Reduced muscle mass and accumulation of visceral fat are independently associated with increased arterial stiffness in postmenopausal women with type 2 diabetes mellitus

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Abstract

Background: Several studies showed that sarcopenia and visceral obesity are associated with arterial stiffness. Thus, their coexistence may be a crucial risk factor of arteriosclerosis. However, little is known about the cross relationships among muscle mass, visceral fat mass, and arterial stiffness in type 2 diabetes mellitus (T2DM).

Methods: We recruited 97 postmenopausal women with T2DM and examine the association of muscle mass and visceral fat mass with brachial-ankle pulse wave velocity (baPWV). Relative skeletal muscle mass index (RSMI) and %trunk fat were evaluated by whole body dual-energy x-ray absorptiometry. Subcutaneous and visceral fat areas were measured by computed tomography.

Results: Multiple regression analyses adjusted for age, duration of T2DM, systolic blood pressure, body mass index, HbA1c, serum creatinine, low-density lipoprotein-cholesterol, uric acid, and the usage of anti-hypertensive drug showed that RSMI was negatively associated with baPWV (β=-0.40, p=0.027), while %trunk fat and visceral fat area were positively associated with it (β=0.29, p=0.004 and β=0.51, p=0.001, respectively). Moreover, after additional adjustment for RSMI, %trunk fat and visceral fat area were positively associated with baPWV (β=0.26, p=0.010 and β=0.46, p=0.003,

respectively) although the association between RSMI and baPWV became marginal after additional adjustment for %trunk fat or visceral fat area (β=-0.30, *p*=0.146 and β=-0.30, *p*=0.085, respectively).

Conclusions: Reduced muscle mass and increased visceral fat are independently associated with increased arterial stiffness in postmenopausal women with T2DM.

Introduction

Type 2 diabetes mellitus (T2DM) is considered as a worldwide important problem because it deteriorates the quality of life and mortality of the patients [1]. Moreover, the prevalence of T2DM is increasing in the elderly population; therefore, it is a very important issue how elderly patients with T2DM should be managed. Recently, sarcopenia has been recognized as one of diabetic complications [2-5]. Asian Working Group for Sarcopenia (AWGS) recently reported that relative skeletal muscle mass index (RSMI), gait speed and handgrip strength are necessary to diagnose sarcopenia [6]. With the aging of the population, sarcopenia is a serious complication with the progressive loss of skeletal muscle mass and function, resulting in frailty and bedridden in elderly patients. On the other hand, the incidence of cardiovascular disease (CVD) in patients with T2DM is known to be elevated by 2 to 3 times compared to non-diabetic subjects [7, 8]. Although sarcopenia and CVD are traditionally viewed as separate entities that increase in prevalence with aging, several clinical studies showed the association between muscle mass and atherosclerosis.

Previously, the Health ABC study, a large scale observational cohort study with older Americans (70-79 years), showed an independent negative association between arterial stiffening

evaluated by carotid-femoral pulse wave velocity (PWV) and skeletal muscle decline [9]. In addition, a cross-sectional study using healthy middle-aged to elderly Japanese men showed that thigh muscle cross-sectional area corrected by body weight was significantly and negatively associated with carotid intima-media thickness and brachial-ankle PWV (baPWV) independently of confounding factors such as age, body height, physical activity, and free testosterone [10]. Even though the pathophysiological mechanism underlying the association between sarcopenia and atherosclerosis have not been fully identified, accumulation of advanced glycation end products (AGEs), which are generated by sequential nonenzymatic chemical glycation of proteins [11] and increased in patients with T2DM [12], may be involved in both diseases [12-15]. Therefore, it is suggested that diabetes-related sarcopenia and atherosclerosis are deeply associated in diabetic patients.

Visceral fat accumulation is well-known to increase the risk of atherosclerotic diseases. Recently, it is recognized that sarcopenia often coexists with visceral obesity, which is called sarcopenic obesity, in elderly subjects. Previous studies have shown that sarcopenic obesity increased the risk of mortality [16-18]. These findings suggest that sarcopenia and visceral obesity are independently and additively associated with the risk of CVD. In the present study, we therefore

aimed to investigate the independent association of RSMI and visceral fat mass with arterial stiffness in patients with T2DM.

Subjects and Methods

Subjects

The subjects in this cross-sectional study were 97 Japanese postmenopausal women with T2DM (age; 65.2 ± 8.9 years). We consecutively enrolled the subjects who visited Shimane University Hospital for evaluation or treatment of T2DM. All participants were postmenopausal women without spontaneous menses for more than 1 year. Patients with renal dysfunction [estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2], nutritional derangements and arterial fibrillation were excluded from this study. We also excluded patients with peripheral artery disease showing ankle-brachial index < 0.9 [19]. There were 5 smokers among the subjects. All 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 and complied with the Helsinki declaration.

Anthropometric and biochemical measurements

Body height (cm) was measured with a Martin metal anthropometer to the nearest 0.1 cm

according to the standard technique, and body weight (kg) was measured using a medical electronic scale and recorded with 0.05 kg precision with the subject wearing light clothes. Body mass index (BMI; kg/m^2) was calculated by the following formula; weight/height in $meter^2$. Blood pressure (BP) (mmHg) was measured after a 5-minute rest in the supine position using mercury sphygmomanometer.

After overnight fasting, serum samples were collected. Biochemical markers were measured by standard methods as previously described [20, 21]. HbA1c was determined by high performance liquid chromatography. The value for HbA1c was estimated as an NGSP (National Glycohemoglobin Standaridization Program) equivalent value calculated by the formula: HbA1c (%) = HbA1c (JDS) (Japan Diabetes Society) (%) + 0.4% [22]. High density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C), triglyceride (TG), fasting plasma glucose (FPG), albumin, and creatinine were evaluated using standard enzymatic methods.

Measurements of muscle mass and fat mass by whole body dual-energy x-ray absorptiometry

Lean body mass of arms and legs, appendicular skeletal muscle mass (ASM) as well

as %trunk fat were evaluated by whole body dual-energy x-ray absorptiometry (DXA) (QDR-4500, Hologic co., Bedford, MA). RSMI was calculated by following formula; ASM/height^2, as previously described [23, 24].

Measurement of visceral and subcutaneous fat area by computed tomography

As previously described [25], visceral and subcutaneous fat areas at the level of the umbilicus were measured using commercially available CT (Toshiba medical systems, Tokyo, Japan), which determined adipose tissue area electronically by setting the attenuation values for the region of interest within a range of -150 and -50 Hounsfield units. Visceral fat area and subcutaneous fat area were determined separately with the use of a trace function, which manually defined the boundary between the visceral and subcutaneous fat with a cursor.

Measurement of baPWV

baPWV was measured using the VaSera VS-1000 (Fukuda DenshiTokyo, Japan), an automated recording device that calculates the time delay between two pulse waves recorded

simultaneously as previously described [26, 27]. Coefficients of variations of measurements of L- and R-PWV were 1.37 and 1.31%, respectively. In the present study, the measurement of baPWV was performed separately from the blood collection so that the participant would not have extra stress. The mean of the right and left baPWV was used in the analysis. There was a highly significant correlation between the right and left baPWV ($r=0.976$, $p<0.001$).

Statistical analysis

Data are expressed as mean ± SD. Pearson's correlation coefficient was used in univariate analyses. Multiple logistic regression analysis was used for multivariate analysis to adjust confounding factors. All analyses were carried out using statistical computer programs, StatView (Abacus Concepts, Berkeley, CA) and IBM SPSS version 19. A p value <0.05 was considered to be significant.

Results

Background data of the subjects and simple correlations of muscular and fatty parameters with various parameters

Clinical characteristics of the subjects are shown in Table 1. The number of patients who had a history CVD, and who took antihypertensive drugs or statin were 8, 48 and 34, respectively. Nineteen, 11, 5, 9, 10 and 19 subjects had been taking sulfonylureas, metformin, thiazolidines, dipeptidyl peptidase-4 inhibitors, α-glucosidase inhibitors and insulins, respectively.

First, we examined simple correlations of muscular and fatty parameters with various parameters including baPWV (Table 2). RSMI was significantly and positively correlated with BMI, subcutaneous fat area and visceral fat area (r=0.85, $p<0.001$, r=0.68, $p<0.001$ and r=0.63, $p<0.001$, respectively) and negatively with baPWV (r=-0.25, $p=0.013$). %trunk fat was significantly and positively correlated with BMI, subcutaneous fat area and visceral fat area (r=0.37, $p<0.001$, r=0.50, $p<0.001$ and r=0.59, $p<0.001$, respectively) and negatively with HDL-C (r=-0.43, $p<0.001$). Subcutaneous fat area was significantly and positively correlated with BMI, systolic BP, diastolic BP, uric acid and visceral fat area (r=0.88, $p<0.001$, r=0.27, $p=0.007$, r=0.29, $p=0.004$, r=0.28,

p=0.007 and r=0.80, p<0.001, respectively) and negatively with age and HDL-C (r=-0.25, p=0.012 and r=-0.25, p=0.013, respectively). Visceral fat area was significantly and positively correlated with BMI, dBP and uric acid (r=0.80, p<0.001, r=0.25, p=0.013 and r=0.32, p=0.001, respectively) and negatively with FPG and HDL-C (r=-0.24, p=0.017 and r=-0.41, p<0.001, respectively).

Association between muscular or fatty parameters and baPWV

Next, multiple regression analyses adjusted for traditional risk factors of CVD such as age, duration of T2DM, systolic BP, BMI, HbA1c, serum creatinine, LDL-C, and uric acid as well as the usage of anti-hypertensive drug were performed (Table 3). RSMI was significantly and negatively associated with baPWV (β=-0.40, p=0.027). In contrast, %trunk fat and visceral fat area were significantly and positively correlated with baPWV (β=0.29, p=0.004 and β=0.51, p=0.001, respectively). After additional adjustment for %trunk fat or visceral fat area, the association between RSMI and baPWV became marginal (β=-0.30, p=0.146 and β=-0.30, p=0.085, respectively). Moreover, after additional adjustment for RSMI, %trunk fat and visceral fat area were still significantly and positively associated with baPWV (β=0.26, p=0.010 and β=0.46, p=0.003,

respectively). Finally, receiver operation curve analyses were performed to examine the cut-off values of RSMI, %trunk fat, and visceral fat area, defined as baPWV > 18.00 m/sec [28]. As shown in Table 4 and Figure 1, the predict value of RSMI with respect to baPWV > 18.00 m/sec was 5.73 kg/m^2 (sensitivity 66.7%, specificity 78.8%, area under the curve 0.745, 95% confidence interval 0.638-0.852, *p*=0.006). The predict value of %trunk fat and visceral fat area were 52.3% and 57.0 cm^2, but the associations were not significant (p=0.490 and p=0.913, respectively).

Discussion

The present study showed that RSMI was negatively associated with baPWV after adjustment for traditional risk factors of CVD in postmenopausal women with T2DM. Moreover, %trunk fat and visceral fat area were positively associated with baPWV even after adjustment for RSMI. These findings indicate that muscle mass reduction and visceral fat accumulation, which are components of sarcopenic obesity, are independently associated with the progress of arterial stiffness in the population.

Recently, Anoop et al. reported a cross-sectional study showing that high body fat and low muscle mass evaluated by leg-to-leg bioelectrical impedance method were associated with increased carotid-femoral PWV in 58 female (age; 56.1 ± 8.8 years) and 110 male (age; 52.7 ± 10.4 years) Asian Indians with T2DM [28]. Of interest, they reported that there are sex differences in the association of fat mass and muscle mass with PWV. PWV was significantly and positively correlated with adiposity measures only in women, and it was significantly and negatively correlated with most measures of fat free mass in men, and only in right and left leg fat free mass in women. There are several strength points of the present study. Although the previous study reported

simple correlation, we performed multiple regression analyses adjusting for various risk factors of CVD. Moreover, we focused on the association in postmenopausal women although we couldn't investigate the sex differences, and the number of subjects was relatively larger in the present study than in the previous one [29]. Furthermore, we evaluated muscle mass and trunk fat by using DXA as well as measured subcutaneous and visceral fat area separately by using CT scan, which are known to be more accurate techniques for quantification of muscle and fat mass [23, 30].

Previous studies showed that AGEs directly induced arterial stiffness and increase CVD-mortality independent of traditional CVD risk factors in women with T2DM [31-33]. Moreover, we recently demonstrated that AGEs directly inhibited myogenesis of myoblastic C2C12 cells [14]. In addition, our clinical study showed that serum level of pentosidine, one of serum AGEs, was inversely associated with muscle mass in postmenopausal women with T2DM [13]. These findings indicate that AGEs can be common aggravating factors for arterial stiffness and muscle mass reduction in postmenopausal women with T2DM. On the other hand, it has been shown that myokines such as irisin and follistatin-like 1, which are produced from skeletal muscle, affect arteriosclerosis [34, 35]. In these studies, serum irisin levels were lower in young patients

with myocardial infarction, and follistatin-like 1 protected against the progression of vascular diseases by suppression of the proliferation of vascular smooth muscle cells [34, 35]. These findings suggest that decrease in myokines caused by loss of muscle might induce arterial stiffness. Although there are no evidence, it is conceivable that arterial stiffness may affect muscle mass. Decrease in muscle blood flow induced by arterial stiffness reduces supply of oxygen and nutrient to muscle, leading to loss of muscle mass. Therefore, there is a cross relationship between arteriosclerosis and sarcopenia though further studies are necessary to clarify the underlying mechanism.

Of note, the present study showed that %trunk fat and visceral fat area were positively associated with baPWV. These are not surprising findings because numerous studies have shown that visceral fat accumulation is a risk factor of atherosclerosis. However, the independent association of RSMI and %trunk fat with baPWV may indicate that sarcopenic obesity is a critical important risk factor of arteriosclerosis in postmenopausal women with T2DM. Fortunately, %trunk fat can be simultaneously evaluated when whole body DXA is examined for assessing sarcopenia. Thus, we should be aware of coexistence of sarcopenia and visceral obesity in a patient.

There are several limitations in our study. First, the sample size was not large enough to

make definite conclusions. Second, we analyzed only subjects who visited our hospital, a tertiary center, for treatment of diabetes mellitus. Therefore, the participants enrolled in this study might have relatively severe states of the disorders and might not be representative of Japanese patients. Third, we also need to investigate the association in men with T2DM. Forth, we did not examine subjects without diabetes. However, it is important that the present study firstly showed the significant association between RSMI and baPWV in postmenopausal women with diabetes even after adjusting for various risk factors for atherosclerosis. Fifth, histories of CVD, malignant disorders, and chronic obstructive lung diseases as well as treatments with statin, and lifestyles such as smoking status and exercise might influence the results of the present study. Sixth, we need to increase the study population of postmenopausal women with T2DM but without hypertension in future, because we can't completely exclude the impact of medication for hypertension on the association. Seventh, we can't diagnose the presence of sarcopenia in this study because we did not examine the measurements of gait speed or handgrip test. Finally, we need to examine not only cross-sectional studies but also longitudinal ones to understand the causal relationship between atherosclerosis and sarcopenia in T2DM.

In conclusion, the present study for the first time showed that reduced muscle mass and increased visceral fat are independently associated with increased arterial stiffness in postmenopausal women with T2DM.

Conflict of interest

All authors (KT, IK and TS) have any conflict of interest.

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Authors' roles: Conceived and designed the study: IK. Corrected and analyzed the data: KT and IK. Contributed equipment/materials: TS. Wrote the paper: KT and IK. Approving final version: All authors.

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follistatin-like 1 functions to reduce neointimal formation after vascular injury. Cardiovasc Res 2014;103:111-20.

Table 1 Baseline characteristics of subjects

Number of subjects	97		
Age (years)	65.2	±	8.9
Duration of T2DM (years)	9.9	±	9.8
BMI (kg/m^2)	24.3	±	5.2
Serum albumin (g/L)	40.5	±	4.4
Serum creatinine (μmol/L)	54.5	±	16.4
sBP (mmHg)	129.0	±	19.5
dBP (mmHg)	75.0	±	11.1
FPG (mmol/L)	8.45	±	3.43
HbA1c (%)	8.3	±	2.6
HbA1c (mmol/mol)	67	±	28
LDL-C (mmol/L)	3.10	±	0.91
HDL-C (mmol/L)	1.52	±	0.40
TG (mmol/L)	1.25	±	0.51
Uric acid (μmol/L)	277.4	±	73.9
baPWV (m/sec)	15.0	±	2.8
RSMI (kg/m^2)	6.38	±	1.08
%trunk fat (%)	50.3	±	6.9
Subcutaneous fat area (cm^2)	180.8	±	100.2
Visceral fat area (cm^2)	100.2	±	58.0

T2DM, type 2 diabetes mellitus; BMI, body mass index; sBP, systolic blood pressure; dBP, diastolic blood pressure; FPG, fasting plasma glucose; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; baPWV, brachial-ankle pulse wave velocity; RSMI, relative skeletal muscle mass index

Table 2 Simple correlations of RSMI, %trunk fat and visceral fat area with various parameters

	RSMI		%trunk fat		Subcutaneous fat area		Visceral fat area	
	r	*p*	r	*p*	r	*p*	r	*p*
Age	-0.12	0.229	-0.09	0.446	-0.25	0.012	-0.18	0.086
Duration of T2DM	0.00	0.996	-0.12	0.352	-0.07	0.544	-0.03	0.772
BMI	0.85	<0.001	0.37	<0.001	0.88	<0.001	0.80	<0.001
Serum albumin	-0.14	0.160	0.10	0.361	0.04	0.723	0.05	0.596
Serum creatinine	0.04	0.674	-0.06	0.571	0.03	0.766	0.05	0.665
sBP	0.13	0.214	0.12	0.267	0.27	0.007	0.14	0.163
dBP	0.19	0.066	0.18	0.108	0.29	0.004	0.25	0.013
FPG	-0.17	0.092	-0.12	0.281	-0.18	0.073	-0.24	0.017
HbA1c	-0.07	0.497	0.00	0.977	-0.10	0.321	-0.17	0.088
LDL-C	0.15	0.135	-0.10	0.379	0.03	0.742	-0.07	0.506
HDL-C	-0.15	0.155	-0.43	<0.001	-0.25	0.013	-0.41	<0.001
TG	-0.05	0.637	0.21	0.058	0.05	0.622	0.13	0.223
Uric acid	0.14	0.178	0.13	0.240	0.28	0.007	0.32	0.001
baPWV	-0.25	0.013	0.22	0.049	-0.17	0.103	-0.03	0.767
RSMI		-		-		-		-
%Trunk fat	0.21	0.058		-		-		-
Subcutaneous fat area	0.68	<0.001	0.50	<0.001		-		-
Visceral fat area	0.63	<0.001	0.59	<0.001	0.80	<0.001		-

T2DM, type 2 diabetes mellitus; BMI, body mass index; sBP, systolic blood pressure; dBP, diastolic blood pressure; FPG, fasting plasma glucose; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; baPWV, brachial-ankle pulse wave velocity; RSMI, relative skeletal muscle mass index

Table 3 Multiple regression analysis between RSMI, %trunk fat, or visceral fat area and baPWV

	RSMI		%trunk fat		Subcutaneous fat area		Visceral fat area	
	β	*p*	β	*p*	β	*p*	β	*p*
Model 1	-0.40	0.027	0.29	0.004	0.25	0.223	0.51	0.001
Model 2	-0.30	0.146						
Model 3	-0.30	0.085						
Model 4			0.26	0.010	0.18	0.385	0.46	0.003

Model 1; adjusted for age, duration of type 2 diabetes mellitus, systolic blood pressure, body mass index, HbA1c, serum creatinine, LDL-C, uric acid, and the presence of anti-hypertensive drug

Model 2; model 1 plus %trunk fat

Model 3; model 1 plus visceral fat area

Model 4; model 1 plus RSMI

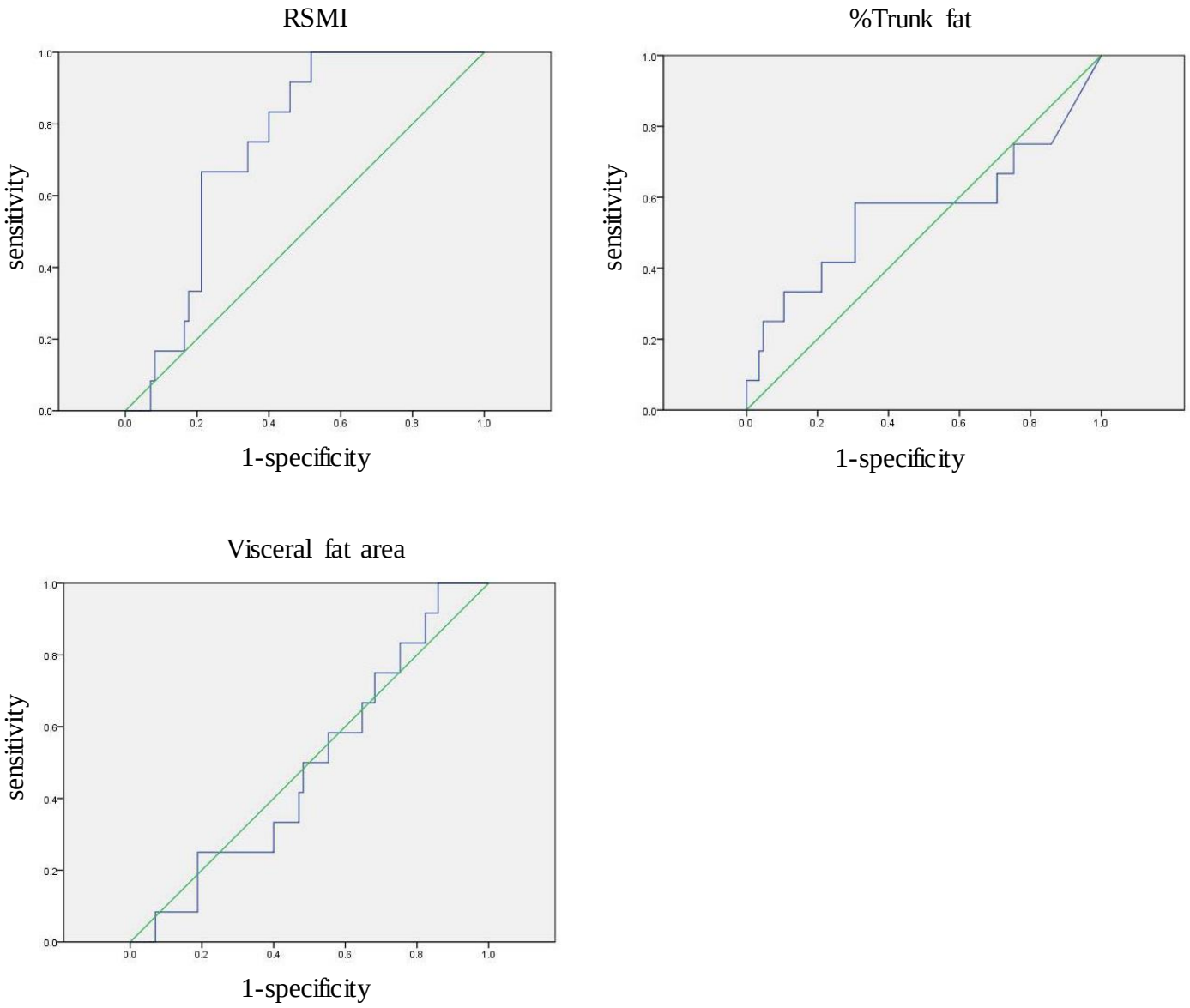
RSMI, relative skeletal muscle mass index; baPWV, brachial-ankle pulse wave velocity

Table 4 ROC analysis between arterial stiffness versus RSMI, %trunk fat and visceral fat area

	cut-off value	sensitivity	specificity	AUC	95% CI	P-value
RSMI	5.73	66.7	78.8	0.745	0.638-0.852	0.006
%Trunk fat	52.3	58.3	30.6	0.562	0.350-0.774	0.490
Visceral fat area	57.0	83.3	24.7	0.490	0.332-0.648	0.913

AUC, area under the curve; 95% CI, 95% confidence interval

Figure 1


RSMI
sensitivity
1-specificity
%Trunk fat
sensitivity
1-specificity
Visceral fat area
sensitivity
1-specificity