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Retrospective Study

Myosteatosis is associated with coronary artery calcification in patients with type 2 diabetes

Myosteatosis and coronary artery calcification

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Abstract

BACKGROUND

Myosteatosis rather than low muscle mass is the major etiologic factor of sarcopenia in patients with type 2 diabetes mellitus (T2DM). Myosteatosis 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 acceleration of T2DM and atherosclerosis.

AIM

The present study investigated the association between myosteatosis and coronary artery calcification (CAC) in patients with T2DM.

METHODS

Patients with T2DM but without major cardiovascular events, who underwent both abdominal and thoracic computerized tomography (CT) scans were included. The mean skeletal muscle attenuation (MMA) was assessed using abdominal CT images at the L3 Level. The CAC score (CACS) was calculated using thoracic CT images by the Agatston

scoring method. Myosteatosis was diagnosed according to the Martin's criteria. Severe CAC (SCAC) was defined when the CACS > 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 myosteatosis, age, diabetes duration, cigarette smoking and alcohol intake were independent risk factors of SCAC. Myosteatosis was significantly associated with increased risk of SCAC (OR = 2.381, *P* = 0.003). The association between myosteatosis and SCAC was significant in the younger (OR = 2.672, 95%CI (1.477, 4.834), *P* = 0.002), rather than 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. In the decision tree analyses, older age was the main variable for SCAC. 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 myosteatosis.

CONCLUSION

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

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

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Core Tip: Myosteatosis rather than low muscle mass is the major etiologic factor of sarcopenia in patients with type 2 diabetes mellitus (T2DM). Myosteatosis may lead to a series of metabolic dysfunctions which are closely associated with the acceleration of T2DM and atherosclerosis. This study showed myosteatosis was a novel risk factor of atherosclerosis in patients with T2DM, especially in the population with younger age or lower traditional risk factors. Therefore, it might make more sense to start strengthening exercises and improving muscle quality at a younger age.

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] Myosteatosis, a marker of muscle quality, has been proposed as a novel risk factor for atherosclerotic cardiovascular diseases, independent of muscle mass.[3-6] Myosteatosis 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 acceleration of T2DM and atherosclerosis (Figure S1).[3, 7, 8]

Computed tomography (CT) is considered as the gold standard for myosteatosis measurement, and lower muscle radiodensity indicates higher fat infiltration (i.e., myosteatosis).[9] Recently, a large-sample study involving 20,986 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. The patients with T2DM have high risks of myosteatosis and atherosclerosis. However, the association between myosteatosis and coronary artery calcification in this population has not been reported yet.

Coronary artery calcification score (CACS), which can be calculated with the Agatston scoring method, is considered as 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 myosteatosis with coronary artery calcification in patients with T2DM. The myosteatosis 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 HOMA2-IR (homeostasis model assessment of insulin resistance) and HOMA2-β (homeostasis model assessment of β-cell function (HOMA-β).

Measurement of body composition and coronary artery calcification

Both abdominal and thoracic CT scans were performed using 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. Myosteatosis was diagnosed according to the Martin's criteria, i.e. MMA < 33 HU with body mass index (BMI) ≥ 25 kg/m^2 or MMA < 41 HU with BMI < 25 kg/m^2.[19] The skeletal muscle index (SMI) (cm^2/m^2) was calculated by normalizing the L3 cross-sectional skeletal muscle area in cm^2 to height in m^2.[20] The fat mass index (kg/m^2), 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^2.[21, 22] The fat mass was calculated with the following formula: fat mass (kg) = 0.042 × (total adipose area at L3 in cm^2) + 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 coronary artery calcification (SCAC) was defined when the CACS was > 300.[14]

Definitions and diagnosis

Coronary heart disease (CHD) was defined as a suspicious history or CHD confirmed with CT coronary angiography. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, and/or use of antihypertensive medications. Dyslipidemia was defined as disorders of lipoprotein metabolism and/or use of lipid medications. Alcohol intake 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 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 were 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 related to 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) ≤ 0.90. For patients who experienced discomfort upon moving and had a resting ABI ≥ 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 ± 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 χ^2 test, as appropriate. The variables with statistical significance between 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 curves (AUCs) of independent factors for SCAC were compared using z test. Youden index were calculated to obtain the cut-off points of age in distinguishing SCAC. Subgroup analyses were stratified based on 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 T2DM + SCAC group. The remaining patients were classified into 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 myosteatosis, CHD, cigarette smoking, alcohol intake, 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 or without myosteatosis is presented in Table S1.

Role of myosteatosis in predicting SCAC

The patients with myosteatosis had significantly higher percentages of SCAC compared with the patients without myosteatosis (35.6% vs. 16.6%). Logistic regression analysis demonstrated that myosteatosis, age, diabetes duration, cigarette smoking and alcohol intake were independent risk factors of SCAC (Fig. 1). The patients with myosteatosis showed increased the risk of SCAC (OR = 2.381, 95%CI (1.347, 4.207), P = 0.003) after adjustment of age, diabetes duration, cigarette smoking and alcohol intake.

The predictive abilities of above five factors alone or in combination for SCAC were assessed using ROC curve analysis (Fig. 2). Age had the highest AUC, followed by diabetes duration, myosteatosis, smoking and drinking. The combined model of the five independent risk factors had a higher AUC than age alone (0.794 vs. 0.734, P = 0.034).

Subgroup analysis

Since the age-specific risk of cardiovascular disease varies by gender, ROC curve analyses were performed to assess the cut-off points of age in predicting SCAC. The values of age > 56.5 years in males and > 63.5 years in females were determined as cut-off points of older age (Fig. 3). The patients with older age showed significantly higher

percentages of SCAC compared with those with younger age (47.3% vs. 13.2% in males and 38.7% vs. 13.4% in females, respectively).

Subgroups stratified based on sex, age, BMI, cigarette smoking, alcohol intake, dyslipidemia and hypertension (Figure 4). The association between myosteatosis and SCAC was significant in the younger (OR = 2.672, 95%CI (1.477, 4.834), P = 0.002), rather than older patients (OR = 1.456, 95%CI (0.863, 2.455), P = 0.188), and more prominent in the patients with lower risk of atherosclerosis, such as BMI < 25 kg/m^2, without cigarette smoking, alcohol intake, dyslipidemia and hypertension.

Construction of CHAID decision tree

CHAID decision tree analysis was performed with the factors of older age, myosteatosis and other significantly different variables between the T2DM + SCAC and T2DM groups. Older age, myosteatosis and cigarette smoking were determined as critical variables and were included in the construction of CHAID decision tree (Fig. 5). Older age was the main variable for SCAC (OR = 5.186, 95%CI (3.543, 7.590), p < 0.001). In the patients with older age, the main factor was cigarette smoking (OR = 2.459, 95%CI (1.486, 4.069), p < 0.001), while in the patients with younger age, the main factor was myosteatosis (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 myosteatosis with coronary artery calcification in patients with T2DM. Logistic regression and CHAID decision tree analyses confirmed that myosteatosis, age, cigarette smoking and alcohol intake were independent factors of SCAC. Moreover, the association between myosteatosis and coronary artery calcification might be more prominent in the younger population.

Two large-sample cross-sectional studies have investigated the relationship of muscle quality with coronary artery calcification in populations other than T2DM. [25] The CARDIA (Coronary Artery Risk Development in Young Adults) study enrolled 3051 participants aged 43 to 55 years and defined coronary artery calcification 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 higher risk of coronary artery calcification (OR 1.6 (1.2–2.1)) after adjusting for cardiovascular disease risk factors.[25] In another study by Lee *et al*, a total of 4068 subjects without cardiovascular diseases were included and significant coronary artery calcification was defined if CACS was > 100.[4] 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 coronary artery calcification 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 myosteatosis and coronary artery calcification. We demonstrated that myosteatosis was significantly associated with SCAC in patients with T2DM, independent of traditional cardiovascular disease risk factors.

Besides myosteatosis, some other factors including age, diabetes duration, smoking and drinking, which are significantly associated with cardiovascular diseases,[26-28] were also identified as independent risk factors of SCAC in our study. It is worth noting that the age-specific risk of cardiovascular disease varies by gender, which is significantly lower in women before the menopause.[29, 30] In this study, the values of age > 56.5 years in males and > 63.5 years in females were determined as cut-off points in predicting SCAC. This result is consistent with a previous study, which demonstrated that the prevalence of CACS > 0 reached >25% in young males with at least 1 risk factor by the age of 40 years, whereas in young females with at least 1 traditional risk factor by the age of 50 years.[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 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 coronary artery calcification in general population. Therefore, myosteatosis might play a more important role than low muscle mass in the development of coronary artery calcification, 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. In the patients with younger age, myosteatosis was the main factor for SCAC and associated with more than 2 folds of SCAC. Therefore, myosteatosis might be one of the possible reasons for the occurrence of severe atherosclerosis in some individuals with younger age. Although myosteatosis was not included in the CHAID decision tree analysis in the subgroup with older age, this does not mean that muscle quality of elderly patients is not important. About 65.8% of the patients with older age are diagnosed as myosteatosis in our study (data not shown), and therefore, myosteatosis cannot truly reflect the difference in their muscle quality. Thus, large epidemiological studies are needed to establish an improved criterion for myosteatosis based on age, especially for myosteatosis in elderly individuals.

Besides CAC, we also concern about the associations of myosteatosis with diabetes complications, hormonal status and usage of medications. Although no difference in the risk of diabetes complications including LEAD, the patients with myosteatosis showed higher risk of CHD. This result supports our conclusion about the association between myosteatosis with SCAC. Hormonal status play important roles in maintaining muscle health. In this cross-section study, the patients with myosteatosis showed no difference in the levels of thyroid hormones. The patients with myosteatosis had higher percentages of insulin, statins and aspirin usage. However, this does not mean these medications induce myosteatosis because of the patients with myosteatosis require these medications as they have a higher risk of CHD and lower level of HOMA2-β.

Our study has several limitations. First, the characteristics of cross-sectional study limited the further exploration of the causal inference and the clarification of the

underlying pathophysiological mechanism between myosteatosis 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 coronary artery calcification, 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 myosteatosis with the features of plaque vulnerability, such as volume and density, which may have opposite relationships with cardiovascular events.[35] Fifth, only thyroid hormones were included in our study. Further studies are required to assess the association of myosteatosis with other hormones, including growth hormone, estrogen, testosterone and adrenal hormones. 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 myosteatosis and SCAC. Second, our study focused on patients with T2DM and this population has a high prevalence of both myosteatosis 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 myosteatosis and SCAC might be more prominent in the individuals with younger age and lower risks of atherosclerosis. This is a novel finding of our study.

CONCLUSION

In conclusion, myosteatosis was a novel risk factor of atherosclerosis in patients with T2DM, especially in the population with younger age or lower traditional risk factors. It might make more sense to start strengthening exercises and improving muscle quality at a younger age. Further follow-up studies are warranted to confirm the role of myosteatosis in cardiovascular events or mortality in patients with T2DM.

ARTICLE HIGHLIGHTS

Research background

Myosteatosis rather than low muscle mass is the major etiologic factor of sarcopenia in patients with type 2 diabetes mellitus (T2DM).

Myosteatosis may lead to a series of metabolic dysfunctions which are closely associated with acceleration of T2DM and atherosclerosis.

Research motivation

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

Research objectives

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

Research methods

Severe coronary artery calcification (SCAC) was defined when the CAC score was > 300.

Logistic regression and decision tree analyses were performed to assess the association between myosteatosis and SCAC.

Research results

Myosteatosis was significantly associated with increased risk of SCAC.

The association between myosteatosis 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 myosteatosis.

Research conclusions

Myosteatosis 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 myosteatosis in cardiovascular events or mortality in patients with T2DM.

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