

Presarcopenia Is an Independent Risk Factor for Carotid Atherosclerosis in Chinese Population with Metabolic Syndrome

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Purpose: To investigate the impacts of skeletal muscle mass on carotid atherosclerosis in Chinese adults with metabolic syndrome (MetS).

Methods: One hundred and ninety-five subjects with MetS had the waist-to-height ratio (WHTR) ≥ 0.5 for all. One hundred and eighty-four subjects without MetS were divided into 2 groups: Non-Mets obese group (WHTR ≥ 0.5 , $n = 118$) and Non-MetS control group (WHTR < 0.5 , $n = 66$). All the groups had no difference in age. Appendicular skeletal muscle mass was acquired and skeletal muscle mass index (SMI) was calculated. Carotid intima-media thickness (IMT) was assessed by ultrasonography. Each group was stratified according to the presence or absence of presarcopenia.

Results: While most parameters showed an increasing trend with WHTR and MetS in both genders, SMI and HDL-C showed a decreasing trend. The prevalence of carotid atherosclerosis showed the same increasing trend. Multivariate logistic regression analyses showed SBP and presarcopenia were both independent risk factors for carotid atherosclerosis in MetS (OR 1.026, $P < 0.001$; OR 2.788, $P = 0.001$, respectively). There was no significant difference in IMT among the three groups with preserved muscle mass whether the participants suffered from obesity or MetS, while there was a significant difference between the two groups with presarcopenia (in male $P = 0.020$, in female $P = 0.009$, respectively). The area under the ROC curve (AUC) was 0.641 ($P < 0.001$) for presarcopenia.

Conclusion: Obesity was a risk factor for sarcopenia independent of age, especially in subjects with metabolic syndrome. In individuals with MetS, our findings suggest that presarcopenia may be an independent risk factor for atherosclerosis and appendicular skeletal muscle mass had potential protective effects for carotid atherosclerosis regardless of gender.

Keywords: skeletal muscle mass, presarcopenia, metabolic syndrome, carotid atherosclerosis

Introduction

Sarcopenia was first proposed in 1989 to describe age-related decrease of muscle mass and used to be recognized as a geriatric syndrome.^{1,2} In 2010, the European Working Group on Sarcopenia in Older People (EWGSOP, the Sarcopenia Working Group) gave a new definition and suggested a conceptual staging as presarcopenia characterized by low muscle mass without impact on muscle strength or physical performance.³ Recently, the concept of sarcopenia is changing: it is now recognized not as an inevitable outcome of ageing, but as a disease condition which could be overcome.⁴ Sarcopenia is more prevalent among people with obesity and exists

with various comorbidities.^{3,4} Several cardiometabolic disorders, including diabetes mellitus, metabolic syndrome (MetS), and cardiovascular disease, have been associated with sarcopenia.

Obesity is reaching epidemic proportions with recent worldwide figures estimated at 1.4 billion and they are rising year by year.⁵ Obesity is now recognized as a chronic low-grade and systemic inflammatory state that predisposes to other chronic conditions including MetS.⁶ The MetS has been clearly demonstrated that the syndrome generally increases with advancing age and that it has a rising prevalence worldwide.^{7,8} The MetS and its constituent components have been reported to be risk factors for cardiovascular disease including atherosclerosis and increase cardiovascular morbidity and mortality.^{9,10} At present, insulin resistance,¹¹ mitochondrial genome-encoded protein expression disorder,¹² cross-talk of adipokines and myokines between adipose tissue, skeletal muscle and other organs,¹³ and inflammatory response⁶ may participate in the onset of a cardiovascular disease associated with MetS.

As one of the most important body compositions in metabolism, skeletal muscle is known to have a role in reversing the detrimental impact of MetS.¹³ Increased skeletal muscle mass can significantly reduce the risk of hypertension, dyslipidemia and type 2 diabetes.¹⁴ Recent studies have shown that sarcopenia and MetS usually coexist,^{15,16} which further increases the risk of cardiovascular disease in adults.¹⁷ Considering the concept that obesity was the common denominator between sarcopenia and MetS, a more robust investigation is necessary to determine the complex association of sarcopenia with MetS. Moreover, whether atherosclerosis associated with MetS is affected by skeletal muscle is still not fully understood.

Materials and Methods

Subjects

Participants for this investigation (n= 394) aged 24–85 years were recruited from the Qilu Hospital of Shandong University. One hundred and ninety-five subjects with MetS were defined by the International Diabetes Federation and the waist-to-height ratio (WHTR) ≥ 0.5 for all.^{7,18} One hundred and eighty-four subjects without MetS were further divided into 2 groups according to WHTR: Non-MetS obese group (WHTR ≥ 0.5 , n = 118) and Non-MetS control group (WHTR < 0.5, n = 66). All the groups had no difference in age. All participants provided written

informed consent, and the study protocol was approved by the medical ethics committee of Qilu Hospital of Shandong University. The ethics approval was given in compliance with the Declaration of Helsinki.

Data Collection

Anthropometric measurements were assessed. Standing height and body weight were measured according to the predetermined protocol. BMI was calculated as the body weight divided by the standing height squared (kg/m^2). Waist circumference and hip circumference were assessed with waist-hip ratio calculated. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured, then the difference value as pulse pressure (PP).

Blood samples were collected from the antecubital vein after the patients had fasted for at least 8 hrs. Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglyceride (TG) levels were measured. Fasting blood glucose and insulin concentrations, hemoglobin A1c (HbA1c) concentrations and uric acid (UA) were measured. HOMA-IR was calculated as multiply fasting blood glucose by insulin then divided by 22.5.¹⁹ HOMA-IR cut-off value was 2.5 to identify individuals with insulin resistance (IR).

Appendicular Skeletal Muscle Mass Index

ASM was acquired by anthropometric SM prediction formulas derived from MRI.²⁰ Most of the studies referring to sarcopenia were conducted mainly through dual-energy X-ray to obtain skeletal muscle mass, the main drawback of which is that the equipment is not portable and common for routine clinical practice, especially in ambulatory settings.^{3,21} As we know, MRI is a gold standard for estimating muscle mass in research,³ so we consulted the literature and chosen an anthropometric prediction model acquired from MRI for an alternative:

$$\text{ASM (kg)} = 0.244 \times \text{BW} + 7.80 \times \text{Ht} - 0.098 \times \text{age} + 6.6 \times \text{sex} + \text{race} - 3.3$$
, where sex = 1 for male and 0 for female, race = -1.2 for Asian, 1.4 for African American, and 0 for white or Hispanic.

The appendicular skeletal muscle mass index (ASMI) was calculated as follows: $\text{ASMI (\%)} = \text{total ASM (kg)} / \text{body weight (kg)} \times 100$, which was modified from the study of Janssen et al.^{22,23} Presarcopenia was defined as 1 standard deviation (SD) below the sex-specific average value of skeletal muscle mass of the reference group.^{16,23}

Carotid Artery Ultrasonography

Individuals underwent an ultrasound examination of the carotid artery according to the Asymptomatic Carotid Artery Plaque Study (ACAPS) protocol.²⁴ The bilateral common carotid arteries were examined by certified sonographers. Subsequently, IMT of the common and internal carotid arteries and bifurcations were measured. Carotid atherosclerosis was defined as a maximal IMT ≥ 1.0 mm.^{25–29} The measurements were made via B mode ultrasonography with a 5–10 MHz linear probe (GE vivid 7, USA).

Statistical Analysis

Statistical analyses were performed using SPSS 20.0 (SPSS, Chicago, IL). Continuous data were presented as mean \pm standard deviation. We evaluated differences in demographic characteristics among the 6 groups based on the WHTR and MetS using one-way ANOVA analysis for normally distributed variables, the Kruskal–Wallis test for skewed variables, and the χ^2 test for categorical variables. The association between metabolic disorders, presarcopenia and IMT was assessed binary logistic regression method. Multivariable logistic regression analyses models were used to assess the independent effect of SMI on the carotid atherosclerosis of MetS patients. Forward: LR selection method (with probability for entry being <0.10) and the backward: LR selection (with probability for entry and removal being 0.05 and 0.10, respectively) procedures were performed sequentially to select and validate potential diagnostic variables. $P < 0.05$ was considered significant. Variables with significant contributions to the IMT were plotted with the receiver-operating characteristic (ROC) curve.

Results

Baseline characteristics of all groups according to gender, WHTR and the presence of MetS were outlined in Table 1. For both males and females, the age had no differences among the three groups. In men, physical parameters (weight, BMI, waist, hip, WHR), metabolic parameters (cholesterol, LDL-C, triglyceride, UA, Glu, insulin, HbA1c, HOMA-IR) and carotid artery parameter (IMT) showed an increasing trend with WHTR and MetS. In women, physical parameters (SBP, DBP, PP, weight, BMI, waist, hip, WHR), metabolic parameters (cholesterol, LDL-C, triglyceride, UA, Glu, insulin, HbA1c, HOMA-IR) and carotid artery parameter (IMT) showed an increasing trend with WHTR and MetS. On the

contrary, SMI and HDL-C showed a decreasing trend both in men and women.

All parameters that differed significantly among the MetS groups, obese groups and control groups were introduced into the binary logistic regression model for univariate analyses. SBP, DBP, PP, waist circumference, cholesterol, triglyceride, LDL-c, IR and presarcopenia were left in the regression model 1 (Table 2). These parameters were further used for multivariate analyses. After validation with forward: LR selection and backward: LR selection, SBP and presarcopenia were left in the regression model 2, the odds ratios of SBP and presarcopenia for detecting carotid atherosclerosis were 1.026 and 2.788, respectively (Table 3).

According to the definition of presarcopenia and carotid atherosclerosis mentioned before, we stratified the study group to explore the relationship between presarcopenia and carotid atherosclerosis. As shown in Figure 1A, the prevalence of carotid atherosclerosis was significantly increased with increased WHTR and MetS in both genders. In female as shown in Figure 1B, there was significant difference in IMT between MetS-presarcopenia group and MetS-nonsarcopenia group ($P = 0.009$), MetS-presarcopenia group and obese-nonsarcopenia group ($P < 0.001$), MetS-presarcopenia group and obese-presarcopenia group ($P = 0.009$), MetS-presarcopenia group and control group ($P < 0.001$). In male, as shown in Figure 1C, there was a significant difference in IMT between MetS-presarcopenia group and obese-presarcopenia group ($P = 0.020$), MetS-presarcopenia group and control group ($P = 0.023$). This result suggests that both metabolic syndrome components and muscle mass play an important role in carotid atherosclerosis. There was no significant difference in IMT among the three groups with preserved muscle mass whether the participants suffered from obesity or MetS (MetS-nonsarcopenia group, obese-nonsarcopenia group and control group), while there was significant difference between the two groups with presarcopenia (MetS-presarcopenia group and obese-presarcopenia group), indicating that muscle mass may have a certain protective effect.

The diagnostic value of MetS parameters and presarcopenia for carotid atherosclerosis is outlined in Figure 2. Based on above results, ROC curves were made in all patients with all risk parameters and the area under the ROC curve (AUC) was 0.641 ($P < 0.001$) for presarcopenia, 0.692 ($P < 0.001$) for SBP, 0.667 ($P < 0.001$) for DBP, 0.627 ($P = 0.001$) for waist

Table I Demographic Characteristics and Clinical Parameters of the Study Population

	Female			Male		
	Non-MetS Control Group (WHTR<0.5)	Non-MetS Obese Group (WHTR≥0.5)	MetS Group (WHTR≥0.5)	Non-MetS Control Group (WHTR<0.5)	Non-MetS Obese Group (WHTR≥0.5)	MetS Group (WHTR≥0.5)
n	48	68	109	18	50	n=83
Age, years	53.26±8.12	53.76±9.00	56.28±6.83	50.50±7.88	51.70±10.15	49.90±9.66
SBP, mmHg	111.27±10.59	116.97±10.41	151.38±21.42*†	118.44±8.22	115.90±9.63	148.59±23.17*†
DBP, mmHg	72.58±7.33	75.01±6.18	91.62±13.61*†	76.33±7.93	78.44±5.86	97.42±13.36*†
PP, mmHg	38.69±7.88	41.96±8.89	59.72±15.27*†	42.11±4.27	37.46±6.97	51.23±16.30*†
Height, cm	160.08±5.01	158.12±4.23*	158.75±4.89	170.06±3.86	169.76±3.82	172.19±4.44†
Weight, Kg	56.61±6.62	63.71±7.49*	72.14±9.71*†	64.92±4.60	75.47±8.19*	88.64±15.20*†
BMI	22.06±2.05	25.45±2.58*	28.53±3.67*†	22.45±1.45	26.16±2.43*	29.84±4.66*†
Waist circumference, cm	74.17±4.13	86.49±6.04*	94.72±9.20*†	80.72±3.98	91.96±4.97*	102.95±9.79*†
Hip circumference, cm	93.50±6.07	100.57±5.64*	105.13±8.09*†	93.44±4.66	101.86±5.46*	107.06±9.52*†
WHR	0.79±0.04	0.86±0.04*	0.90±0.06*†	0.87±0.03	0.90±0.04*	0.96±0.05*†
Cholesterol, mmol/L	4.43±0.72	4.74±0.88	5.54±1.12*†	4.29±1.01	4.63±0.61	5.20±1.08*†
HDL-C, mmol/L	1.60±0.34	1.57±0.33	1.33±0.38*†	1.52±0.39	1.41±0.28	1.10±0.23*†
LDL-C, mmol/L	2.69±0.67	2.99±0.74	3.72±1.00*†	2.57±0.83	3.03±0.57	3.42±0.92*†
Triglyceride, mmol/L	0.92±0.31	1.11±0.50	2.16±1.41*†	0.95±0.44	1.13±0.37	2.45±1.12*†
UA, μmol/L	222.38±45.67	234.69±72.64	294.21±69.88*†	301.24±97.37	309.00±59.12	371.22±84.14*†
Glu, mmol/L	4.70±0.40	4.92±0.63	6.79±2.84*†	4.71±0.69	5.02±0.55	6.42±2.01*†
Insulin, μU/mL	9.71±3.50	11.79±5.34	19.23±8.19*†	7.27±1.36	11.26±5.03	21.89±12.97*†
HbA1c, %	4.53±0.20	4.71±0.37	5.56±1.37*†	4.50±0.29	4.65±0.30	5.30±0.94*†
HOMA-IR	2.01±0.89	2.65±1.38	5.81±3.65*†	1.54±0.40	2.55±1.31	6.27±4.60*†
IMT, mm	0.84±0.94	0.81±0.46	1.18±0.81*†	0.68±0.71	0.81±0.75	1.20±0.90*†
ASMI, %	30.27±1.84	28.41±1.59*	27.78±1.44*†	40.51±1.47	38.14±1.81*	36.62±1.63*†

Notes: In female, * $P<0.05$ compared with Non-MetS control group (WHTR<0.5); † $P<0.05$ compared with Non-MetS obese group (WHTR≥0.5). In male, * $P<0.05$ compared with Non-MetS control group (WHTR<0.5); † $P<0.05$ compared with Non-MetS obese group (WHTR≥0.5).

Abbreviations: MetS, metabolic syndrome; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; BMI, body mass index; WHR, waist-hip ratio; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; UA, uric acid; Glu, glucose; HbA1c, hemoglobin A1c; IMT, intima-media thickness; ASMI, appendicular skeletal muscle mass.

circumference, 0.610 ($P = 0.005$) for TC, 0.614 ($P = 0.003$) for LDL-C, 0.610 ($P = 0.005$) for triglyceride, 0.569 ($P = 0.079$) for insulin resistance, respectively.

Discussion

This population-based study demonstrated that obesity was a risk factor for muscle mass loss independent of age, especially in subjects with metabolic syndrome. Furthermore, in subjects with simple obesity, the reduction in muscle mass did not affect carotid atherosclerosis, and the reduction in muscle mass in the case of metabolic syndrome promoted carotid atherosclerosis. Muscle content had potential protective effects on carotid atherosclerosis regardless of gender.

WHTR, as a simple screening tool, was reliable as BMI and waist circumference in identifying metabolic and

vascular differences between populations.³⁰ In a recent study, WHTR appeared to be the best indicator of dyslipidemia, hyperglycemia, and CVDs.¹⁸ So in the present study, we used this parameter as a cutoff of control group and obese group. Consistent with the previous finding,⁴ accelerated muscle loss occurs in people with diabetes and obesity. The present study also found that as the severity of disease increased, from simple obesity to metabolic syndrome, SMI was gradually decreasing, and the incidence of carotid atherosclerosis was gradually increasing.

The MetS are highly associated with increased morbidity and mortality of atherosclerotic cardiovascular disease (ASCVD). Large-scale population studies have shown that obesity, elevated triglycerides, and LDL-C, hypertension, and hyperglycemia in metabolic syndrome

Table 2 Multivariate Logistic Regression Analyses Model 1 in Patients with MetS and Healthy Controls

Factors	β	SE	Wals	P	OR	95% CI
SBP, mmHg	0.024	0.005	16.947	0.000	1.024	1.014–1.035
DBP, mmHg	0.030	0.009	12.224	0.000	1.031	1.013–1.048
PP, mmHg	0.028	0.008	12.214	0.000	1.029	1.013–1.045
Waist circumference, cm	0.034	0.011	10.270	0.001	1.035	1.013–1.056
Cholesterol, mmol/L	0.311	0.119	6.862	0.009	1.365	1.081–1.723
Triglyceride, mmol/L	0.237	0.116	4.198	0.040	1.268	1.010–1.591
LDL-C, mmol/L	0.385	0.138	7.777	0.005	1.470	1.121–1.927
IR	0.604	0.293	4.233	0.040	1.829	1.029–3.251
Presarcopenia	1.140	0.266	18.342	0.000	3.126	1.855–5.266

Abbreviations: CI, confidence interval; OR, odds ratio; SE, standard error; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; LDL-C, low-density lipoprotein cholesterol; IR, insulin resistance.

Table 3 Multivariate Logistic Regression Analyses Model 2 in Patients with MetS and Healthy Controls

Factors	β	SE	Wals	P	OR	95% CI
SBP, mmHg	0.021	0.006	13.549	<0.001	1.026	1.010–1.033
Presarcopenia	1.025	0.296	11.960	0.001	2.788	1.559–4.985
Constant	−4.497	0.807	31.040	<0.001	0.011	

Abbreviations: CI, confidence interval; OR, odds ratio; SE, standard error; SBP, systolic blood pressure.

all contribute to coronary atherosclerosis.⁹ Although the pathogenic processes of developing presarcopenia have not been fully understood, presarcopenia and MetS may share common pathophysiologic mechanisms.⁶ Increased insulin resistance, which is a major causative factor of MetS,³¹ can also aggravate presarcopenia via mitochondrial dysfunction³² and the degradation of muscle protein by the activation of the ubiquitin-proteasome proteolytic pathway.^{33,34} Additionally, insulin resistance is the key link between metabolic syndrome and ASCVD.^{31,35,36}

Sanada et al¹⁷ have shown that the coexistence of sarcopenia and MetS in adult Japanese women significantly increases the risks of cardiovascular disease. Studies have also shown that skeletal muscle mass can affect carotid intima thickness^{37,38} and is closely related to the occurrence of subclinical atherosclerosis.^{39–42} The present study suggested that both metabolic syndrome components and muscle mass loss play an important role in carotid atherosclerosis. Binary logistic regression analysis showed that SBP and presarcopenia were both

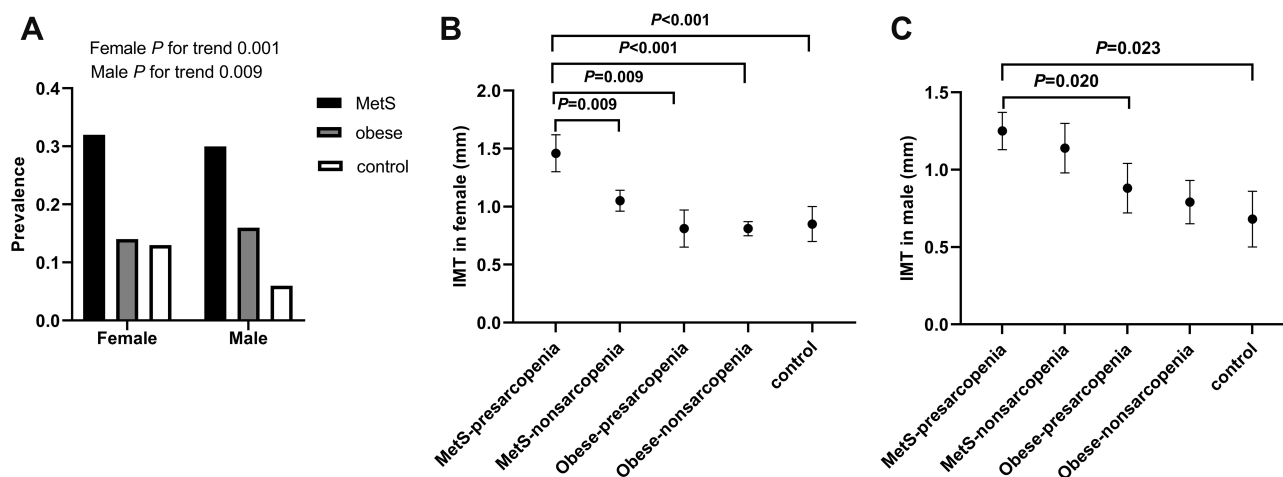


Figure 1 (A) Comparison of the prevalence of carotid atherosclerosis in both genders. (B) and (C) Comparison of IMT among the study groups stratified according to ASMI in both genders.

Abbreviations: MetS, metabolic syndrome; IMT, intima-media thickness.

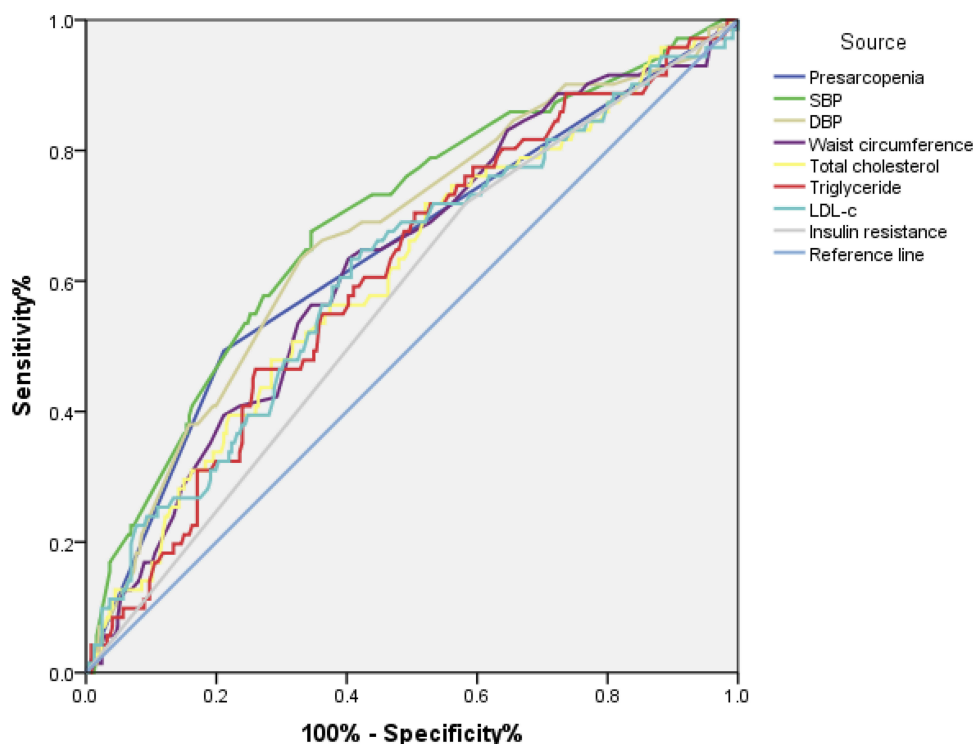


Figure 2 Receiver operating characteristic (ROC) curve analysis of different parameters for predicting carotid atherosclerosis. The area under the curve (AUC) was 0.641 for presarcopenia ($P < 0.001$), 0.692 for SBP ($P < 0.001$), 0.667 for DBP ($P < 0.001$), 0.627 for waist circumference ($P = 0.001$), 0.610 for TC ($P = 0.005$), 0.614 for LDL-C ($P = 0.003$), 0.610 for triglyceride ($P = 0.005$), 0.569 for insulin resistance ($P = 0.079$), respectively.

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol.

independent risk factors for carotid atherosclerosis. The AUC for presarcopenia confirmed it.

According to our findings, muscle mass declines with advancing obese and metabolic disorders, and that this liaison favors the obesity-related and metabolism-related acceleration of atherogenesis.⁴³ Obesity and sarcopenia influenced each other, which may lead to a vicious cycle. The reduction in physical activity due to sarcopenia induced decreased energy expenditure and increased the possibility of obesity. As visceral obesity increased, catabolic inflammatory responses were upregulated and contributed to reduced muscle mass.¹³ Moreover, our study examined the differential effects of presarcopenia and metabolic disorders on the risks of carotid atherosclerosis. That is, despite the gender, compared with individuals with preserved skeletal muscle mass, subjects with presarcopenia had a higher risk of carotid atherosclerosis independent of the status of obesity as well as metabolic syndrome.

Sarcopenia lacks early diagnostic tools and debate is continuing about how best to define and measure sarcopenia. These results were encouraging. Firstly, it was verified that the protective effect of muscle mass in the development of atherosclerosis and would encourage people to

pay attention to the function of skeletal muscle mass in the early stage of the disease. Secondly, it could promote the development of a simple mobile phone application to monitor muscle mass anytime and anywhere.

Our study had some limitations that warrant discussion. First of all, this study stems from a cross-sectional study, which allows no conclusion on cause and effect. Secondly, the sample size of this study is relatively small, and it has certain limitations in the wide-scale promotion of the research results. Thirdly, the determination of the muscle mass of the subjects in this study is based on the anthropometric formula calculation method, instead of the dual-energy X-ray, bioelectrical impedance and other objective methods by means of instruments and equipment. Because the formula applies to a different population, there may be some deviations between the calculation results and the real values. Ideally, using an objective method such as dual-energy X-ray to carry out a follow-up study in a larger population may help to further clarify the relationship between muscle mass and metabolism syndrome atherosclerosis.

In conclusion, obesity was a risk factor for muscle mass loss independent of age, especially in subjects with

metabolic syndrome. Furthermore, despite the gender, subjects with presarcopenia had a higher risk of carotid atherosclerosis independent of the status of obesity as well as metabolic syndrome compared with individuals with preserved skeletal muscle mass. Muscle content had potential protective effects on carotid atherosclerosis regardless of gender.

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Disclosure

The authors report no conflicts of interest in this work.

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