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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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ORIGINAL ARTICLE

Observational Study

Skeletal muscle loss is associated with diabetes in middle-aged and older Chinese men without non-alcoholic fatty liver disease

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Author contributions: Chen LY did the study design and literature research, wrote the manuscript, and made critical editing; Chen LY and Lin HD made definition of intellectual content and did data analysis; Chen LY, Xia MF, Wu L, Li Q, Hu Y, Ma H, Gao X, and Lin HD participated in the data acquisition and clinical study; Gao X and Lin HD contributed to study concept and did the critical review and editing of the manuscript; Gao X was the guarantor of integrity of the entire study; Lin HD contributed to statistical analysis; all authors approved the final draft of the manuscript and agreed to submit it for publication.

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Abstract

BACKGROUND

Skeletal muscle, a key insulin target organ, has been reported to be associated with diabetes mellitus (DM). Compared to non-diabetic patients, diabetic patients have decreased muscle mass and a higher prevalence of sarcopenia, and patients with sarcopenia may be at increased risk of developing diabetes. In individuals with nonalcoholic fatty liver disease (NAFLD), sarcopenia is associated with the severity of fibrosis and steatosis. Previous studies have demonstrated that NAFLD is strongly associated with DM and sarcopenia.

AIM

To determine the relationship between skeletal muscle mass and DM in Chinese middle-aged and elderly men, and whether the association is affected by NAFLD.

METHODS

Skeletal muscle mass was calculated as appendicular skeletal muscle mass (ASM) in kg/body weight × 100%. Liver fat content (LFC) was measured using a quantitative ultrasound method.

RESULTS

As the ASM decreased, fasting blood glucose (FBG), 2-h postprandial blood glucose (2hBG), and LFC increased in both genders, as did the prevalence of DM and NAFLD. Spearman analysis showed that the ASM was negatively correlated with the FBG, 2hBG, and LFC. Stepwise logistic regression analysis showed that after adjustments, the ASM quartile was negatively associated with the presence of DM in males, but not in females. Subgroup analysis showed that the ASM

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quartiles remained negatively correlated with the presence of DM in the non-NAFLD population (including males and females), but no correlation was found between ASM quartiles and the presence of DM in the NAFLD population. When stratified by LFC quartiles, ASM was negatively correlated with the presence of DM in the first and second LFC quartiles in males.

CONCLUSION

Skeletal muscle mass loss was shown to be associated with the presence of DM in males, but not in females; NAFLD weakens this association. The results suggested that the stratified management of diabetes mellitus should be considered according to skeletal muscle mass and NAFLD.

Key Words: Diabetes mellitus; Liver fat content; Non-alcoholic fatty liver disease; Skeletal muscle mass

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Core Tip: Aging is becoming more severe in China. The present study showed that decreased skeletal muscle mass is associated with the presence of diabetes mellitus in males but not in females; non-alcoholic fatty liver disease weakens this association. The results suggested that stratified management of diabetes mellitus should be considered according to skeletal muscle mass and non-alcoholic fatty liver disease.

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INTRODUCTION

The progressive decrease in skeletal muscle mass, strength, and function is known as sarcopenia. Sarcopenia significantly increases with age[1]. With the growth of the aging society, sarcopenia has become a major focus of worldwide public health research and public policy[2]. Skeletal muscle loss reduces mobility in the elderly and increases the risk of fractures and falls[3,4]. In addition, skeletal muscle loss is closely related to metabolic disorders, tumors, and other chronic diseases[5-8]. As the largest non-fat component of the human body, skeletal muscle is responsible for 80% of postprandial glucose disposition[9]. As an important insulin target organ for glucose uptake and utilization, skeletal muscle loss leads to a systemic metabolic disorder, which is closely related to diabetes mellitus (DM)[9,10]. Compared to non-diabetics, patients with DM have lower muscle mass and a high prevalence of sarcopenia[11-13]. Conversely, reduced skeletal muscle mass may also increase the risk of DM[14].

Non-alcoholic fatty liver disease (NAFLD) is a chronic liver disease caused by abnormal accumulation of fat in the liver. Previous studies have shown that NAFLD often coexists with the occurrence and progression of type 2 DM or is associated with an increased risk of type 2 DM[15]. A meta-analysis showed that 28%-70% of type 2 DM patients have NALFD[16]. Another summarization of data concluded that 22.5% of NAFLD patients have type 2 DM[17]. Taken together, the above findings suggest that interactions exist between NAFLD and type 2 DM. Because skeletal muscle mass loss may also increase the risk of DM[14], skeletal muscle may indirectly affect the development of NAFLD. Indeed, previous studies have shown that age-related skeletal muscle mass reduction is associated with NAFLD[18,19]. Other studies have reported that sarcopenia is associated with the severity of fibrosis and steatosis independent of inflammation, insulin resistance, and obesity in patients with NAFLD and metabolic disorders[20,21]. Although large population studies are needed to assess the impact of interactions between sarcopenia, DM, and NAFLD progression, no such research has been conducted to determine the relationship between sarcopenia, DM, and NAFLD progression in a Chinese community population. In the

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present study, we recruited participants ≥ 45 years of age from Changfeng Community in Shanghai to conduct a large-scale community population study to determine the association between skeletal muscle mass (SMM), DM, and NAFLD, and to provide new evidence for the prevention and treatment of NAFLD and DM.

MATERIALS AND METHODS

Participants

A total of 5626 residents ≥ 45 years of age were enrolled from Changfeng community in Shanghai between May 2010 and December 2012 according to the Shanghai Changfeng Study which has been reported elsewhere[22]. The inclusion criteria were as follows: (1) The subjects were 45 years of age and older; (2) people with autonomous capacity were able to cooperate with the research; and (3) without acute diseases such as myocardial infarction, acute stroke, and acute infection. Participants meeting the following criteria were excluded: (1) Lacking biochemical and liver fat content (LFC) data; (2) lacking dual energy X-ray absorptiometry (DXA) data; and (3) viral hepatitis and excessive alcohol consumption. Following application of the inclusion and exclusion criteria, 3969 subjects were included in the study (1370 males and 2599 females).

The details of the research were explained to all participants and written informed consent was obtained from all of them. The study was approved by the Ethics Committee of Zhongshan Hospital of Fudan University (No. 2008-119).

Data collection

All participants were interviewed and the medical histories were recorded by trained researchers using a standard questionnaire. Then, standing height and body weight were measured without shoes and outer clothing. The body mass index (BMI) was calculated as the weight in kg divided by the height in m squared (kg/m^2). Resting blood pressure (BP), including systolic BP (SBP) and diastolic BP (DBP), were measured three times with an electronic BP monitor (Omron Model HEM-752 FUZZY; Omron Co., Dalian, China) and the average data were calculated.

Blood samples were collected after overnight fasting for at least 10 h. Biochemical indices, including fasting blood glucose (FBG), total cholesterol (TC), triglycerides (TG), and high-density lipoprotein-cholesterol (HDL-C), were measured with an automated bio-analyzer (Hitachi 7600; Tokyo, Japan). Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald equation. The 2-h postprandial blood glucose (2hBG) level was determined following a 75-g oral glucose load for non-diabetics or a 100-g steamed bread meal for patients diagnosed with DM. An electrochemiluminescence immunoassay was used to measure the serum insulin concentration. The homeostasis model assessment for insulin resistance (HOMA-IR) was calculated by multiplying the FBG (mmol/L) times fasting insulin (mU/L) and dividing by 22.5.

Hepatic ultrasonography scanning was performed by an experienced technician using a GE Logiq P5 scanner (GE Healthcare, Milwaukee, WI, United States) with a 4-MHz probe. The liver ultrasound images were analyzed with ImageJ 1.41o (National Institutes of Health, Bethesda, MD, United States) and standardized using a tissue-mimicking phantom (Model 057; Computerized Imaging Reference Systems, Norfolk, VA, United States). The participants' details were blinded to the technician. LFC was measured according to the method described in detail elsewhere[23]. The LFC was calculated using the following equation: LFC (%) = 62.592 × standardized US hepatic/renal ratio + 168.076 × standardized US hepatic attenuation rate - 27.863.

Body composition, including lean mass and fat mass (FM), was measured using DXA (Lunar iDXA; GE Healthcare). All measurements were carried out by a single, trained technician at a single clinical center. Manual DXA analysis software was used to analyze all DXA scans. The FM percentage (FM%) was calculated by dividing FM by total body mass. The SMM was calculated as weight adjusted by the appendicular skeletal muscle mass (ASM) [ASM% = ASM (kg)/body weight (kg) × 100%][20].

Definitions

Obesity was defined as a BMI ≥ 28 kg/m^2 according to Chinese criteria[24]. DM was defined as a FBG ≥ 7.0 mmol/L or a 2hBG ≥ 11.1 mmol/L based on oral glucose tolerance test by the 1999 WHO criteria[25], or self-reported current hypoglycemic treatment. NAFLD was diagnosed when the LFC exceeded a cut-off value of 9.15% by ultrasonography, excluding excessive alcoholic intake and virus hepatitis[23].

Statistical analysis

All statistical analyses were performed using SPSS software (version 19.0; SPSS, Inc., Chicago, IL, United States). Continuous data are presented as the mean ± SD except for skewed variables, which are presented as the median with the inter-quartile range in parentheses (25%-75%). All subjects were divided into four groups according to gender-specific quartiles of ASM% as follows: Males (Q1, ≥ 32.0%; Q2, ≥ 30.5%-< 32.0%; Q3, ≥29.0%-< 30.5%; and Q4: < 29.0%); females (Q1, ≥ 26.8%; Q2, ≥25.5%-< 26.8%; Q3, ≥ 24.3%-< 25.5%; and Q4, < 24.3%). Analysis of variance or the Kruskal-Wallis test was used for inter-group comparisons of continuous data, whereas the chi-squared test was used for comparisons of categorical variables. The Spearman analysis was performed to assess the relationships between the ASM% and blood glucose concentration, as well as other clinical parameters. Multivariate logistic regression analyses were performed to determine the association of ASM% quartiles with DM after adjusting for age, smoking, DM family history, FM, interaction between FM and ASM% quartiles, obesity, BP, serum TG, HDL-C, and HOMA-IR (in order). The interaction between ASM% and FM was included in the multiple regression models because there were significant correlations between ASM%, FM, and blood glucose concentration. To further determine whether NAFLD affects the relationship between SMM and DM, subgroup analysis was performed based on the presence of NAFLD and LFC quartiles. *P*-values < 0.05 were considered statistically significant.

RESULTS

Characteristics of subjects

A total of 3969 subjects were included; the mean age was 63.3 years and the mean BMI was 24.1 kg/m^2. The characteristics of the subjects are shown in Table 1. All subjects with a lower ASM% were older and had a higher body weight and BP (specifically, a higher BMI, FM, FM%, SBP, and DBP). The lipid disorders were aggravated in subjects with a lower ASM%, who had higher TC, TG, and LDL-C concentrations, and a lower HDL-C concentration. The most noteworthy findings were that the FBG, 2hBG, HOMA-IR, and LFC levels increased gradually, as well as the prevalence of DM and NAFLD, with ASM% decreasing in both male and female participants (P < 0.001).

Effects of SMM on glucose metabolism and other metabolic parameters

The Spearman analysis showed that in addition to age, body composition, and metabolic parameters, including BMI, FM, FM%, TG, LDL-C, SBP, and DBP, the ASM% was negatively correlated with the FBG, 2hBG, HOMA-IR, and LFC levels (P < 0.001; Table 2).

To further determine whether a low ASM% was associated with the presence of DM, we performed logistic stepwise regression analysis with ASM% quartiles as independent variates and the presence of DM as a dependent variate. As shown in Table 3, a crude analysis showed that the odds ratios (ORs) for DM were 0.665 [95% confidence interval (CI): 0.592-0.746) in males and 0.775 (95%CI: 0.710-0.840) in females. The relationship remained significant in males after adjusting for age, smoking, family history of DM, FM, FM × ASM%, obesity, SBP, TG, HDL-C, and HOMA-IR in order (OR = 0.537; 95%CI: 0.312-0.923), but the association was not apparent in females (OR = 0.985; 95%CI: 0.614-1.580; Table 3).

Effect of NAFLD on relationship between SMM and DM

NAFLD increases the prevalence and risk of type 2 DM[15]. Indeed, we showed that the ASM% was negatively associated with LFC. Thus, we performed logistic analysis to determine the effect of NAFLD on the relationship between SMM and the presence of DM, as shown in Table 4. Among the 2658 non-NAFLD participants, the ASM% quartile was negatively correlated with the presence of DM in males and females before adjustment. After multiple adjustments, the negative association remained significant in males (OR = 0.330; 95%CI: 0.157-0.694) but not in females (OR = 0.800; 95%CI: 0.416-1.537). Among the 1311 NAFLD patients, the correlation between the ASM% and DM was absent after adjustments in both genders.

Because NAFLD was diagnosed by LFC in the present study, LFC was displayed as a continuous variable. We further stratified the population by LFC quartiles from low to high. In the first three LFC quartiles in males and the first two LFC quartiles in females before adjustments, the ASM% quartiles were negatively correlated with the presence of DM. The relationship remained significant in the first and second quartiles

Table 1 Characteristics of male participants according to appendicular skeletal muscle mass (%) quartiles, *n* (%)

Male	Quartiles of ASM%				*P* value	Female	Quartiles of ASM%				*P* value
	Q1	Q2	Q3	Q4			Q1	Q2	Q3	Q4	
	n = 343	*n* = 343	*n* = 343	*n* = 342			*n* = 649	*n* = 651	*n* = 649	*n* = 650	
Age (yr)	61.6 ± 8.8	63.2 ± 8.9[a]	63.2 ± 8.9[a]	69.4 ± 10.1[a]	< 0.001	Age, yr	60.8 ± 8.7	61.7 ± 8.8[a]	62.9 ± 9.4[a]	64.8 ± 9.7[a]	< 0.001
BMI (kg/m^2)	22.7 ± 2.9	24.3 ± 3.4[a]	24.3 ± 3.4[a]	25.6 ± 2.9[a]	< 0.001	Weight, kg	55.1 ± 8.1	58.0 ± 8.3[a]	59.8 ± 8.6[a]	62.6 ± 9.7[a]	< 0.001
WC, cm	80.6 ± 9.1	85.8 ± 7.7[a]	85.8 ± 7.7[a]	91.7 ± 8.5[a]	< 0.001	BMI, kg/m^2	22.0 ± 2.7	23.5 ± 2.9[a]	24.4 ± 3.1[a]	26.0 ± 3.7[a]	< 0.001
FM, kg	17.9 ± 4.6	20.3 ± 4.3[a]	20.3 ± 4.3[a]	24.5 ± 4.9[a]	< 0.001	WC, cm	76.4 ± 7.9	80.5 ± 8.6[a]	82.8 ± 8.5[a]	87.5 ± 9.4[a]	< 0.001
FM%	22.4 ± 4.2	27.2 ± 3.2[a]	27.2 ± 3.2[a]	33.1 ± 3.3[a]	< 0.001	FM, kg	20.0 ± 4.1	22.5 ± 4.2[a]	24.8 ± 4.8[a]	27.6 ± 5.8[a]	< 0.001
ASM%	32.6 ± 1.9	30.6 ± 1.0[a]	30.6 ± 1.0[a]	27.2 ± 1.6[a]	< 0.001	FM%	32.2 ± 3.9	36.3 ± 2.9[a]	38.8 ± 3.0[a]	42.4 ± 3.4[a]	< 0.001
SBP, mmHg	129 ± 18	134 ± 17[a]	134 ± 17[a]	141 ± 19[a]	< 0.001	ASM%	27.7 ± 2.0	25.7 ± 0.8[a]	24.5 ± 0.6[a]	22.8 ± 1.1[a]	< 0.001
DBP, mmHg	76 ± 11	78 ± 11[a]	78 ± 11[a]	77 ± 10	0.014	SBP, mmHg	129 ± 20	132 ± 19[a]	135 ± 20[a]	138 ± 19[a]	< 0.001
FBG, mmol/L	5.4 ± 1.4	5.7 ± 1.7[a]	5.7 ± 1.7[a]	6.0 ± 1.7[a]	< 0.001	DBP, mmHg	72 ± 10	74 ± 10[a]	75 ± 9	76 ± 10[a]	< 0.001
2hBG, mmol/L	6.7 ± 2.5	7.6 ± 2.9[a]	7.6 ± 2.9[a]	8.9 ± 3.7[a]	< 0.001	FBG, mmol/L	5.3 ± 1.0	5.4 ± 1.2[a]	5.5 ± 1.3[a]	5.7 ± 1.7[a]	< 0.001
HOMA-IR	1.2 (0.8-1.9)	1.8 (1.2-2.5)[a]	1.8 (1.2-2.5)[a]	2.5 (1.7-3.9)[a]	< 0.001	2hBG, mmol/L	6.8 ± 2.6	7.2 ± 2.5[a]	7.7 ± 4.0[a]	8.3 ± 3.4[a]	< 0.001
TG, mmol/L	1.2 (0.9-1.8)	1.4 (1.0-2.0)[a]	1.4 (1.0-2.0)[a]	1.6 (1.2-2.2)[a]	< 0.001	HOMA-IR	1.6 (1.0-2.3)	1.8 (1.2-2.6)[a]	2.1 (1.4-3.2)[a]	2.3 (1.6-3.6)[a]	< 0.001
TC, mmol/L	4.6 ± 0.8	4.7 ± 0.8[a]	4.7 ± 0.8[a]	4.7 ± 0.8[a]	0.049	TG, mmol/L	1.2 (0.9-1.8)	1.4 (1.0-2.0)[a]	1.5 (1.1-2.1)	1.6 (1.2-2.2)[a]	< 0.001
HDL-C, mmol/L	1.40 ± 0.37	1.26 ± 0.29[a]	1.26 ± 0.29[a]	1.20 ± 0.25[a]	< 0.001	TC, mmol/L	5.2 ± 0.8	5.3 ± 0.9	5.3 ± 0.9	5.4 ± 1.0[a]	< 0.001
LDL-C, mmol/L	2.59 ± 0.72	2.75 ± 0.74	2.75 ± 0.74	2.72 ± 0.72[a]	0.004	HDL-C, mmol/L	1.64 ± 0.42	1.54 ± 0.37[a]	1.48 ± 0.34	1.46 ± 0.33[a]	< 0.001
LFC%	3.9 (1.9-7.8)	5.0 (2.3-10.8)[a]	5.0 (2.3-10.8)[a]	6.3 (2.6-13.3)[a]	< 0.001	LDL-C, mmol/L	2.86 ± 0.75	3.02 ± 0.79[a]	3.04 ± 0.83[a]	3.14 ± 0.86[a]	< 0.001
NAFLD *n* (%)	68 (19.9)	107 (31.2)[a]	107 (31.2)[a]	141 (41.2)[a]	< 0.001	LFC, %	4.8 (2.5-9.7)	5.8 (2.7-11.6)[a]	5.9 (2.7-11.8)[a]	7.1 (3.2-13.6)[a]	< 0.001
DM *n* (%)	42 (12.3)	81 (23.6)[a]	81 (23.6)[a]	123 (35.8)[a]	< 0.001	NAFLD *n* (%)	171 (26.3)	214 (32.9)[a]	219 (33.7)[a]	275 (42.3)[a]	< 0.001
						DM *n* (%)	88 (13.6)	106 (16.3)	152 (23.4)[a]	158 (24.3)[a]	< 0.001

[a]*P* < 0.05, compared with Q1. The quartiles of ASM% were divided as follows: Male, (Q1, ≥ 32.0%; Q2, ≥ 30.5%-32.0%; Q3, ≥ 29.0%-< 30.5%; Q4: < 29.0%) and female, (Q1, ≥ 26.8%; Q2, ≥ 25.5% -< 26.8%; Q3, ≥ 24.3%-< 25.5%; Q4, < 24.3%).

BMI: Body mass index; WC: Waist circumference; FM: Fat mass; ASM: Appendicular skeletal muscle mass; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FBG: Fasting blood glucose; 2hBG: 2-h postprandial blood glucose; HOMA-IR: Homeostasis model assessment for insulin resistance; TG: Triglycerides; TC: Total cholesterol; HDL-C: High-density lipoprotein-cholesterol; LDL-C: Low-density lipoprotein cholesterol; LFC: Liver fat content; NAFLD: Non-alcoholic fatty liver disease; DM: Diabetes mellitus.

in males after adjustment; however, the correlation no longer existed after adjustments in the third and fourth quartiles in males and in all quartiles in females (Table 5).

DISCUSSION

Several studies have determined the relationship between SMM and DM. Specifically, SMM loss increases the risk of DM in the middle-aged and elderly[10-14]. A cohort study conducted by Korean researchers also showed that a lower ASM% increases the risk of DM, even in the young and middle-aged[26]. The results of our study not only confirmed these findings, but also showed a gender difference in the relationship between muscle loss and DM. In the current study, the FBG, 2hBG, and HOMA-IR increased with the prevalence of DM while ASM% decreased in male and female participants. The SMM, as measured by ASM%, was negatively associated with the

Table 2 Spearman analysis of appendicular skeletal muscle mass (%) and other clinical parameters

	ASM%	
	Male (*r*, *P* value)	Female (*r*, *P* value)
Age (years)	-0.317, < 0.001	-0.164, < 0.001
BMI (kg/m$^{2)}$	-0.347, < 0.001	-0.441, < 0.001
WC (cm)	-0.452, < 0.001	-0.448, < 0.001
FM (kg)	-0.605, < 0.001	-0.590, < 0.001
FM (%)	-0.792, < 0.001	-0.799, < 0.001
FBG (mmol/L)	-0.177, < 0.001	-0.106, < 0.001
2hBG (mmol/L)	-0.254, < 0.001	-0.201,< 0.001
HOMA-IR	-0.385, < 0.001	-0.264, < 0.001
TG (mmol/L)	-0.198, < 0.001	-0.193, < 0.001
TC (mmol/L)	-0.049, 0.071	-0.087, < 0.001
HDL-C (mmol/L)	0.213, < 0.001	0.162, < 0.001
LDL-C (mmol/L)	-0.075, 0.006	-0.119, < 0.001
SBP (mm Hg)	-0.244, < 0.001	-0.192, < 0.001
DBP (mm Hg)	-0.075, 0.006	-0.139, < 0.001
LFC (%)	-0.149, < 0.001	-0.113, < 0.001

ASM: Appendicular skeletal muscle mass; BMI: Body mass index; WC: Waist circumference; FM: Fat mass; FBG: Fasting blood glucose; 2hBG: 2-h postprandial blood glucose; HOMA-IR: Homeostasis model assessment for insulin resistance; TG: Triglycerides; TC: Total cholesterol; HDL-C: High-density lipoprotein-cholesterol; LDL-C: Low-density lipoprotein cholesterol; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; LFC: Liver fat content.

Table 3 Multivariate-adjusted associations of appendicular skeletal muscle mass (%) quartiles with diabetes mellitus

	Male	Female
	OR (95%CI, *P* value)	OR (95%CI, *P* value)
Unadjusted	0.665	0.775
	(0.592-0.746, < 0.001)	(0.710-0.847, < 0.001)
Model 1	0.527	0.505
	(0.336-0.826, 0.005)	(0.342-0.745, 0.001)
Model 2	0.640	0.728
	(0.401-1.020, 0.051)	(0.481-1.101, 0.133)
Model 3	0.537	0.985
	(0.312-0.923, 0.024)	(0.614-1.580, 0.950)

Model 1: Adjusted for age, cigarette smoking, diabetes family history, FM, and FM × ASM% quartiles, and obesity. Model 2: Adjusted for covariates in Model 1 plus SBP, TG, and HDL-C. Model 3: Adjusted for covariates in Model 3 plus HOMA-I. OR: Odds ratio; FM: fat mass; ASM: Appendicular skeletal muscle mass; SBP: Systolic blood pressure; TG: Triglycerides; HDL-C: High-density lipoprotein-cholesterol; HOMA-IR: Homeostasis model assessment for insulin resistance.

blood glucose concentration, but logistic stepwise regression analysis showed that SMM loss may be associated with the presence of DM in males. The dissociation of SMM loss and DM in women is noteworthy, especially after adjustment by FM and lipid parameters. The reason underlying this interesting phenomenon is not apparent; however, one reason may be that the subjects in the present study were elderly. A previous study showed that as age increases, the body fat percentage gradually increases, which is more pronounced in older women[26]. Another possible

Table 4 Multivariate-adjusted associations of appendicular skeletal muscle mass (%) quartiles with diabetes mellitus in participants with or without non-alcoholic fatty liver disease

	Male	Female
	OR (95%CI, *P* value)	OR (95%CI, *P* value)
	Non-NAFLD (*n* = 2658)	
Unadjusted	0.635	0.770
	(0.548-0.736, < 0.001)	(0.682-0.870, < 0.001)
Model 1	0.403	0.581
	(0.221-0.735, 0.003)	(0.344-0.981, 0.042)
Model 2	0.455	0.807
	(0.246-0.842, 0.012)	(0.463-1.409, 0.452)
Model 3	0.330	0.800
	(0.157-0.694, 0.003)	(0.416-1.537, 0.503)
	NAFLD (*n* = 1311)	
Unadjusted	0.789	0.845
	(0.650-0.956, 0.016)	(0.739-0.966, 0.014)
Model 1	1.259	0.508
	(0.542-2.924, 0.592)	(0.265-0.975, 0.042)
Model 2	1.954	0.710
	(0.788-4.851, 0.148)	(0.355-1.418, 0.332)
Model 3	1.328	1.106
	(0.435-4.055, 0.619)	(0.485-2.523, 0.810)

Model 1: Adjusted for age, cigarette smoking, diabetes family history, FM, FM × ASM% quartiles, and obesity. Model 2: Adjusted for covariates in Model 1 plus SBP, TG, and HDL-C. Model 3: Adjusted for covariates in Model 3 plus HOMA-IR. OR: Odds ratio; FM: Fat mass; ASM: Appendicular skeletal muscle mass; SBP: Systolic blood pressure; TG: Triglycerides; HDL-C: High-density lipoprotein-cholesterol; HOMA-IR: Homeostasis model assessment for insulin resistance.

explanation is the difference in body fat distribution between genders. As reported, age and gender are important factors influencing plasma lipid levels, such as TC, LDL-C, and HDL-C, and females are more likely to have insulin resistance and lipid disorders than males as age increases[27]. Although the body fat percentage of females is higher than age-matched males, and the accumulation of intra- and inter-muscular fat is more significant in females than in males as age increases[28], females have more type I muscle fibers than males, which contributes to stronger oxidative function in skeletal muscle[29]. In addition, hormones, especially estrogen, can influence TG and free fatty acid metabolism[30]. The estrogen decreases with aging, especially in postmenopausal women, which may result in a TG reduction, and is associated with a reduced risk of DM[31]. In addition, in the process of aging, the decline in SMM is more remarkable in males than in females, which also contributes to the more significant effect of SMM loss on the risk of DM in males[32]. This physiologic differences of females from males might neutralize the effect of SMM reduction on DM, and thus reduce its association with the presence of DM. The results of our study suggested that gender-stratified management of DM according to the SMM should be considered. Indeed, increased SMM might have a more beneficial effect on improving glucose metabolism in males.

NAFLD is an important risk factor for DM[15-17], and several previous studies have demonstrated that low SMM is also closely associated with NAFLD[18-21]. In the present study, the SMM was negatively associated with LFC, which was in agreement with previous results[18,19]. Whether LFC influences the relationship between sarcopenia and DM is unknown. As an important risk factor for DM, excessive liver fat accumulation could lead to insulin resistance, mitochondrial dysfunction, and hyperlipidemia[33,34]. Reducing the LFC may be more important with respect to improving DM in patients with NAFLD[15-17]. Our results showed that a relationship

Table 5 Multivariate-adjusted associations of appendicular skeletal muscle mass (%) quartiles with diabetes mellitus in participants with different liver fat content, *n* (%)

LFC	DM	OR (95%CI, *P* value)	OR (95%CI, *P* value)
Male		Unadjusted	After adjusted
Q1 (*n* = 389)	82 (21.1)	0.635 (0.504-0.799, < 0.001)	0.308 (0.102-0.932, 0.032)
Q2 (*n* = 350)	66 (18.8)	0.540 (0.416-0.700, < 0.001)	0.184 (0.049-0.685, 0.012)
Q3 (*n* = 306)	74 (24.2)	0.760 (0.599-0.963, 0.023)	0.678 (0.158-2.908, 0.601)
Q4(*n* = 325)	116 (35.7)	0.830 (0.665-1.035, 0.099)	1.561 (0.440-5.539, 0.491)
Female			
Q1 (*n* = 605)	84 (13.9)	0.828 (0.672-1.021, 0.077)	0.964 (0.311-2.990, 0.949)
Q2 (*n* = 642)	92 (14.3)	0.745 (0.609-0.913, 0.004)	0.517 (0.170-1.578, 0.247)
Q3 (*n* = 685)	118 (17.2)	0.739 (0.615-1.887, 0.091)	0.750 (0.274-2.048, 0.574)
Q4 (*n* = 667)	210 (31.5)	0.871 (0.750-1.011, 0.070)	1.122 (0.445-2.830, 0.808)

The quartiles of LFC were divided as follows: Q1: < 2.53%; Q2: ≥ 2.53%-< 5.52%; Q3: ≥ 5.52%- < 11.61%; Q4: ≥ 11.61%. Adjusted factors: Age, cigarette smoking, diabetes family history, FM, FM × ASM% quartiles, obesity, SBP, TG, HDL-C, and HOMA-IR. LFC: Liver fat content; DM: Diabetes mellitus; OR: Odds ratio; FM: Fat mass; ASM: Appendicular skeletal muscle mass; SBP: Systolic blood pressure; TG: Triglycerides; HDL-C: High-density lipoprotein-cholesterol; HOMA-IR: Homeostasis model assessment for insulin resistance.

between SMM and DM existed in the non-NAFLD male population and was not present in the NAFLD population. Further analysis in our study revealed an association between SMM and DM that persisted in males with an LFC < 5.52%, which was similar to a histopathologic diagnosis of fatty liver. The findings also indicate that in males with a LFC < 5.52%, increasing SMM may prevent DM. In the male non-NAFLD population, SMM enhancement might facilitate DM treatment.

The mechanism underlying the relationship between low SMM and DM is not fully understood. It is known that insulin resistance and systemic inflammation play important roles in the development of both SMM reduction and DM[9,10,35,36]. As an important target organ of insulin action, skeletal muscle plays an important role in maintaining glucose metabolism stability[9,10]. Decreased SMM, which is often accompanied by intermuscular fat accumulation, increases macrophage infiltration, mitochondrial dysfunction, and inflammatory factors release, thus contributing to insulin resistance and reducing glucose uptake and utilization[37,38]. The current study also showed that in the male population, age-related SMM loss is independently associated with the presence of DM after adjustment for obesity, HOMA-IR, and all components of metabolic syndrome, which suggest that there may be other mechanisms to account for this association. Although it is unclear whether SMM loss is the cause or consequence of DM, direct crosstalk between skeletal muscle and glucose metabolism has been demonstrated. Previous studies have shown that skeletal muscles secrete a variety of cytokines, such as IL-6 and irisin, that regulate insulin sensitivity, promote glucose uptake by skeletal muscle cells, reduce liver gluconeogenesis, and improve glucose metabolism by acting on adipose tissue, the liver, and other tissues [39,40]. Impairment of muscle secretary function due to muscle loss may contribute to the development of DM.

The current study is the first to assess the influence of NAFLD on the association of DM with gender- and age-related SMM in a large-scale community population. Our findings may develop a new perspective for prevention of DM, especially in the male non-NAFLD population. There were also several limitations in the current study. First, the study had a cross-sectional design, which cannot demonstrate a causal relationship between SMM and DM. Thus, it is necessary to further verify our findings in a prospective cohort study. Second, the association between SMM loss and DM only existed in the first and second LFC quartiles, and the cut-off point for LFC should be further conformed. Third, several serum myokines were not detected in the current study, which might help explore the mechanisms underlying the relationship between low SMM and DM. Finally, this study was not able to collect/analyze current DM prevalence data for these patients with non-diabetic sarcopenia in 2010-2012.

CONCLUSION

In conclusion, SMM loss was shown to be associated with the presence of DM in Chinese middle-aged and elderly males without NAFLD. Our results suggest a new practical strategy to facilitate personalized intervention of DM by increasing SMM in males without NAFLD.

ARTICLE HIGHLIGHTS

Research background

Aging is getting worse in China. Sarcopenia has become a major focus of public health research on aging.

Research motivation

There seems to be a close relationship between non-alcoholic fatty liver disease (NAFLD), diabetes mellitus (DM), and skeletal muscle mass (SMM).

Research objectives

We tried to determine the association between SMM, DM, and NAFLD in a Chinese population.

Research methods

Three thousand nine hundred and sixty-nine participants > 45 years of age from Changfeng Community in Shanghai were recruited to conduct a large-scale community population study. All participants were interviewed and the medical histories were recorded by trained researchers using a standard questionnaire. Blood samples were collected after overnight fasting for at least 10 h from each participant. The data related to SMM, DM, and NAFLD were analyzed.

Research results

In the current study, the fasting blood glucose, 2-h postprandial blood glucose, and homeostasis model assessment for insulin resistance increased with the prevalence of DM while appendicular skeletal muscle mass (ASM)% decreased in male and female participants. The SMM, as measured by ASM%, was negatively associated with the blood glucose concentration, but logistic stepwise regression analysis showed that SMM loss may be associated with the presence of DM in males. The dissociation of SMM loss and DM in women is noteworthy, especially after adjustment for fat mass and lipid parameters.

Research conclusions

SMM loss was shown to be associated with the presence of DM in Chinese middle-aged and elderly males without NAFLD.

Research perspectives

Our results suggest a new practical strategy to facilitate personalized intervention of DM by increasing SMM in males without NAFLD.

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