

# World Journal of *Diabetes*

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**AIMS AND SCOPE**

The primary aim of *World Journal of Diabetes* (*WJD*, *World J Diabetes*) is to provide scholars and readers from various fields of diabetes with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

*WJD* mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

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## Retrospective Study

# Myosteatosi s is associated with coronary artery calcification in patients with type 2 diabetes

Fu-Peng Liu, Mu-Jie Guo, Qing Yang, Yan-Ying Li, Yan-Gang Wang, Mei Zhang

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## Abstract

### BACKGROUND

Myosteatosi s, rather than low muscle mass, is the primary etiologic factor of sarcopenia in patients with type 2 diabetes mellitus (T2DM). Myosteatosi s may lead to a series of metabolic dysfunctions, such as insulin resistance, systematic inflammation, and oxidative stress, and all these dysfunctions are closely associated with the acceleration of T2DM and atherosclerosis.

### AIM

To investigate the association between myosteatosi s and coronary artery calcification (CAC) in patients with T2DM.

### METHODS

Patients with T2DM, who had not experienced major cardiovascular events and had undergone both abdominal and thoracic computed tomography (CT) scans, were included. The mean skeletal muscle attenuation was assessed using abdominal CT images at the L3 level. The CAC score was determined from thoracic CT images using the Agatston scoring method. Myosteatosi s was diagnosed according to Martin's criteria. Severe CAC (SCAC) was defined when



the CAC score exceeded 300. Logistic regression and decision tree analyses were performed.

## RESULTS

A total of 652 patients with T2DM were enrolled. Among them, 167 (25.6%) patients had SCAC. Logistic regression analysis demonstrated that myosteatosi, age, duration of diabetes, cigarette smoking, and alcohol consumption were independent risk factors of SCAC. Myosteatosi was significantly associated with an increased risk of SCAC (OR = 2.381,  $P = 0.003$ ). The association between myosteatosi and SCAC was significant in the younger patients (OR = 2.672, 95%CI: 1.477-4.834,  $P = 0.002$ ), but not the older patients (OR = 1.456, 95%CI: 0.863-2.455,  $P = 0.188$ ), and was more prominent in the population with lower risks of atherosclerosis. The decision tree analyses prioritized older age as the primary variable for SCAC. In older patients, cigarette smoking was the main contributing factor for SCAC, while in younger patients, it was myosteatosi.

## CONCLUSION

Myosteatosi is a novel risk factor for atherosclerosis in patients with T2DM, especially in the population with younger ages and fewer traditional risk factors.

**Key Words:** Type 2 diabetes; Myosteatosi; Muscle quality; Coronary artery calcification; Atherosclerosis; Cardiovascular diseases

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**Core Tip:** Myosteatosi, rather than low muscle mass, is the primary etiologic factor of sarcopenia in patients with type 2 diabetes mellitus (T2DM). Myosteatosi may lead to a series of metabolic dysfunctions that are closely associated with the acceleration of T2DM and atherosclerosis. This study demonstrated that myosteatosi was a novel risk factor for atherosclerosis in patients with T2DM, especially in the population with younger ages and fewer traditional risk factors. Therefore, this indicates the potential benefit of initiating muscle-strengthening exercises and improving muscle quality at a younger age.

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## INTRODUCTION

The prevalence of diabetes, especially type 2 diabetes mellitus (T2DM), has been dramatically increasing in China, from 10.9% in 2013 to 12.4% in 2018, and atherosclerotic cardiovascular disease is the leading cause of mortality in these patients[1,2]. Myosteatosi, a marker of muscle quality, has been proposed as a novel risk factor for atherosclerotic cardiovascular diseases, independent of muscle mass[3-6]. Myosteatosi may lead to a series of metabolic dysfunctions, such as insulin resistance, systematic inflammation, and oxidative stress, and all these dysfunctions are closely associated with the acceleration of T2DM and atherosclerosis (Supplementary Figure 1)[3,7,8].

Computed tomography (CT) is considered the gold standard for myosteatosi measurement, and lower muscle radiodensity indicates higher fat infiltration (*i.e.*, myosteatosi)[9]. Recently, a large-sample study involving 20986 participants indicated that the patients with T2DM had significantly higher values of muscle mass but significantly lower values of muscle quality[10,11]. Therefore, low muscle quality rather than low muscle mass is the major characteristic change of skeletal muscle in patients with T2DM. Patients with T2DM have high risks of myosteatosi and atherosclerosis. However, the association between myosteatosi and coronary artery calcification (CAC) in this population has not been reported yet.

CAC score (CACS), which can be calculated with the Agatston scoring method, is considered a useful tool for identifying coronary atherosclerosis. The risk of coronary events in patients with CACS > 300 across various ethnic groups has a nearly 10-fold increase[12-14]. In Australia, CACS is used to help define the risk in the primary prevention of cardiovascular diseases[15]. The long-term (> 10 years) prognostic value of CACS in cardiovascular diseases has also been validated in patients with T2DM[16].

Herein, we performed this cross-sectional study to analyze the association of myosteatosi with CAC in patients with T2DM. The myosteatosi and CACS were evaluated with abdominal and thoracic CT, respectively.

## MATERIALS AND METHODS

### Study population

Patients with T2DM who were hospitalized in the Department of Endocrinology, Affiliated Hospital of Jining Medical University between January 2017 and December 2021 were included in this study. They all underwent abdominal and thoracic CT scans. The exclusion criteria included: (1) Patients with age < 30 or > 80 years old; (2) patients with a history of major cardiovascular events (*i.e.*, myocardial infarction, congestive heart failure, coronary stent implantation, and cerebrovascular accidents); and (3) patients with consumptive or critical diseases (*i.e.*, malignant tumors, abnormal thyroid function, and stage V diabetic nephropathy). At admission, all patients were informed that their medical records may be used for research purposes unless they indicate their opposition. For the present study, no patient indicated opposition. This study was approved by the Ethics Committee of the Affiliated Hospital of Jining Medical University (No. 2021-08-C001).

### Laboratory measurements and assessment of diabetic complications

All biochemical and immune indexes were measured in the laboratory of our hospital. Fasting glucose and C-peptide were measured for calculating homeostasis model assessment 2 of insulin resistance and homeostasis model assessment 2 of beta-cell function (HOMA2- $\beta$ ).

### Measurement of body composition and CAC

Both abdominal and thoracic CT scans were performed using a Dual-Source Flash CT scanner (Siemens, Erlangen, Germany). The body composition was assessed using abdominal axial CT images at the L3 level and the Slice-O-Matic software (V.5.0, TomoVision, Montreal, Quebec, Canada), as described in our previous study[17]. The CT attenuation thresholds were from -29 to 150 Hounsfield Unit (HU) for skeletal muscle, from -150 to -30 HU for visceral adipose tissue, and from -190 to -30 HU for intramuscular and subcutaneous adipose tissue[18]. The mean skeletal muscle attenuation (MMA), which was automatically calculated by the software, was shown as the mean radiation attenuation of skeletal muscle in HU. Myosteatosi was diagnosed according to Martin's criteria, *i.e.* MMA < 33 HU with body mass index (BMI)  $\geq 25$  kg/m<sup>2</sup> or MMA < 41 HU with BMI < 25 kg/m<sup>2</sup>[19]. The skeletal muscle index (SMI) (cm<sup>2</sup>/m<sup>2</sup>) was calculated by normalizing the L3 cross-sectional skeletal muscle area in cm<sup>2</sup> to height in m<sup>2</sup>[20]. The fat mass index (kg/m<sup>2</sup>), which is proposed by VanItallie *et al*[21] and is an indicator of nutritional status, was calculated by normalizing fat mass in kg to height in m<sup>2</sup>[21,22]. The fat mass was calculated with the following formula: fat mass (kg) = 0.042  $\times$  (total adipose area at L3 in cm<sup>2</sup>) + 11.2[22]. The CACS was calculated based on the thoracic CT images by the automated software of syngo *via* and with the Agatston method. Severe CAC (SCAC) was defined when the CACS was > 300[14].

### Definitions and diagnosis

Coronary heart disease (CHD) was defined as a suspected history of CHD confirmed through CT coronary angiography. Hypertension was defined as systolic blood pressure  $\geq 140$  mmHg, diastolic blood pressure  $\geq 90$  mmHg, and/or use of antihypertensive medications. Dyslipidemia was defined as disorders of lipoprotein metabolism and/or the use of lipid medications. Alcohol consumption was defined as consuming at least 30 g of alcohol per week for at least a year. Cigarette smoking was defined as smoking at least 100 cigarettes in a lifetime[23]. Diabetic complications were assessed systematically according to the guidelines for the prevention and control of T2DM in China[24]. Diabetic nephropathy was diagnosed when there was elevated urinary albumin excretion and reduced estimated glomerular filtration rate in the absence of other primary causes of kidney damage. Diabetic peripheral neuropathy referred to the symptoms or signs of peripheral nerve dysfunction in diabetic patients that cannot be attributed to other causes. Asymptomatic patients must be diagnosed by physical examination or neuro-electrophysiological examination. Diabetic retinopathy was diagnosed by an ophthalmologist who specialized in diabetic retinopathy, according to the international clinical grading standard for diabetic retinopathy. Lower-extremity arterial disease was diagnosed if the patients had a resting ankle-brachial index (ABI)  $\leq 0.90$ . For patients who experienced discomfort upon moving and had a resting ABI  $\geq 0.90$ , lower-extremity arterial disease was also diagnosed if the ABI decreased by 15%-20% after a treadmill test.

### Statistical analysis

Continuous variables with normal distribution are presented as mean  $\pm$  standard deviation, whereas those with non-normal distribution are presented as median and interquartile range. Categorical variables are described by the number and percentage. The characteristics of the study population were compared using independent samples *t*-test, Mann-Whitney *U* test, or  $\chi^2$  test, as appropriate. The variables with statistical significance between the two groups were enrolled in the logistic regression analysis to identify independent factors for SCAC. Receiver operating characteristic (ROC) curves were plotted and the area under the curve (AUC) of independent factors for SCAC was compared using the *z*-test. The Youden index was calculated to determine the cut-off points of age in distinguishing SCAC. Subgroups were stratified based on the risk factors of atherosclerosis. The Chi-squared Automatic Interaction Detection (CHAID) decision tree analysis was further performed based on the identified independent factors. The minimum parent and child nodes were determined as 100 and 50, respectively. Statistical analysis was performed using SPSS software (V.26.0). The two-sided *P* value less than 0.05 was considered statistically significant.



## RESULTS

### Characteristics of the study population

A total of 652 patients with T2DM were enrolled in this study. The characteristics of the study population are presented in Table 1. There were 425 (65.2%) males and 227 (34.8%) females. Among the 652 patients, 167 (25.6%) had SCAC and were classified into the T2DM + SCAC group. The remaining patients were classified into the T2DM group. Patients in the T2DM + SCAC group had higher values of age, diabetes duration, fasting glucose, creatinine, blood urea nitrogen, and cystatin C; had higher percentages of myosteatosi, CHD, cigarette smoking, alcohol consumption, aspirin usage, hypertension, diabetic nephropathy, and diabetic retinopathy; and received more types of antidiabetics, lipid-lowering, and antihypertensive drugs. However, they had lower values of hemoglobin, alanine transaminase, low-density lipoprotein, free triiodothyronine, and SMI. The comparison of clinical characteristics of patients with and without myosteatosi is presented in the Supplementary Table 1.

### Role of myosteatosi in predicting SCAC

The patients with myosteatosi exhibited significantly higher percentages of SCAC compared with those without myosteatosi (35.6% *vs* 16.6%). Logistic regression analysis revealed that myosteatosi, age, duration of diabetes, cigarette smoking, and alcohol consumption were independent risk factors for SCAC (Figure 1). Patients with myosteatosi showed an increased risk of SCAC (OR = 2.381, 95%CI: 1.347-4.207, *P* = 0.003) after adjustment for age, diabetes duration, cigarette smoking, and alcohol consumption.

The predictive abilities of the aforementioned five factors for SCAC were evaluated using ROC curve analysis (Figure 2). Age had the highest AUC, followed by duration of diabetes, myosteatosi, cigarette smoking, and drinking. The combined model of the five independent risk factors yielded a higher AUC than age alone (0.794 *vs* 0.734, *P* = 0.034).

### Subgroup analysis

Given the variation in age-specific risk of cardiovascular disease by gender, ROC curve analyses were conducted to determine the cut-off points of age in predicting SCAC. The cut-off points for older age were identified as age > 56.5 years in males and age > 63.5 years in females (Figure 3). Patients in the older age group exhibited significantly higher percentages of SCAC compared to those in the younger age group (47.3% *vs* 13.2% in males and 38.7% *vs* 13.4% in females).

Subgroup stratification based on sex, age, BMI, cigarette smoking, alcohol consumption, dyslipidemia, and hypertension was performed (Figure 4). The association between myosteatosi and SCAC was found to be significant in younger patients (OR = 2.672, 95%CI: 1.477-4.834, *P* = 0.002) rather than in older patients (OR = 1.456, 95%CI: 0.863-2.455, *P* = 0.188), and was more prominent in patients with a lower risk of atherosclerosis, such as BMI < 25 kg/m<sup>2</sup>, without cigarette smoking, alcohol consumption, dyslipidemia, and hypertension.

### Construction of CHAID decision tree

CHAID decision tree analysis was conducted using the older age, myosteatosi, and other significantly different factors between the T2DM + SCAC and T2DM groups. Older age, myosteatosi, and cigarette smoking were determined as critical variables and were included in the construction of the CHAID decision tree (Figure 5). The primary variable for SCAC was older age (OR = 5.186, 95%CI: 3.543-7.590, *P* < 0.001). Among patients of older age, the primary factor was cigarette smoking (OR = 2.459, 95%CI: 1.486-4.069, *P* < 0.001), while among younger patients, the primary factor was myosteatosi (OR = 2.672, 95%CI: 1.477-4.834, *P* = 0.001).

## DISCUSSION

To the best of our knowledge, this is the first study to investigate the relationship of myosteatosi with CAC in patients with T2DM. Logistic regression and CHAID decision tree analyses confirmed that myosteatosi, age, cigarette smoking, and alcohol consumption were independent factors of SCAC. Moreover, the association between myosteatosi and CAC might be more prominent in the younger population.

Two large-sample cross-sectional studies have investigated the relationship of muscle quality with CAC in populations other than T2DM[25]. The Coronary Artery Risk Development in Young Adults study enrolled 3051 participants aged 43 to 55 years and defined CAC with CACS > 0[25]. Compared with those with the lowest quartile, the young adults with the upper quartile of abdominal intermuscular adipose tissue volume had a higher risk of CAC [OR 1.6 (1.2-2.1)] after adjusting for cardiovascular disease risk factors[25]. In another study by Lee *et al*[4], a total of 4068 subjects without cardiovascular diseases were included and significant CAC was defined if CACS was > 100. They found that the higher ratio of the muscle area with normal attenuation to the total abdominal muscle area was strongly associated with a lower prevalence of significant CAC after adjustment[4]. Different from these two studies, our study focused on patients with T2DM, and this population is associated with high risks of both myosteatosi and CAC. We demonstrated that myosteatosi was significantly associated with SCAC in patients with T2DM, independent of traditional cardiovascular disease risk factors.

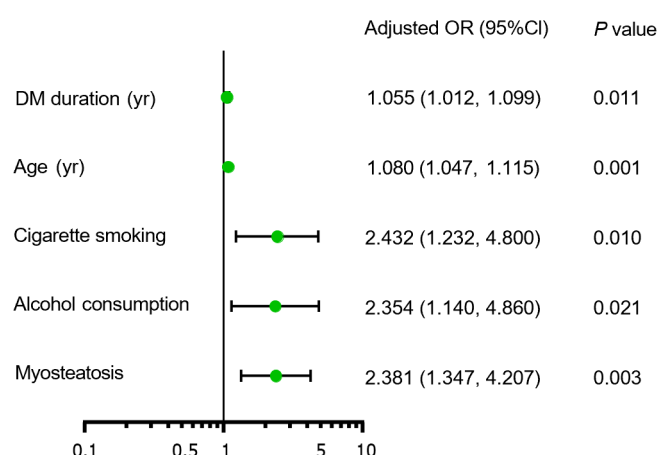
In our study, we found that in addition to myosteatosi, factors such as age, duration of diabetes, smoking, and drinking[26-28] were identified as independent risk factors for SCAC. It is worth noting that the age-specific risk of cardiovascular disease varies by gender, being significantly lower in women before menopause[29,30]. We determined

Table 1 Characteristics of the study population

Variables	All patients (n = 652)	T2DM group (n = 485)	T2DM + SCAC group (n = 167)	P value
Male (%)	425 (65.2)	312 (64.3)	113 (67.7)	0.453
Age (yr)	55.95 ± 10.87	53.75 ± 10.62	62.34 ± 8.94	< 0.001
Diabetes duration (yr)	8.97 ± 7.13	7.87 ± 6.36	12.15 ± 8.22	< 0.001
Body mass index (kg/m <sup>2</sup> )	25.79 ± 3.66	25.87 ± 3.61	25.56 ± 3.79	0.358
Fasting glucose (mmol/L)	7.67 ± 2.23	7.53 ± 2.19	8.09 ± 2.31	0.018
Fasting C peptide (ng/mL)	2.27 ± 1.06	2.25 ± 0.97	2.32 ± 1.30	0.581
Hemoglobin A1c (%)	8.71 ± 2.19	8.76 ± 2.23	8.59 ± 2.06	0.384
HOMA2-β	166.51 ± 93.75	169.89 ± 92.31	155.97 ± 97.78	0.170
HOMA2-IR	5.62 ± 2.67	5.55 ± 2.48	5.84 ± 3.20	0.314
Hemoglobin (g/L)	138.69 ± 21.98	139.77 ± 22.44	135.52 ± 20.30	0.032
Albumin (g/L)	43.14 ± 4.51	43.34 ± 4.31	42.55 ± 5.01	0.071
Alanine transaminase (U/L)	18.20 (13.30, 27.80)	19.35 (13.93, 28.90)	15.90 (12.20, 21.90)	< 0.001
Creatinine (mg/L)	61.38 ± 16.65	60.30 ± 15.78	64.49 ± 18.66	0.010
Blood urea nitrogen (mg/dL)	5.65 ± 1.59	5.52 ± 1.45	6.04 ± 1.90	< 0.001
Cystatin C (mg/L)	1.00 ± 0.29	0.97 ± 0.25	1.11 ± 0.35	< 0.001
Triglycerides (mmol/L)	1.44 (0.98, 2.24)	1.44 (0.98, 2.32)	1.39 (0.95, 1.99)	0.199
Total cholesterol (mmol/L)	4.63 ± 1.56	4.70 ± 1.33	4.44 ± 2.09	0.059
HDL (mmol/L)	1.18 ± 0.38	1.18 ± 0.40	1.16 ± 0.33	0.506
LDL (mmol/L)	2.77 ± 1.18	2.86 ± 1.22	2.53 ± 1.05	0.002
FT3 (pmol/L)	4.53 ± 1.40	4.61 ± 1.57	4.30 ± 0.71	0.016
FT4 (pmol/L)	16.58 ± 3.04	16.57 ± 3.08	16.59 ± 2.91	0.943
TSH (pmol/L)	2.25 ± 1.41	2.24 ± 1.37	2.30 ± 1.54	0.597
SBP (mmHg)	136.23 ± 19.06	136.10 ± 19.82	136.63 ± 16.72	0.736
DBP (mmHg)	81.13 ± 13.00	81.19 ± 13.43	80.95 ± 11.68	0.840
MMA (HU)	36.41 ± 7.29	37.24 ± 7.23	34.02 ± 6.95	< 0.001
Myosteatorsis (%)	309 (47.4)	199 (41.0)	110 (65.9)	< 0.001
CHD (%)	166 (25.5)	96 (19.8)	70 (41.9)	< 0.001
SMI (cm <sup>2</sup> /m <sup>2</sup> )	46.71 ± 9.31	47.18 ± 9.30	45.34 ± 9.23	0.027
FMI (kg/m <sup>2</sup> )	8.56 ± 1.79	8.51 ± 1.79	8.68 ± 1.79	0.290
Cigarette smoking (%)	261 (40.0)	170 (35.1)	91 (54.5)	< 0.001
Alcohol intake (%)	295 (45.2)	204 (42.1)	91 (54.5)	0.007
Dyslipidemia (%)	369 (56.6)	282 (58.1)	87 (52.1)	0.176
Hypertension (%)	308 (47.2)	215 (44.3)	93 (55.7)	0.012
Diabetic complications (%)	564 (86.5)	410 (84.5)	154 (92.2)	0.012
DN (%)	247 (37.9)	169 (34.8)	78 (46.7)	0.007
DPN (%)	498 (76.4)	362 (74.6)	136 (81.4)	0.091
LEAD (%)	105 (16.1)	73 (15.1)	32 (19.2)	0.223
DR (%)	185 (28.4)	118 (24.3)	67 (40.1)	< 0.001
Antidiabetics (%)	569 (87.3)	411 (84.7)	158 (94.6)	0.001
Insulin (%)	249 (38.2)	172 (35.5)	77 (46.1)	0.016

Metformin (%)	434 (66.6)	310 (63.9)	124 (74.3)	0.017
Sulphonylureas (%)	312 (47.9)	230 (47.7)	82 (49.1)	0.720
Acarbose (%)	257 (39.4)	180 (37.1)	77 (46.1)	0.044
Others (%)	167 (25.6)	120 (24.7)	47 (28.1)	0.411
Lipid-lowering drugs (%)	140 (21.5)	84 (17.3)	56 (33.5)	< 0.001
Statins (%)	131 (20.1)	75 (15.5)	56 (33.5)	< 0.001
Fibrates (%)	9 (1.4)	9 (1.9)	0 (0.0)	0.121
Antihypertensive drugs (%)	237 (36.3)	158 (32.6)	79 (47.3)	0.001
ACE inhibitors (%)	33 (5.1)	20 (4.1)	13 (7.8)	0.068
ARBs (%)	105 (16.1)	71 (14.6)	34 (20.4)	0.088
Calcium antagonists (%)	134 (20.6)	89 (18.4)	45 (26.9)	0.020
$\beta$ -Blockers (%)	64 (9.8)	36 (7.4)	28 (16.8)	0.001
Diuretics (%)	32 (4.9)	22 (4.5)	10 (6.0)	0.533
Aspirin (%)	145 (22.2)	84 (17.3)	61 (36.5)	< 0.001

T2DM: Type 2 diabetes mellitus; SCAC: Severe coronary artery calcification; HOMA2- $\beta$ : Homeostasis model assessment 2 of beta-cell function; HOMA2-IR: Homeostasis model assessment 2 of insulin resistance; HDL: High-density lipoproteins; LDL: Low-density lipoproteins; FT3: Free triiodothyronine; FT4: Free thyroxine; TSH: Thyroid-stimulating hormone; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; CHD: Coronary heart disease; SMI: Skeletal muscle index; MMA: Mean skeletal muscle attenuation; FMI: Fat mass index; DN: Diabetic nephropathy; DPN: Diabetic peripheral neuropathy; LEAD: Lower extremity arterial disease; DR: Diabetic retinopathy; ACE: Angiotensin-converting enzyme; ARB: Angiotensin II receptor blocker.

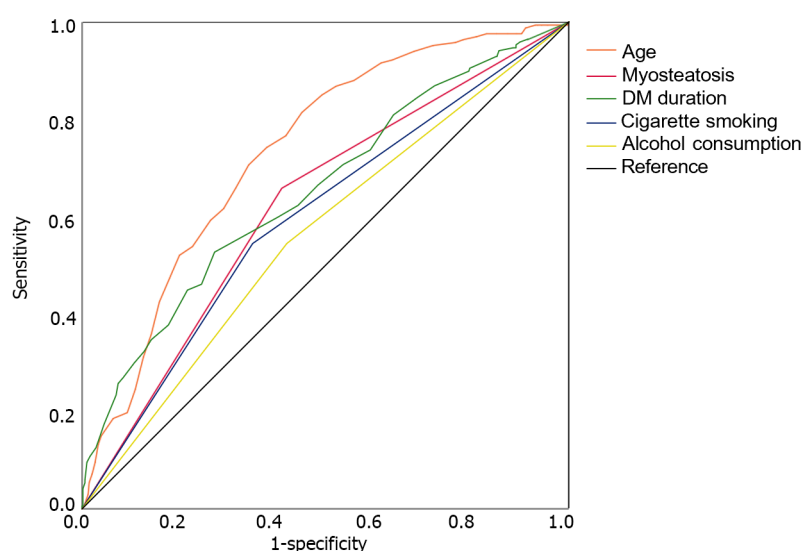


**Figure 1** Forest plot of independent factors identified from logistic linear regression for severe coronary artery calcification. DM: Diabetes mellitus.

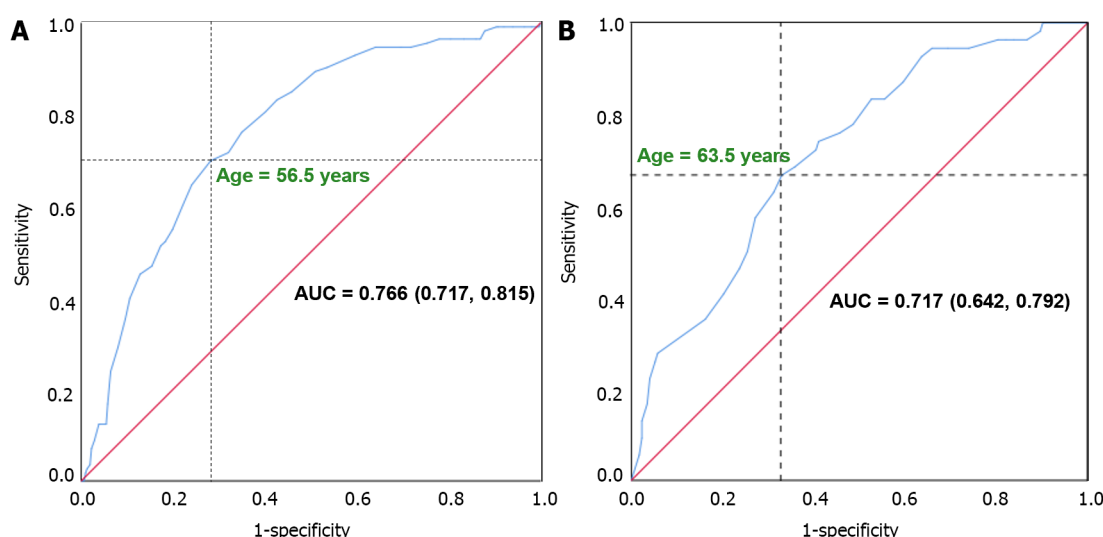
the cut-off age values for predicting SCAC to be > 56.5 years in males and > 63.5 years in females. This finding aligns with a previous study, which revealed that the prevalence of CACS > 0 exceeded 25% in young males with at least one risk factor by the age of 40, and in young females with at least one traditional risk factor by the age of 50[31].

Muscle mass has been regarded as a predictor for coronary atherosclerosis in previous studies[32,33]. However, these studies are limited by the use of dual-energy X-ray absorptiometry or bioelectrical impedance analysis, which are not allowed to be used to evaluate muscle quality. In our study, both logistic regression and CHAID decision tree analyses showed no significant association between SMI and SCAC, even when SMI was transferred into a binary variable according to the diagnostic criteria of low muscle mass (data not shown)[9]. This result is consistent with the study by Lee *et al*[4], which assessed the association between muscle quality and CAC in the general population. Therefore, myosteatorsis might play a more important role than low muscle mass in the development of CAC, especially in the population with T2DM.

CHAID algorithm for decision tree analysis was used to visualize the relationship between SCAC and related factors in an easy-to-interpret tree image. Myosteatorsis was a primary factor for SCAC in younger patients and was associated with a more than two-fold increased risk of SCAC. Therefore, the occurrence of severe atherosclerosis in certain younger individuals might be attributed to myosteatorsis. It is important to note that while myosteatorsis was not included in the CHAID decision tree analysis for the older age subgroup, the quality of muscle in elderly patients remains significant.



**Figure 2** Receiver operating characteristic curve analysis of risk factors for severe coronary artery calcification alone or in combination. DM: Diabetes mellitus.



**Figure 3** Cut-off points of age for severe coronary artery calcification. A. Subgroup of males; B. Subgroup of females. AUC: Area under the curve.

Our study revealed that approximately 65.8% of older patients were diagnosed with myosteatosi (data not shown), and therefore, myosteatosi cannot truly reflect the difference in their muscle quality. Thus, large epidemiological studies are needed to establish an improved criterion for myosteatosi based on age, especially for myosteatosi in elderly individuals.

In addition to CAC, we also assessed the associations of myosteatosi with diabetes complications, hormonal status, and medication usage. Although no difference was found in the risk of diabetes complications, patients with myosteatosi exhibited a higher risk of CHD. This finding supports our conclusion regarding the association between myosteatosi with SCAC. Hormonal status plays a crucial role in maintaining muscle health. In this cross-sectional study, patients with myosteatosi showed no significant differences in the levels of thyroid hormones. Further research is necessary to evaluate the association of myosteatosi with other hormones, including growth hormone, estrogen, testosterone, and adrenal hormones. Patients with myosteatosi had a higher prevalence of insulin, statins, and aspirin usage. However, this does not imply that these medications induce myosteatosi, as patients with myosteatosi require these medications due to their elevated risk of CHD and lower levels of HOMA2- $\beta$ .

Our study has several limitations. First, the characteristics of the cross-sectional study limited the further exploration of the causal inference and the clarification of the underlying pathophysiological mechanism between myosteatosi and coronary atherosclerosis. Second, we did not assess the muscle function (*e.g.*, handgrip strength and gait speed), which is highly associated with muscle quality[34]. Third, some information that may be associated with CAC, such as the family history of premature cardiovascular disease and the physical activity of patients, was missing. Fourth, our study did not analyze the association of myosteatosi with the features of plaque vulnerability, such as volume and density, which may

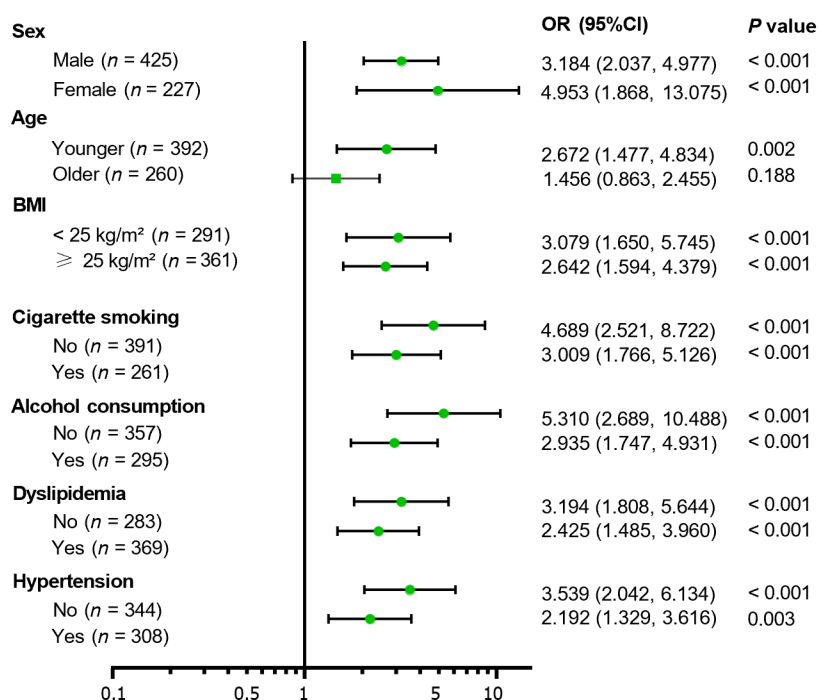


Figure 4 Subgroup analyses of myosteatosi in predicting severe coronary artery calcification. BMI: Body mass index.

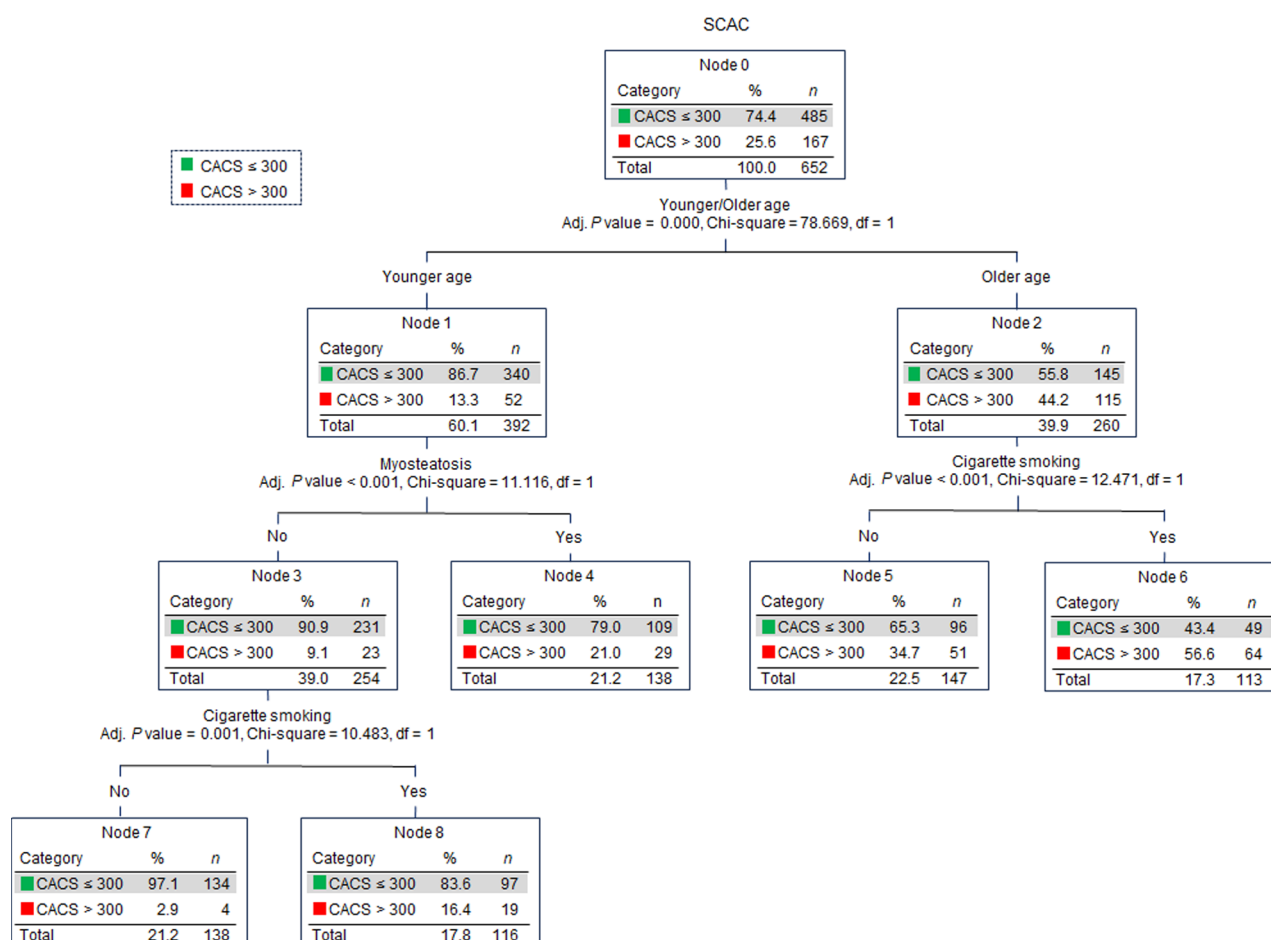


Figure 5 Chi-squared automatic interaction detection decision tree analysis. SCAC: severe coronary artery calcification; CACS: Severe coronary artery calcification score.

have opposite relationships with cardiovascular events[35]. Lastly, because our study was conducted in Chinese adults with T2DM, the findings may not be readily generalizable to other populations or ethnicities.

However, our study also has several strengths. First, this study included a large sample of 652 individuals and used CT-derived measures of both myosteatorosis and SCAC. Second, our study focused on patients with T2DM and this population has a high prevalence of both myosteatorosis and atherosclerotic cardiovascular diseases. Third, most of the important biochemical variables were available and all the diabetic complications were assessed by professional clinicians. Fourth, the CHAID decision tree analysis highlighted that the association between myosteatorosis and SCAC might be more prominent in individuals with younger ages and lower risks of atherosclerosis. This is a novel finding of our study.

## CONCLUSION

In conclusion, myosteatorosis was a novel risk factor for atherosclerosis in patients with T2DM, especially in the population with younger ages or fewer traditional risk factors. This suggests the potential benefit of initiating muscle-strengthening exercises and improving muscle quality at a younger age. Further follow-up studies are warranted to validate the role of myosteatorosis in cardiovascular events or mortality in patients with T2DM.

## ARTICLE HIGHLIGHTS

### Research background

Myosteatorosis rather than low muscle mass is the major etiologic factor of sarcopenia in patients with type 2 diabetes mellitus (T2DM). Myosteatorosis may lead to a series of metabolic dysfunctions which are closely associated with acceleration of T2DM and atherosclerosis.

### Research motivation

The association between myosteatorosis and coronary atherosclerosis in patients with T2DM has not been reported yet.

### Research objectives

To investigate the association between myosteatorosis and coronary artery calcification (CAC) in patients with T2DM.

### Research methods

Severe CAC (SCAC) was defined when the CAC score was > 300. Logistic regression and decision tree analyses were performed to assess the association between myosteatorosis and SCAC.

### Research results

Myosteatorosis was significantly associated with increased risk of SCAC. The association between myosteatorosis and SCAC was significant in the younger, rather than older patients, and was more prominent in the population with lower risks of atherosclerosis.

In the patients with older age, the main factor for SCAC was cigarette smoking, while in the patients with younger age, the main factor was myosteatorosis.

### Research conclusions

Myosteatorosis was a novel risk factor of atherosclerosis in patients with T2DM, especially in the population with younger age or lower traditional risk factors.

### Research perspectives

Follow-up studies are warranted to confirm the role of myosteatorosis in cardiovascular events or mortality in patients with T2DM.

## FOOTNOTES

**Co-corresponding authors:** Yan-Gang Wang and Mei Zhang.

**Author contributions:** Zhang M and Wang YG designed research; Zhang M, Wang YG and Liu FP contributed to study protocols and analysis plans; Liu FP, Guo MJ, Yang Q, and Li YY interpreted the data; Liu FP and Yang Q drafted the manuscript; Liu FP, Yang Q, and Guo MJ were the guarantors of this work, thereby having full access to all the data in the study and taking responsibility for the data's integrity and accuracy of the analysis; all authors were involved in the critical review of the results and have contributed to, read, and approved the final manuscript. Zhang M and Wang YG were designated as co-corresponding authors. First, the research was performed as a collaborative effort, and the designation of co-corresponding authors accurately reflected the distribution of responsibilities and efforts involved in completing the study and the resulting paper. Second, the research team encompassed authors with a variety of



expertise and skills from different fields, making the designation of co-corresponding authors the most suitable choice to reflect this diversity. Third, Zhang M and Wang YG made substantial and equal contributions throughout the research process. Selecting these researchers as co-corresponding authors acknowledged and respected their equal contributions while recognizing the spirit of teamwork and collaboration in this study. In summary, we believe that designating Zhang M and Wang YG as co-corresponding authors is appropriate for our manuscript as it accurately reflects our team's collaborative spirit, equal contributions, and diversity.

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