ORIGINAL ARTICLE

Elevated serum pentosidine is independently associated with the high prevalence of sarcopenia in Chinese middle-aged and elderly men with type 2 diabetes mellitus

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ABSTRACT

Aims/Introduction: Sarcopenia has recently been recognized as another complication associated with diabetes, but its early screening still lacks clinical markers. Here, we aimed to investigate the relationship between serum levels of pentosidine, which is an advanced glycation end-product, and sarcopenia in Chinese middle-aged and elderly men with type 2 diabetes mellitus and evaluate whether pentosidine could be used as a kind of screening maker.

Materials and Methods: A total of 182 male type 2 diabetes mellitus patients aged ≥50 years were selected in the cross-sectional study for whole-body dual-energy X-ray measurement and calculating the appendicular skeletal muscle mass index. At the same time, handgrip strength and gait speed were assessed. According to the updated consensus on Asian sarcopenia in 2019, the patients were divided into the sarcopenia group ($n = 83$) and non-sarcopenia group ($n = 99$). Serum pentosidine levels in the two groups were detected using enzyme-linked immunosorbent assay.

Results: Serum pentosidine was significantly higher in the sarcopenia group (191.27 pmol/mL) than in the non-sarcopenia group (34.93 pmol/mL). Serum pentosidine was negatively correlated with appendicular skeletal muscle mass index and handgrip strength ($r = -0.30$ and -0.25, respectively; $P < 0.05$), but not gait speed. The prevalence of sarcopenia increased as the quartile of serum pentosidine increased ($P < 0.05$). The association between pentosidine and the prevalence of sarcopenia was still significant after additional adjustments (odds ratio 1.01, $P < 0.05$).

Conclusions: Pentosidine is an independent risk factor for sarcopenia in Chinese middle-aged and elderly men with type 2 diabetes mellitus. The detection of serum pentosidine levels in clinics might be helpful for the monitoring of type 2 diabetes mellitus complicated with sarcopenia.

INTRODUCTION

As the standard of living improves and the population ages, the number of elderly patients with type 2 diabetes mellitus in China will increase significantly in the future[1,2]. To actively prevent and cure a variety of complications of elderly patients with diabetes, and improve their quality of life are the focus of research. Sarcopenia, a kind of geriatric syndrome with loss of

muscle mass plus a decrease in muscle strength and/or physical performance[3], is known to seriously harm the health of the elderly, resulting in an increase in clinical adverse events, such as falls, re-hospitalization and even death[3,4]. Recently, sarcopenia has been recognized as a diabetic complications[5–7]. A previous study showed that patients with type 2 diabetes mellitus have significant excessive loss of skeletal muscle mass and lower muscle strength, especially in inferior limbs[7], and the risk of sarcopenia in type 2 diabetes mellitus patients is threefold higher than individuals without diabetes[8]. However, the early

clinical screening markers of diabetes-related sarcopenia still remain unclear.

Advanced glycation end-products (AGEs) are covalent compounds produced by non-enzymatic binding of glucose and protein[9], accumulating in various parts of diabetes patients and leading to the development of diabetic complications, such as nephropathy and retinopathy[10,11]. The chronic accumulation of AGEs in muscle tissue was recently suggested to directly obstruct muscle synthesis[12], which is related to the occurrence of sarcopenia[13]. More than 20 different AGEs have been identified in human blood and tissues, and in foods. Due to their great heterogeneity, there is no specific test for AGEs operational measurement[14]. Pentosidine is a kind of AGEs metabolite, which has been proved to have a good correlation with AGEs[15] and can reflect serum levels of AGEs in the body[16]. Here, we assume that pentosidine could be used as an early monitoring marker of diabetes-related sarcopenia.

In the present study, we therefore aimed to compare serum pentosidine levels of the sarcopenia group with the non-sarcopenia group in Chinese middle-aged and elderly men with type 2 diabetes mellitus, and to explore the association of serum pentosidine with sarcopenia, as well as its components (muscle mass assessed using the appendicular skeletal muscle mass index [ASMI], muscle strength and physical performance).

MATERIALS AND METHODS

Participants
A total of 246 independent ambulatory male patients with type 2 diabetes mellitus aged ≥50 years, who were hospitalized in the Department of Endocrinology, Affiliated Changzhou the Second People's Hospital of Nanjing Medical University, Changzhou, China, for treatment of diabetes, including regular follow up from July 2018 to August 2020, were recruited. Among them, 64 patients met the exclusion criteria: (i) acute diabetic complications, such as diabetic ketoacidosis; (ii) malignant tumor; (iii) acute infection or inflammatory diseases, such as tuberculosis; (iv) weight loss surgery; (v) dyskinesia; (vi) severe hepatic or renal diseases, including elevated transaminase up to twofold the normal upper limit under unknown causes, or stage ≥4 of chronic kidney disease (estimated glomerular filtration rate <30 mL/min); (vii) acute cardiocerebrovascular events within half a year; (viii) other endocrine diseases, such as thyroid dysfunction and Cushing's syndrome; (ix) autoimmune diseases, such as rheumatoid arthritis; and (x) steroids, sex hormones and other drugs that affect muscle metabolism used within half a year. In the present cross-sectional study, we analyzed the data of 182 patients.

This study was approved by the ethics committee of Affiliated Changzhou the Second People's Hospital of Nanjing Medical University, and all participants signed the informed consent.

Assessment of ASMI
Percentage of body fat (%body fat), fat mass, visceral fat area, whole-body and appendicular skeletal muscle mass were obtained by dual-energy X-ray absorptiometry (Hologic Inc., Marlborough, MA, USA). ASMI was calculated using the following formula (ASMI = appendicular skeletal muscle mass [ASM] / height^2 [kg/m^2])[17].

Measurement of handgrip strength
Handgrip strength of both hands was measured using a grip dynamometer (JAMA, Lafayette, IN, USA). Patients were required to keep their forearms horizontal to the ground in a sitting position before testing. The distance of the grip was adjusted in an appropriate range, and patients were instructed to hold the handle of the dynamometer with the greatest effort[18]. Measurements were taken twice per hand and the maximum value was used for statistical analysis[3].

Measurement of gait speed
Usual gait speed measurement was carried out using a 6-m walking test[3,17]. Before testing, a total 12-m straight line was drawn on the flat ground, marking the starting point, the 3-m point, the 9-m point and the end-point, respectively. The patient was required to walk at the normal pace from the starting point. When walking to the 3-m point, the timer control started counting and the time ended at the 9-m point. Measurements were taken three times, and the fastest pace value was used for analysis.

Definition of sarcopenia
Sarcopenia of the middle-aged and elderly male patients was defined using the updated consensus on sarcopenia diagnosis and treatment issued by Asian Working Group for Sarcopenia in 2019[3]; that is, the cut-off for decreased muscle mass: dual-energy X-ray absorptiometry, ASMI <7.0 kg/m^2 in men; low muscle strength was determined by handgrip strength <28 kg for men; and criteria for low physical performance was 6-m walk <1.0 m/s. Patients with loss of muscle mass, plus low muscle strength and/or low physical performance were diagnosed as sarcopenia[3]. In the present study, the participants were divided into the sarcopenia group ($n = 83$) and non-sarcopenia group ($n = 99$) according to whether they were complicated with sarcopenia or not.

Detection of serum pentosidine levels
For the detection of serum pentosidine levels, 5 mL of fasting venous blood was taken from patients and put into the coagulation-promoting tube. After coagulation, the serum was separated by a centrifuge at a speed of 1,400 g and centrifuged for 10 min. Serum pentosidine was detected using an enzyme-linked immunosorbent assay kit[14], purchased from Tongwei Company, Shanghai, China.

Other clinical data
The duration of diabetes was collected from the medical records of patients, and their blood pressure, height and weight were measured on the day of hospitalization. The body mass

index ([BMI]; BMI = weight/height^2 [kg/m^2]) was calculated. Therapeutic regimens of participants were available for the study, and exercise habits (at least 150 min a week over a year) were investigated using a structured questionnaire[19].

Glycosylated hemoglobin (HbA1c), fasting plasma glucose, triglyceride, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, serum creatinine and uric acid were examined in the hospital using standard laboratory methods. The Chronic Kidney Disease Epidemiology Collaboration formula was used to calculate the estimated glomerular filtration rate[20].

Fundus photography or fluorescein angiography was carried out to evaluate diabetic retinopathy. Color Doppler ultrasonography of carotid artery and extremities was used to evaluate diabetic macroangiopathy. The bone mineral density T-value was measured by dual-energy X-ray absorptiometry to determine osteopenia (−2.5 < T < −1.0) or osteoporosis (T ≤ −2.5)[21]. Diabetic neuropathy was diagnosed in patients who met at least two of the following criteria: complaint of bilateral sensory symptoms in the toes and soles of the feet (specifically, at least two of the following: numbness, pain and dysesthesia), a bilaterally diminished or absent Achilles tendon reflex, and a bilaterally decreased vibratory sensation in the inner malleolus[22].

Statistical analysis

Continuous variables consistent with normal distribution were expressed as the mean ± standard deviation, and comparisons between the two groups were assessed using the *t*-test. Continuous variables of skewed distribution were expressed as the median (upper and lower quartile), and comparisons were assessed using the Mann–Whitney *U*-test. Categorical variables were expressed as the frequency (%) and the assessment of the χ^2-test was used. The correlation between serum pentosidine and other clinical parameters was analyzed using the Spearman correlation analysis. The association of serum pentosidine levels with diabetes-related sarcopenia was analyzed using multivariate logistic regression analysis, including stratified serum pentosidine as dummy variables. In the present study, we selected age, BMI, visceral fat area, ASM and HbA1c according to the $P < 0.05$ results of the univariate logistic regression analysis with sarcopenia as adjusting variables for multiple regression analysis. All analysis was carried out using SPSS Statistics 23 software (IBM Corp., Armonk, NY, USA). A *P*-value <0.05 was considered statistically significant.

RESULTS

Comparison of clinical characteristics in the two groups

The clinical characteristics of the participants in the sarcopenia group and in the non-sarcopenia group are shown in Table 1. There were no differences for age, diabetes duration, exercise habits, medication, estimated glomerular filtration rate, and frequency of retinopathy, macroangiopathy, neuropathy and osteopenia/osteoporosis between the two groups. ASMI,

handgrip strength and gait speed in the sarcopenia group were significantly lower than those in the non-sarcopenia group. Sarcopenia patients had higher HbA1c, and lower bodyweight, BMI, %body fat, fat mass, visceral fat area, whole body skeletal muscle mass, ASM and triglyceride than those of control patients. Compared with the non-sarcopenia group, serum pentosidine levels in the sarcopenia group were significantly higher (Table 1).

Prevalence of sarcopenia after quartile grouping of serum pentosidine

The prevalence of sarcopenia according to the quartile of serum pentosidine is shown in Table 2. All participants in the present study were divided into quartiles according to levels of serum pentosidine (1st quartile: ≤16.33 pmol/mL, 2nd quartile: 16.34~85.39 pmol/mL, 3rd quartile: 85.40~239.62 pmol/mL, 4th quartile: ≥239.63 pmol/mL). In middle-aged and elderly male patients with type 2 diabetes mellitus, the prevalence of sarcopenia increased as the quartile of serum pentosidine increased (Table 2).

Correlation analysis between serum pentosidine and associated clinical parameters

The correlation analysis between serum pentosidine and other clinical parameters is shown in Appendix S1. Pentosidine levels were positively correlated with HbA1c and fasting plasma glucose, and negatively correlated with BMI, ASM, ASMI and handgrip strength (Table 3).

Odds ratios of the risk for type 2 diabetes mellitus complicated with sarcopenia

The odds ratios of the risk for sarcopenia in middle-aged and elderly men with type 2 diabetes mellitus are shown in Table 4. Age, BMI, visceral fat area, ASM, serum pentosidine and HbA1c were selected as independent variables for the multivariate logistic regression analysis. It was found that high BMI and high ASM were independent protective factors for sarcopenia in middle-aged and elderly male patients with type 2 diabetes mellitus, whereas high serum pentosidine and high visceral fat area were independent risk factors (Table 4). Furthermore, logistic regression analysis was carried out by replacing serum pentosidine with serum pentosidine quartiles. The results showed that elevated serum pentosidine quartile was an independent risk factor for sarcopenia in middle-aged and elderly male patients with type 2 diabetes mellitus. When serum pentosidine increased by one quartile, the risk of sarcopenia was 4.8-fold higher than the previous quartile (odds ratio 4.77, 95% confidence interval 2.17–10.49), as shown in Table 5.

DISCUSSION

Although sarcopenia is a diabetic complication, its early screening still lacks clinical markers. The present study showed for the first time that pentosidine levels were negatively correlated with indices of muscle mass and strength in Chinese middle-

Table 1 | Clinical characteristics of the participants in the type 2 diabetes mellitus sarcopenia group and in type 2 diabetes mellitus non-sarcopenia group

	Non-sarcopenia group (n = 99)	Sarcopenia group (n = 83)	P
Age (years)	60.2 ± 6.4	62.1 ± 7.3	0.069
Weight (kg)	76.4 ± 8.8	65.4 ± 8.8	<0.001
BMI (kg/m^2)	27.3 ± 2.6	23.3 ± 2.5	<0.001
Fat mass (kg)	21.2 ± 5.5	17.2 ± 4.7	<0.001
%Body fat (%)	28.1 ± 4.7	26.7 ± 4.9	0.044
Visceral fat area (cm^2)	151.8 ± 49.9	114.7 ± 45.1	<0.001
SBP (mmHg)	135.3 ± 14.7	135.8 ± 17.5	0.812
DBP (mmHg)	81.3 ± 9.6	80.5 ± 9.5	0.527
Duration of diabetes (years)	8.0 (3.0–10.0)	10.0 (5.0–16.0)	0.082
Exercise habit (%)	46.5	36.1	0.160
HbA1c (%)	9.0 (7.6–10.6)	10.1 (8.5–11.4)	0.001
Serum pentosidine (pmol/mL)	34.93 (5.24–141.47)	191.27 (55.46–346.95)	<0.001
FPG (mmol/L)	7.20 (6.54–9.80)	7.91 (6.76–11.30)	0.201
TC (mmol/L)	4.35 ± 0.94	4.28 ± 1.28	0.663
TG (mmol/L)	1.46 (1.09–2.43)	1.18 (0.81–1.70)	0.002
LDL-C (mmol/L)	2.40 ± 0.77	2.31 ± 0.85	0.432
HDL-C (mmol/L)	1.00 (0.83–1.14)	1.06 (0.86–1.21)	0.130
UA (μmol/L)	284.5 (246.0–341.0)	283.3 (223.3–340.0)	0.301
Scr (μmol/L)	67.6 (60.1–76.1)	64.9 (58.3–78.0)	0.295
eGFR (mL/min)	97.8 ± 11.6	98.6 ± 16.0	0.720
Retinopathy (%)	24.2	26.5	0.726
Macroangiopathy (%)	65.7	75.9	0.132
Neuropathy (%)	71.7	83.1	0.069
Osteopenia/osteoporosis (%)	56.6	65.1	0.243
Sulfonylureas (%)	47.5	37.3	0.169
Metformin (%)	34.3	21.7	0.060
Thiazolidinediones (%)	29.3	19.3	0.119
α-Glucosidase inhibitor (%)	20.2	13.3	0.214
Insulin (%)	73.7	63.9	0.150
Statin (%)	75.8	85.5	0.099
Whole–body skeletal muscle mass (kg)	50.5 ± 4.7	43.7 ± 4.7	<0.001
ASM (kg)	22.8 ± 2.0	19.1 ± 1.9	<0.001
ASMI (kg/m^2)	7.7 ± 0.5	6.4 ± 0.5	<0.001
Handgrip strength (kg)	40.4 ± 10.3	29.1 ± 9.0	<0.001
Gait speed (m/s)	1.1 ± 0.2	1.0 ± 0.1	<0.001

Continuous values consistent with normal distribution are shown as mean ± standard deviation. Continuous values of skewed distribution are shown as median (upper and lower quartile). Categorical values are shown as frequency. %Body fat, percentage of body fat; ASM, appendicular skeletal muscle mass; ASMI, appendicular skeletal muscle mass index; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; SBP, systolic blood pressure; Scr, serum creatinine; TC, total cholesterol; TG, triglyceride; UA, uric acid.

Table 2 | Prevalence of sarcopenia according to the quartile of serum pentosidine

Men (n = 182)	Quartile of serum pentosidine (pmol/mL)				
	1st quartile (n = 46)	2nd quartile (n = 45)	3rd quartile (n = 46)	4th quartile (n = 45)	P
Sarcopenia (%)	8 (17.4)	18 (40.0)	24 (52.2)	33 (73.3)	<0.001

Values are shown as number (frequency). Serum pentosidine levels are as follows: 1st quartile (≤16.33), 2nd quartile (16.34–85.39), 3rd quartile (85.40–239.62) and 4th quartile (≥239.63), respectively.

Table 3 | Correlation analysis between serum pentosidine and associated clinical parameters

Variables	r	P
BMI	−0.18	0.014
HbA1c	0.20	0.006
FPG	0.15	0.038
ASM	−0.19	0.011
ASMI	−0.30	<0.001
Handgrip strength	−0.25	0.001

Correlation coefficients (r) and P are calculated using the Spearman correlation analysis. ASM, appendicular skeletal muscle mass; ASMI, appendicular skeletal muscle mass index; BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin.

Table 4 | Odds ratios of the risk for sarcopenia in middle-aged and elderly men with type 2 diabetes mellitus

Variables	β	OR	95% CI	P
Age	0.09	1.09	0.97–1.23	0.161
BMI	−1.23	0.29	0.15–0.55	<0.001
Visceral fat area	0.03	1.03	1.01–1.06	0.020
HbA1c	0.003	1.00	0.73–1.37	0.987
Serum pentosidine	0.01	1.01	1.01–1.02	<0.001
ASM	−1.16	0.32	0.18–0.56	<0.001

Age, body mass index (BMI), visceral fat area, glycosylated hemoglobin (HbA1c), serum pentosidine and appendicular skeletal muscle mass (ASM) were selected according to the positive (P < 0.05) results of the univariate logistic regression analysis with sarcopenia as independent variables for the multivariate logistic regression analysis, which showed that high BMI and high ASM were independent protective factors for sarcopenia in type 2 diabetes mellitus, whereas high serum pentosidine and high visceral fat area were independent risk factors. When BMI or ASM increased by 1 unit, the occurrence of sarcopenia was approximately 0.7 (odds ratio 0.29 and 0.32, respectively) lower than the previous unit. As for serum pentosidine or visceral fat area, when increased by 1 unit, the risk of sarcopenia was 1.01 and 1.03 times higher, respectively, than the previous unit.

Table 5 | Odds ratios of the risk for sarcopenia in middle-aged and elderly men with type 2 diabetes mellitus (after quartile grouping of serum pentosidine)

Variables	β	OR	95% CI	P
Age	0.08	1.08	0.96–1.22	0.187
BMI	−1.12	0.33	0.18–0.61	<0.001
Visceral fat area	0.03	1.03	1.00–1.06	0.032
HbA1c	0.06	1.06	0.78–1.45	0.707
Serum pentosidine quartiles	1.56	4.77	2.17–10.49	<0.001
ASM	−1.14	0.32	0.18–0.56	<0.001

Age, body mass index (BMI), visceral fat area, glycosylated hemoglobin (HbA1c), serum pentosidine and appendicular skeletal muscle mass (ASM) were selected according to the positive (P < 0.05) results of the univariate logistic regression analysis with sarcopenia as independent variables for the multivariate logistic regression analysis, which showed that high BMI and high ASM were independent protective factors for sarcopenia in type 2 diabetes mellitus, whereas high serum pentosidine and high visceral fat area were independent risk factors. After replacing serum pentosidine with serum pentosidine quartiles, when BMI or ASM increased by 1 unit, the occurrence of sarcopenia was approximately 0.7 (odds ratio 0.33 and 0.32, respectively) lower than the previous unit. As for visceral fat area, the risk of sarcopenia was 1.03-fold higher than the previous unit. When serum pentosidine increased by one quartile, the risk of sarcopenia was approximately 4.8-fold higher than the previous quartile.

aged and elderly men with type 2 diabetes mellitus, and elevated serum pentosidine was independently associated with the high prevalence of sarcopenia in type 2 diabetes mellitus, suggesting that AGEs might cause damage to skeletal muscle in diabetes patients. The detection of serum pentosidine levels could be helpful for the monitoring of type 2 diabetes mellitus complicated with sarcopenia.

AGEs, a kind of irreversible cross-linked polymer, which are produced through non-enzymatic glycation of glucose with amino-terminals of multiple proteins in body[9], accumulate in various tissues of diabetes patients and animal models, regulate intracellular signaling through binding to AGEs-receptors, such as RAGE, and activate nuclear factor-κB-induced inflammation reaction and oxidative stress[23], leading to the occurrence and development of nephropathy, retinopathy and other chronic diabetic complications[10,11].

Interestingly, AGEs have also been regarded as a kind of potential aging marker to participate in the occurrence of sarcopenia in the elderly[12,13,24]. Pentosidine is a common serological metabolite of AGEs, which is reported to have a positive correlation with AGEs and can represent the serum accumulation of AGEs in the body[15,16]. Previous studies showed that the increase of AGEs and/or serum pentosidine was an independent related factor of low ASMI in middle-aged and elderly people[13,25], and might contribute to the changes of muscle strength and function[26]. Eguchi *et al.*[27] even found that after correcting age and other factors, elderly women only with decreased cervical muscle mass (dropped head syndrome) had significantly higher levels of serum pentosidine than those in the normal control group. In addition to inflammatory reaction and oxidative stress[5], the decline of muscle mass caused by AGEs is associated with the inhibition of muscle anabolic signaling through the mammalian target of rapamycin complex 1 signaling pathway[28]. AGEs can directly decrease protein kinase B phosphorylation, reduce the expression of mammalian target of rapamycin complex 1 and then inhibit skeletal muscle synthesis. *In vitro* experiments in which AGEs decreased the regeneration of C2C12 myoblasts and lit on reduction of protein kinase B phosphorylation[29]. Furthermore, Chiu *et al.*[30]. recently observed that the expression of dystrophin, such as MAFbx, was also upregulated in murine myotubes when AGEs

given to them reduced the myotubes diameter, indicating that AGEs might simultaneously activate muscle degradation signaling to accelerate muscle atrophy.

Thus, we hypothesized that AGEs might be associated with diabetes-related sarcopenia and that chronic hyperglycemia accelerates the accumulation of AGEs and then inhibits muscle synthesis or promotes atrophy through the aforementioned mechanisms in elderly patients with type 2 diabetes mellitus. However, there are few studies on the relationship between AGEs or serum pentosidine and type 2 diabetes mellitus complicated with sarcopenia, and no studies in China, despite the increasing number of Chinese elderly patients with type 2 diabetes mellitus. In the present study, we took Chinese middle-aged and elderly men with type 2 diabetes mellitus as subjects, and found that pentosidine levels were negatively correlated with ASM, ASMI and handgrip strength, and elevated serum pentosidine was independently associated with the high prevalence of sarcopenia under the diabetic condition, suggesting that AGEs accumulation might cause damage to skeletal muscle in diabetes patients. The results were consistent in diabetic rodent models[30]. Intraperitoneal injection for 4 weeks of streptozotocin-induced diabetes resulted in greater serum AGEs in mice and the skeletal muscle mass significantly decreased. Whereas Ala-Cl, an AGEs scavenger, could attenuate this condition, promote repair after muscle injury, and increase the cross-sectional area and mass of skeletal muscle[30].

The results further clarified that the harmful effect of AGEs was specific to ASMI and handgrip strength, but not correlated with gait speed, namely physical performance. A reason for the discrepancy might be the status or phase of diabetes. Indeed, previous studies found lower physical performance or function, but not muscle quality decline in patients with relatively mild diabetes[31,32], indicating that decline in physical performance might precede muscle mass decrease, which consequently weakens the relationship between hyperglycemia reflected by AGEs and physical performance decline during the late phase of diabetes.

It has been reported that sarcopenia could depend on age[32] and the duration of diabetes[33], despite the negative results the present analysis showed. A possible reason might be that some kinds of antidiabetic medications, such as insulin sensitizers, attenuate the decline of muscle mass and muscle function[34] whereas the use of stains, a type of lipid-lowering agent, is associated with muscle weakness[35]. The frequencies of patients who were prescribed insulin sensitizers and statins were approximately 40 and 60%, respectively, which might confound the association of age or the duration of diabetes and sarcopenia in the present study population.

In the present study, serum pentosidine, but not HbA1c, was related to the occurrence of sarcopenia. Previous studies showed that AGEs reflected integration of past long-term glycemic control and were more stable than HbA1c[15]. It was also reported that lower limb muscle strength was inversely correlated with AGEs, but not HbA1c in patients with type 1

diabetes[36]. Thus, it is suggested that sarcopenia in patients with type 2 diabetes mellitus could also be associated with chronic long-term hyperglycemia, not short-term glycemic control.

In addition, another difference of clinical characteristics in the present study between the type 2 diabetes mellitus sarcopenia group and the type 2 diabetes mellitus non-sarcopenia group was adiposity. Patients with sarcopenia showed lower BMI, %body fat, fat mass and visceral fat area compared with patients without sarcopenia. High BMI was an independent protective effect on sarcopenia in the population. Although previous studies showed that obese patients with type 2 diabetes mellitus had lower muscle strength than healthy bodyweight participants because of lipotoxicity[37], It was recently reported that the mechanism of lipotoxicity might be involved with the decrease in lipid storage capacity of adipocytes and ectopic fat accumulation in peripheral tissues, such as the liver and skeletal muscle[5]. A study reported that the accumulation of intramuscular fat was inversely correlated with lower limb muscle function in elderly individuals[38]. However, we could not evaluate the intramuscular fat, so the detailed mechanism of which could not be clarified in the present study.

Different from previous clinical studies[6,13] in which only the decline of muscle mass was used to diagnose sarcopenia, the present study strictly followed the updated consensus on diagnosis and treatment of Asian sarcopenia in 2019, taking ASMI, handgrip strength and gait speed as diagnostic indicators of sarcopenia to avoid omitting patients with decreased muscle strength and physical function. In addition, although an increasing number of scholars believe that sarcopenia is one of the complications of diabetes, the exact mechanism of diabetes damage to skeletal muscle is still unclear[32]. There are few studies on the relationship between AGEs or serum pentosidine and type 2 diabetes mellitus complicated with sarcopenia, only in elderly women[6] or in specific samples from Japan[32], but no studies in China, although type 2 diabetes mellitus was also reported to be associated with sarcopenia in Chinese older adults. In the present study, it was found that serum pentosidine could be used as an independent risk factor for sarcopenia in middle-aged and elderly male patients with type 2 diabetes mellitus, which supplemented Chinese male data to some extent, and suggested that poor glycemic control could increase the risk of sarcopenia in type 2 diabetes mellitus patients. The early detection of serum pentosidine levels in clinics might be helpful to monitor type 2 diabetes mellitus patients with sarcopenia.

There were several limitations to this present study. First, the sample size of participants from a single hospital in China was not large enough to make definite conclusions. Second, we detected pentosidine, reflecting serum levels of AGEs in middle-aged and elderly male patients with type 2 diabetes mellitus. Although there was a good correlation between them, serum pentosidine was just a part of AGEs, which did not indicate other AGEs metabolites, such as pyrrolidine, were also associated with diabetes-related sarcopenia. Third, we could not

evaluate the parameter of insulin resistance, which might be involved in serum pentosidine[6]. Fourth, we were also unable to assess the influence of lifestyle, including diet and physical exercise, especially resistance training, on the decline of muscle mass or strength, which might impact diabetes-related sarcopenia[3,4]. However, we evaluated the exercise habits of the participants, and found that there were no differences between sarcopenia patients and non-sarcopenia patients. Finally, although we suggested that elevated AGEs in serum might be risk factors of sarcopenia, it was impossible to determine the causal relationship between AGEs and the incidence of sarcopenia because of the cross-sectional design. It is necessary to carry out more prospective studies.

In conclusion, the present study showed that serum pentosidine levels were inversely associated with indices of muscle mass and strength in Chinese middle-aged and elderly men with type 2 diabetes mellitus. Elevated serum pentosidine was an independent risk factor for sarcopenia, and the detection of serum pentosidine levels in clinic might be helpful for the monitoring of type 2 diabetes mellitus complicated with sarcopenia in the population.

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DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1 | Correlation analysis between serum pentosidine and other clinical parameters.