proportion. The ASM/height^2, BMD and bone metabolism markers were analyzed by Spearman's partial coefficient analysis adjusting for age. Multivariate linear regression analysis was used to analyze the correlation between the BMD of hip, lumbar spine and femoral neck, and other variables. Logistic analysis was used to calculate the odds ratios (ORs) and 95% confidence intervals. Based on the cut-off value of osteoporosis, the effect of low mass of muscle was determined. To evaluate the clinical value of ASM/height^2 in predicting osteoporosis, receiver operating characteristic (ROC) curves were plotted and the area under the curve was calculated. We carried out a post-hoc analysis of the incidence of osteoporosis in the sarcopenia group and non-sarcopenia group, and the post-hoc analysis was 98.9%.

RESULTS

Basic characteristics

Patient characteristics are shown in Table 1. The present retrospective study included 447 patients with type 2 diabetes mellitus, average age of 66.1 ± 9.5 years and BMI of 24.4 ± 3.7 kg/m^2. The BMD of the total lumbar spine, femur neck and total hip were higher in men (1.073 vs 0.925, 0.827 vs 0.738, 0.896 vs 0.809, all $P < 0.01$) compared with women. The levels of FBG, TC, TG, HDL-C, PINP and the incidence of osteoporosis were significantly lower in men compared with women. The levels of ASM, ASM/height^2 and proportion of smoking or alcohol consumption were significantly higher in men than those in women.

Table 1 | Patient characteristics, stratified by sex

	Total patients (n = 447)	Male patients (n = 255)	Female patients (n = 192)	P
Age (years)	66.1 ± 9.5	65.0 ± 9.8	67.6 ± 8.8	0.003
Diabetes duration (years)	8.0 ± 6.8	7.6 ± 6.9	8.5 ± 6.7	0.177
Systolic blood pressure (mmHg)	139.4 ± 22.3	136.9 ± 21.5	142.8 ± 22.8	0.006
Diastolic blood pressure (mmHg)	77.4 ± 12.6	78.3 ± 12.6	76.3 ± 12.5	0.103
BMI (kg/m^2)	24.4 ± 3.7	24.0 ± 3.3	25.0 ± 4.1	0.003
Medicine used (%)				
Insulin	56.4%	55.3%	57.8%	0.630
Metformin	46.5%	48.6%	43.8%	0.338
Statins	32.9%	31.8%	34.4%	0.611
Calcium channel blockers	42.3%	40.0%	45.3%	0.288
Smoking (current or ever)	28.6%	49.4%	1.0%	<0.001
Alcohol consumption (current or ever)	21.7%	36.9%	1.6%	<0.001
Laboratory findings				
FBG (mmol/L)	8.9 ± 3.2	8.5 ± 2.7	9.3 ± 3.7	0.030
HbA1c (mmol/L)	9.9 ± 2.4	10.1 ± 2.6	9.5 ± 2.0	0.003
TC (mmol/L)	4.47 ± 1.22	4.29 ± 1.09	4.69 ± 1.35	0.001
TG (mmol/L)	1.82 ± 1.57	1.65 ± 1.10	2.05 ± 2.01	0.009
HDL-C (mmol/L)	1.00 ± 0.26	0.96 ± 0.25	1.06 ± 0.26	<0.001
LDL-C (mmol/L)	2.58 ± 0.93	2.51 ± 0.88	2.67 ± 0.99	0.087
Albumin (g/L)	37.7 ± 4.7	38.3 ± 4.2	36.8 ± 5.0	0.001
Creatinine (μmol/L)	72.0 ± 31.8	78.6 ± 30.0	63.2 ± 31.9	<0.001
Uric acid (μmmol/L)	314.2 ± 98.0	327.7 ± 101.1	296.2 ± 91.0	0.001
PTH (pg/mL)	43.60 ± 22.18	43.08 ± 21.04	44.43 ± 24.10	0.739
PINP (ng/mL)	14.95 ± 22.08	13.14 ± 19.76	17.36 ± 24.67	0.045
β-CTX (ng/mL)	0.38 ± 0.24	0.35 ± 0.25	0.41 ± 0.23	0.072
25(OH)D (ng/mL)	58.42 ± 22.71	60.54 ± 20.93	55.71 ± 24.66	0.155
Calcium (mmol/L)	2.19 ± 0.11	2.19 ± 0.11	2.19 ± 0.11	0.812
ASM	19.07 ± 4.04	21.72 ± 2.67	15.52 ± 2.55	<0.001
ASM/height^2	7.23 ± 1.77	7.71 ± 0.72	6.44 ± 0.93	<0.001
BMD				
Total lumbar (g/cm^2)	1.009 ± 0.312	1.073 ± 0.363	0.925 ± 0.201	<0.001
Femur neck (g/cm^2)	0.788 ± 0.148	0.827 ± 0.135	0.738 ± 0.149	<0.001
Total hip (g/cm^2)	0.858 ± 0.162	0.896 ± 0.148	0.809 ± 0.166	<0.001
Osteoporosis	15.1%	9.8%	21.9%	0.001

Values are the mean ± standard deviation or number (%). $P < 0.05$ was deemed significant (comparison between men and women group). 25(OH)D, 25-hydroxy-vitamin; ASM, appendicular skeletal muscle mass; BMI, body mass index; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PTH, parathyroid hormone; TC, total cholesterol; TG, triglyceride.

Spearman's partial correlations between ASM/height^2, bone metabolism markers and BMD

Figure 1 shows that ASM/height^2 was positively correlated with the lumbar spine BMD (r = 0.245 in men and 0.285 in women, $P < 0.001$), femoral neck BMD (r = 0.376 in men and 0.292 in women, $P < 0.001$) and total hip BMD (r = 0.394 in men and 0.332 in women, $P < 0.001$). After age adjustment, Spearman's partial correlation analysis showed that ASM/height^2 was still associated with BMD, procollagen of type 1 N-propeptide, parathyroid hormone and albumin-corrected calcium (Table 2). The Spearman's partial correlation coefficients (r) of total lumbar, total hip, femur neck and serum calcium were 0.250, 0.404, 0.378 and 0.259 in male groups, and 0.209, 0.212, 0.228 and 0.314 in female groups, respectively. The ASM/height^2 was negatively correlated with parathyroid hormone (r = –0.324 in men and –0.302 in women, $P < 0.05$).

Linear regression analysis for BMD

Tables 3 and 4 show multivariate linear regression analysis of BMD between age and BMI. Age, sex and BMI have a significant impact on the prevalence of osteoporosis. Therefore, we carried out subgroup analyses by sex, BMI and age. After adjusting age, duration of diabetic, systolic blood pressure, diastolic blood pressure, smoking, alcohol consumption, TG, TC,

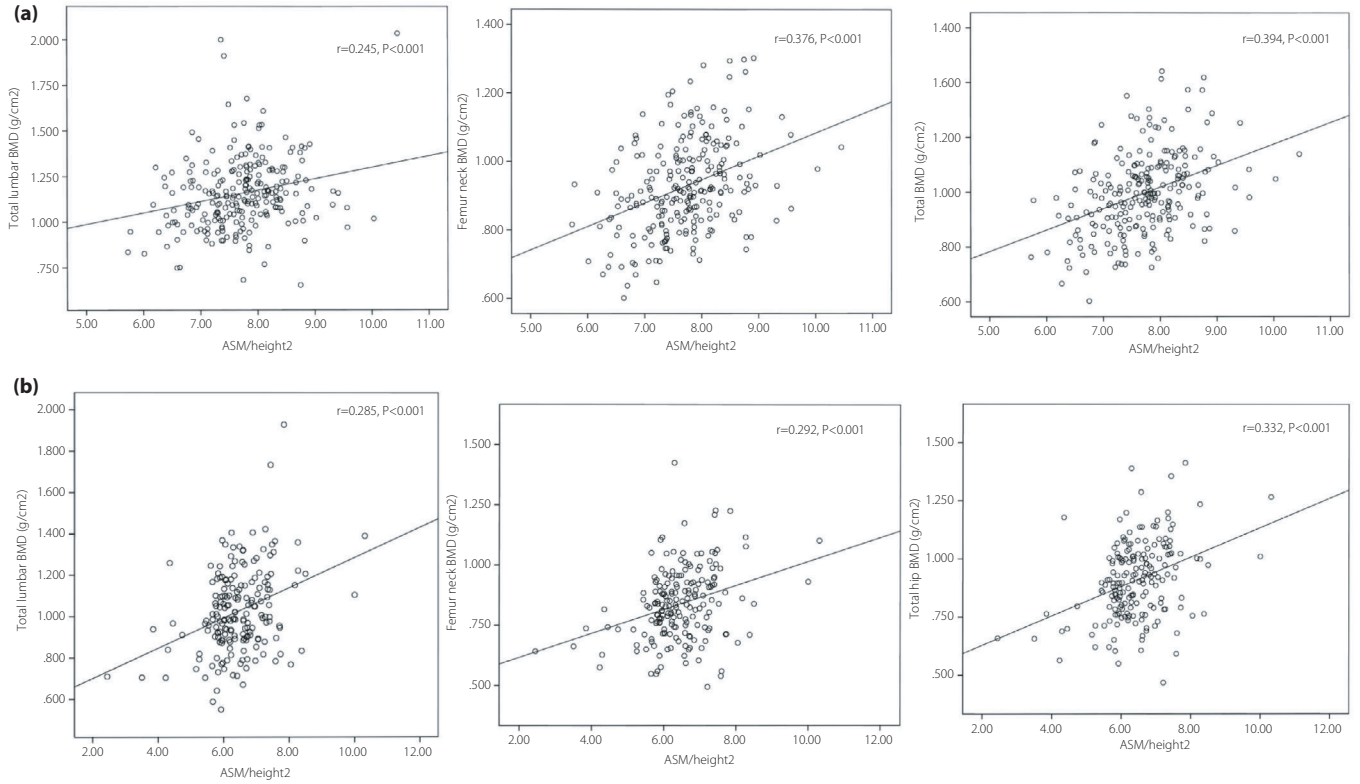

Figure 1 | Scatter diagrams showing the correlation between the appendicular skeletal muscle mass (ASM)/height^2 and bone mineral density (BMD).

Table 2 | Correlation analysis between appendicular skeletal muscle mass/height^2, bone mineral density and bone metabolism markers adjusted for age

Variables	Male		Female	
	r	*P*	*r*	*P*
Total lumbar BMD	0.250	0.000	0.209	0.001
Total hip BMD	0.404	0.000	0.212	0.002
Femur neck BMD	0.378	0.000	0.228	0.001
PTH	–0.324	0.017	–0.302	0.042
PINP	0.432	0.001	0.237	0.048
β-CTX	–0.046	0.740	–0.019	0.909
25(OH)D	0.013	0.925	–0.190	0.246
Albumin-corrected Calcium	0.259	0.050	0.314	0.040

25(OH)D, 25-hydroxy-vitamin; BMD, bone mineral density; PTH, parathyroid hormone.

Table 3 | Appendicular skeletal muscle mass/height^2 was independent association with bone mineral density based on the cross-categorization of body mass index and sex

	18.5 ≤ BMI < 24		BMI ≥24	
	β	*P*	β	*P*
Male				
Total lumbar	0.236	0.029	0.147	0.272
Total hip	0.323	0.008	0.096	0.478
Femur neck	0.260	0.033	0.145	0.279
Female				
Total lumbar	0.413	<0.001	0.374	0.039
Total hip	0.504	<0.001	0.267	0.048
Femur neck	0.449	0.001	0.270	0.042

BMI, body mass index.

HDL-C, LDL-C, creatinine, HbA1c, uric and FBG, ASM/height^2 showed an independent relationship to BMD in the total lumbar spine, hip and femoral neck in the group with BMI <24 kg/m^2 (β values were 0.236, 0.323 and 0.260 in the male group, and 0.413, 0.504 and 0.449 in the female group, respectively). In women with a BMI >24 kg/m^2, ASM/height^2 was independently associated with BMD in the total lumbar spine, hip and femoral neck (β values were 0.374, 0.267 and 0.270, respectively), but not in the male group. ASM/height^2 was independently associated with BMD in the total hip and femoral neck (β values were 0.347 and 0.317, respectively) in men aged <65 years. In women aged <65 years, ASM/height^2 was independently associated with BMD at total lumbar, hip

Table 4 | Appendicular skeletal muscle mass/height^2 was independent association with bone mineral density based on the cross-categorization of age and sex

	Age <65 years		Age ≥65 years	
	β	*P*	β	*P*
Male				
Total lumbar	0.059	0.548	0.284	0.042
Total hip	0.347	<0.001	0.398	0.033
Femur neck	0.317	0.001	0.399	0.030
Female				
Total lumbar	0.349	0.001	0.053	0.731
Total hip	0.379	0.001	0.185	0.210
Femur neck	0.397	<0.001	0.053	0.731

and femoral neck (β values were 0.349, 0.379 and 0.397, respectively). In men aged >65 years, ASM/height^2 was independently associated with BMD at the total hip, lumbar and femoral neck (β values were 0.398, 0.284 and 0.399, respectively).

Logistic regression analyses for osteoporosis

Table 5 shows a logistic regression analysis used to examine the relationship between ASM/height^2 and osteoporosis. Although the OR decreased after adjusting age, diabetes duration, systolic blood pressure, diastolic blood pressure, smoking, alcohol consumption, TG, TC, HDL-C, LDL-C, albumin, creatinine, uric, HbA1c, FBG, the association between ASM/height^2 and osteoporosis remained significant (OR 6.036 in men and OR 4.079 in women, $P < 0.05$).

Prognostic value of ASM/height^2

The ROC curve was used to analyze the influence of ASM/height^2 on the diagnosis of osteoporosis (Figure 2). The area under the ROC curve reached 0.722 for men and 0.686 for women. In the male groups. the optimal cut-off value for ASM/height^2 in predicting of osteoporosis was 7.87kg/m^2, with sensitivity of 43% and specificity 96%. The optimal cut-off value for ASM/height^2 in predicting osteoporosis was 5.94kg/m^2, with sensitivity of 80% and specificity 57% in female groups.

DISCUSSION

To the best of our knowledge, the present study is the first to explore the relationship between ASM/height^2, BMD and osteoporosis in patients with type 2 diabetes mellitus. The main finding of our study was that in patients with type 2 diabetes mellitus, ASM/height^2 was positively correlated with BMD, at femur neck, total lumbar and total hip, and negatively correlated with osteoporosis.

It is well known that type 2 diabetes mellitus patients are at an increased risk of osteoporosis and have accelerated skeletal muscle mass loss[3,14]. It is also known that patients with type 2 diabetes mellitus have a higher incidence of sarcopenia than non-type 2 diabetes mellitus patients. However, the relationship between osteoporosis and sarcopenia in type 2 diabetes mellitus patients has been unknown so far. Considering the present findings and the results of previous studies, patients with sarcopenia, especially those with type 2 diabetes mellitus, might have a high risk for osteoporosis.

Increasing evidence shows that there are many common pathways between sarcopenia and osteoporosis[15], and these conditions are present in a considerable number of individuals[10,16]. The previous cross-sectional studies have reported an increase proportion of patients with sarcopenia with BMD values corresponding to osteoporosis. On the contrary, Locquet *et al.*[10,14] found that an increased incidence of sarcopenia, decreased strength of muscle, low muscle mass and impaired physical performance were increased in the elderly participants with low BMD levels. The association between sarcopenia and osteoporosis varied by publication, with reported risks increasing from twofold to 12-fold. Some of these differences can be explained by cohort particularities (e.g., age, sex, comorbidities). Therefore, the causal relationship between the two diseases remains controversial.

Decreased muscle mass will lead to the deterioration of insulin sensitivity, which in turn leads to diabetes[17]. Diabetes mellitus and other systemic diseases caused by sarcopenia can cause both muscle loss and abnormal bone metabolism[18]. The present results show that low ASM/height^2 is a significant risk factor for lower BMD and osteoporosis in patients with type 2 diabetes mellitus. To our knowledge, this is the first report showing a direct association between ASM/height^2, BMD and osteoporosis in type 2 diabetes mellitus. ASM/height^2 might be a simple predictor of BMD in patients with type 2 diabetes mellitus.

An association between sarcopenia and osteoporosis has been established in individuals with chronic liver disease[19], inflammatory bowel disease, chronic obstructive pulmonary disease and healthy individuals[20-22]. The prevalence of osteoporosis and sarcopenia was increased in elderly women with low grip strength and muscle mass[23]. Therefore, ASM/height^2 might be a simple predictor of osteoporosis in patients with these diseases.

According to the 2019 Asian Working Group of Sarcopenia, the height-adjusted mass of muscle cut-off points for men and women are 7.0kg/m^2 and 5.7kg/m^2 [7], respectively. An important aspect of the present study was the use of ROC curves to calculate cut-off values. The ASM/height^2 cut-off value was 7.87kg/m^2 for men and 5.94 kg/m^2 for women. These values were slightly higher than the Asian Working Group of Sarcopenia guideline, and can be used as a value required for bone health.

In the present study, the effect was greater in men (OR 6.036; $P = 0.001$) compared with women (OR 4.079, $P = 0.008$) with sarcopenia, even after adjusting age, duration of diabetes, TG, TC, HDL-C, LDL-C albumin, creatinine, uric, HbA1c and FPG. This has been confirmed in previous studies, showing that a stronger relationship between muscle mass and

Table 5 | Logistic regression analysis for osteoporosis

Variables	SE	Male		SE	Female	
		odds ratio	*P*		odds ratio	*P*
Age	0.037	0.961 (0.894, 1.033)	0.961	0.027	1.055 (1.000, 1.112)	0.050
Diabetes duration	0.050	1.010 (0.915, 1.114)	0.846	0.036	1.013 (0.944, 1.087)	0.725
TC	2.217	1.217 (0.068, 2.121)	0.456	0.965	0.812 (0.122, 5.380)	0.829
TG	1.442	0.133 (0.008, 2.243)	0.162	0.389	1.017 (0.474, 2.181)	0.966
HDL-C	3.501	0.068 (0.000, 26.638)	0.309	1.608	4.386 (0.187, 10.268)	0.358
LDL-C	2.343	0.206 (0.002, 20.326)	0.500	1.080	0.999 (0.120, 8.297)	0.999
Albumin	0.087	0.767 (0.647, 0.910)	0.002	0.065	0.855 (0.753, 0.971)	0.016
Creatinine	0.015	0.998 (0.969, 1.029)	0.917	0.009	0.997 (0.981, 1.015)	0.766
Uric acid	0.005	1.002 (0.993, 1.011)	0.714	0.003	1.004 (0.998, 1.015)	0.224
HbA1c	0.136	1.100 (0.843, 1.435)	0.482	0.117	0.958 (0.761, 1.205)	0.713
FPG	0.143	0.901 (0.681, 1.193)	0.467	0.054	1.035 (0.930, 1.151)	0.529
ASM/height <7.87 kg/m^2 in men or <5.94 kg/m^2 in women	0.528	6.036 (2.389, 15.325)	0.001	0.531	4.079 (1.440, 11.559)	0.008

ASM, appendicular skeletal muscle mass, FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SE, standard error; TC, total cholesterol; TG, triglyceride.

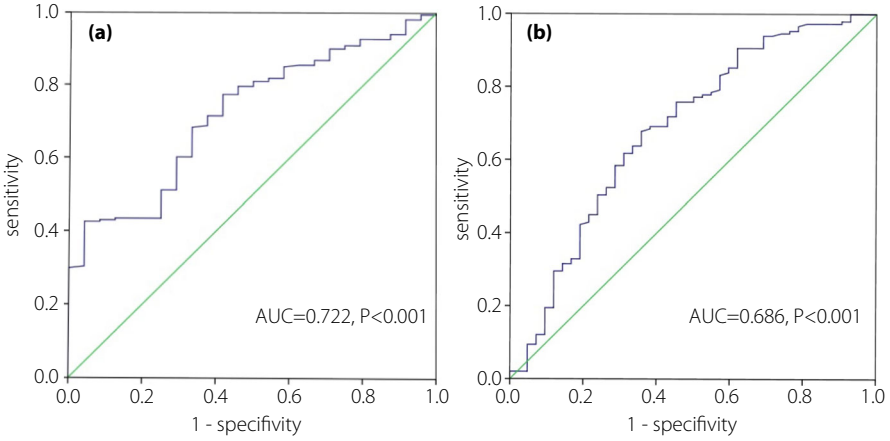

Figure 2 | (a) Receiver operating characteristic analysis of the appendicular skeletal muscle mass (ASM)/height^2 for osteoporosis among men. (b) Receiver operating characteristic analysis of the ASM/height^2 for osteoporosis among women.

bone mass is closer in men than in women[24-26]. The sex distinction in the relationship between muscle and bone can be explained by sex-specific effects of sex hormones. In men, changes in bone and muscle are controlled by elevated testosterone and insulin-like growth factor-1 level, which lead to increased muscle strength and mass, whereas in women, higher levels of estrogen lead to bone mass tending to growth more rapidly in relation to muscle[24,25]. Aging causes muscle and bone loss in both men and women; and the relationship between muscle and bone mass is influenced by sex differences in the rate of muscle and bone loss[26]. In particular, age-related declines in insulin-like growth factor-1 and testosterone levels might result in bone and muscle loss in men, whereas the absolute level and degree of decline in testosterone in women are much lower, and the muscle mass can be relatively preserved. Furthermore, mechanical stress and estrogen have a common pathway involving estrogen receptor α, and a decrease in estrogen receptor α reduces the ability of mechanical stress to induce an osteogenic response[27-29]. This resetting of mechanical parameters caused by estrogen deficiency can explain the decoupling between mass of muscle and BMD in women, whereas the relationship between muscle mass and actual BMD is stronger in men.

However, the current work had some limitations. First, the causal relationship between ASM/height^2 and BMD was difficult to assess in this cross-sectional study. As this study was based on the previous data, several vital parameters received limited analysis, which affects control selection. Second, we did not assess the

strength of muscle and the degree of muscle function. Muscle strength and physical performance are considered to be components of sarcopenia according to the modern definition of the European Working Group on Sarcopenia in the Elderly[7]. Assessment of physical performance and muscle strength is also very important in the assessment of activities of daily living. In further research, we will use physical performance and muscle strength as the independent variables to determine the relationship between sarcopenia and osteoporosis. Third, in the present study population, blood glycemic control was poor, so there was no subgroup analysis of blood glucose levels. Further research is required to examine the relationship between osteoporosis and sarcopenia considering the influence of blood glucose levels. Fourth, some parameters that might affect the results have been ignored in the present study (e.g., physical activity, dietary habits, estrogen level, menopausal status).

To conclude, we report the first study that shows lower ASM/height^2 is strongly associated with osteoporosis and low BMD in patients with type 2 diabetes mellitus. The risk of osteoporosis was increased when the diagnostic cut-off value of sarcopenia was 7.87 kg/m^2 in men and 5.94 kg/m^2 in women, respectively.

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DISCLOSURE

The authors declare no conflict of interest.

Approval of the research protocol: This study has been approved by the Ethics Committee of the Second Affiliated Hospital of Wenzhou Medical University.

Informed Consent: The written informed consent of all subjects was obtained following the Declaration of Helsinki.

Approval date of Registry and the Registration No. of the study/trial: No. LCKY2017-21, date: July 2017.

Animal Studies: N/A

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