Association between sarcopenic overweight and left ventricular diastolic dysfunction and remodeling in patients with type 2 diabetes

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To the Editor: Left ventricular (LV) hypertrophy and diastolic dysfunction are prevalent in patients with type 2 diabetes mellitus (T2DM)[1] and contribute to an increased rate of cardiovascular events. The multifactorial pathological state may be linked to overweight and obesity. However, the definitions of obesity based on body mass index (BMI) resulted in discrepancies in the impact on cardiometabolic risk in different studies. Thus, the exact association between overweight/obesity and diabetic cardiomyopathy is yet controversial. Sarcopenia, age-related decline in muscle mass and strength, also showed an association with cardiovascular disease.[2] Moreover, individuals with high BMI but low muscle mass may not be noticeable but need to be considered. Studies have demonstrated that sarcopenic overweight and obesity are associated with variable cardiometabolic diseases. Diabetes may coexist with sarcopenia or obesity. However, research on the association between sarcopenia and LV diastolic function, LV remodeling, and the association with sarcopenic overweight and obesity is lacking. This study sought to investigate whether sarcopenia and sarcopenic overweight and obesity are independently related to preclinical LV diastolic dysfunction and LV remodeling in patients with T2DM.

Herein, we conducted a retrospective review of patients with type 2 diabetes under the official approval of the Ethics Committee of the First Affiliated Hospital of Fujian Medical University (No. 2017-131).

A total of 2350 subjects who underwent comprehensive health examinations, including echocardiography between March 2008 and October 2019, were recruited in this study. Written informed consent was obtained from all the patients. The inclusion criteria were patients diagnosed with T2DM. The exclusion criteria were as follows: (1) Patients had T1DM, gestational diabetes, or secondary diabetes; (2) Critical illness, such as ketoacidosis, hypertonic non-ketone coma, end-stage kidney disease, and liver disease; and (3) Athletic patients.

Clinical data were collected and maintained in a digital database. The information of patients' clinicopathological characteristics, including age, gender, height, weight, BMI, course of the disease, hypoglycemic drugs, insulin use, smoking history, and drinking history, was collected. Serum creatinine, total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and glycated hemoglobin (HbA1C) levels were measured after 10 h of overnight fasting. The estimated glomerular filtration rate (eGFR, $mL \cdot min^{-1} \cdot 1.73 \ m^{-2}$) was calculated.[3] The body composition was determined by dual-energy X-ray absorptiometry (DEXA) using a Lunar Prodigy scanner (GE Lunar Corporation, Madison, WI, USA). The muscle mass index was calculated as appendicular skeletal muscle mass (ASMI) $(kg)/height^2 \ (m^2)$. The following echocardiography factors were measured: left ventricular diastolic diameter (LVDd), interventricular septal thickness (IVST), and left ventricular posterior wall end-diastolic thickness (LVPWT), stroke volume (SV), cardiac output (CO), and ejection fraction (EF). Early diastolic transmitral velocities (E), septal early diastolic annular velocities (e), and lateral e were obtained in the apical four-chamber view. The average e was the average of septal e and lateral e. The LV mass and relative wall thickness (RWT, cm) were calculated as described previously.[3]

These criteria of T2DM, LV remodeling, LV diastolic dysfunction, diabetic retinopathy (DR), diabetic kidney disease (DKD), diabetic peripheral neuropathy (DPN), and diabetic peripheral autonomic neuropathy (DPAN) have been applied in previous studies.[3,4] Obesity was defined as BMI $\geq 28 \ kg/m^2$, while overweight was defined as BMI ≥ 24 and $<28 \ kg/m^2$ as the working group on obesity in China. Obesity was classified into the overweight group

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due to simple grouping in the present study. The ASMI cutoff point for diagnostic sarcopenia was 7.0 and 5.4 kg/m² for men and women, respectively, as initially proposed by the Asian Working Group on Sarcopenia.

Statistical data were presented as mean ± standard deviation, median (interquartile range), or proportions. The analysis of variance and Kruskal–Wallis tests were performed to determine the differences between Gaussian variables and non-Gaussian variables. Linear regression and multivariate logistic regression were used to evaluate the association. P value <0.050 considered statistically significant. Propensity score matching (PSM) was performed based on the following potential confounding factors: age, gender, diabetes duration, history of hypertension, and use of angiotensin-converting enzyme inhibitors (ACEI)/angiotensin receptor blocker (ARB). Also, an unbalanced matching strategy of 2:3:4:1 ratio was applied to the overweight with sarcopenia group, which had the smallest sample size. Statistical analyses were conducted using the R software, version 3.5.1.

As shown in Supplementary Table 1, http://links.lww.com/CM9/A760, a significant difference was detected in age, gender, diabetes duration, history of hypertension, and use of ACEI/ARB among the four groups ($P < 0.050$) before PSM. However, no significant difference was observed after PSM. The discrepancies among the four groups were observed in HbA1c, eGFR, and the use of β-R blockers, calcium channel blockers, statins, and aspirin before PSM but disappeared after PSM. However, the discrepancies among the four groups still existed in cardiometabolic variables, including heart rate, electrocardio indexes corrected Q-T interval (Q-Tc), SV, CO, E, average e, IVST, LVDd, LVM, LVPWT, RWT, rate of LV diastolic dysfunction, and LV remodeling. Of the 2350 patients, 17.2% had DR, 30.9% had DKD, 44.7% had DPN, and 51.1% had diabetic autonomic neuropathy [Supplementary Table 1, http://links.lww.com/CM9/A760].

Furthermore, the multivariate regression analysis adjusted for age, duration of diabetes, and other confounding factors showed that ASMI was negatively associated with heart rate (B = −2.176, $P < 0.001$) and positively associated with SV (B = 3.337, $P < 0.001$) and CO (B = 0.048, $P < 0.001$), while BMI was only positively associated with SV (B = 0.448, $P < 0.001$). However, a negative association between ASMI and heart rate (B = −2.174, $P < 0.001$) and a positive association between ASMI and SV (B = 3.604, $P < 0.001$) and CO (B = 0.170, $P < 0.001$) were observed even after PSM. This phenomenon disappeared in BMI. Data are shown in Supplementary Table 2, http://links.lww.com/CM9/A760.

To further determine the potential associations, multivariate logistic regression analysis was performed by adjustment of confounding factors [Figure 1]. Compared to individuals with normal-weight without sarcopenia, those with normal-weight and sarcopenia, overweight without sarcopenia, and overweight with sarcopenia had adjusted odds ratio (ORs) of 1.493 (95% confidence interval [CI]: 1.133–1.966, $P = 0.004$), 1.783 (95% CI: 1.385–2.296, $P < 0.001$), and 2.602 (95% CI: 1.677–4.038, $P < 0.001$), respectively, for LV diastolic dysfunction. Moreover, those had adjusted ORs of 1.394 (95% CI: 1.045–1.859, $P = 0.024$), 1.289 (95% CI: 0.991–1.675, $P = 0.058$), and 2.041 (95% CI: 1.362–3.057, $P < 0.001$), respectively, for LV remodeling [Figure 1A and 1B]. Furthermore, the associations were analyzed in subgroups with or without diabetic complications. Data showed those with overweight without sarcopenia (OR: 1.700, 95% CI: 1.274–2.269, 1.865 [1.305–2.664], 1.693 [1.247–2.298], 2.144 [1.466–3.136]; $P < 0.050$), overweight with sarcopenia (OR: 1.888, 95% CI: 1.151–3.098, 2.519 [1.335–4.755], 1.791 [1.011–3.174], 2.356 [1.253–4.429]) were associated with LV diastolic dysfunction in patients without DR, DKD, DPN, and DPAN, respectively. Otherwise, only those with overweight with sarcopenia showed an association with LV remodeling in patients without aforementioned diabetic complications (OR:
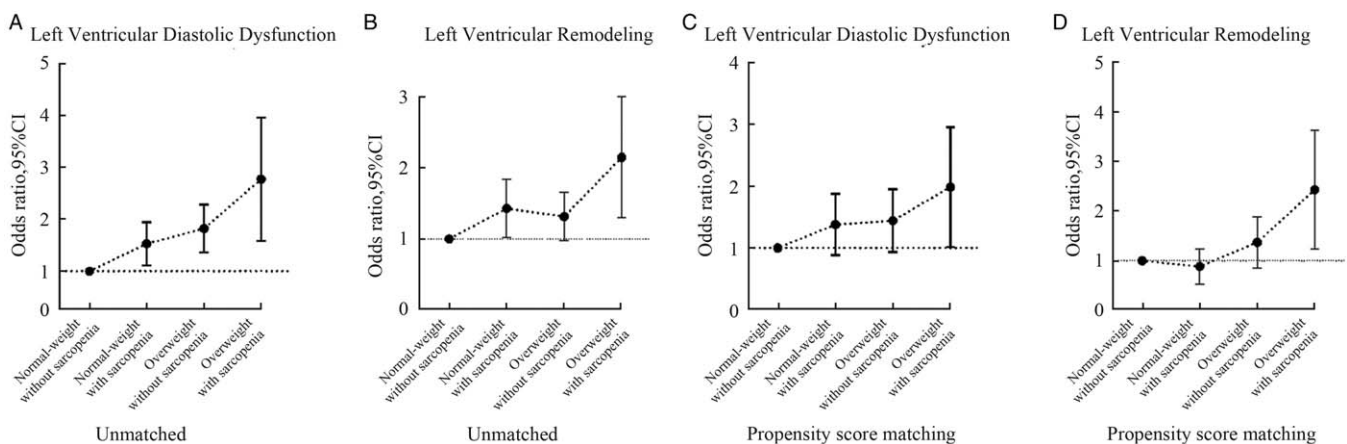
Figure 1: Association between sarcopenia, sarcopenic overweight, and LV diastolic dysfunction, LV remodeling. Before PSM, confounding factors, including age, sex, diabetes duration, SBP, DBP, hypertension history, HbA1c, TCH, LDL, TG, HDL, eGFR, current smoker, current drinker, and drug usage (insulin therapy, metformin and non-metformin, β-R blockers, CCB, statins, aspirin, and ACEI/ARB), were adjusted. After PSM, confounding factors, including DBP, hypertension history, TCH, LDL, TG, HDL, and drug usage (β-R blockers, CCB, and ACEI/ARB), were adjusted. ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; CCB: Calcium channel blockers; CI: Confidence interval; DBP: Diastolic blood pressure; eGFR: Estimated glomerular filtration rate; HbA1c: Glycated hemoglobin; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; LV: Left ventricular; OR: Odds ratio; PSM: Propensity score matching; SBP: Systolic blood pressure; TCH: Total cholesterol; TG: Triglycerides.

1.919, 95% CI: 1.225–3.006, 1.921 [1.086–3.399], 1.796 [1.050–3.071], 2.987 [1.630–5.474]; $P < 0.050$). Data are presented in Supplementary Table 3, http://links.lww.com/CM9/A760. Interestingly, after PSM and adjustment for some confounding factors, only individuals with overweight and sarcopenia had significantly adjusted ORs of 1.825 (95% CI: 1.103–3.019, $P = 0.019$) and 2.238 (95% CI: 1.349–3.713, $P = 0.002$) for LV diastolic dysfunction and LV remodeling, respectively [Figure 1C and 1D]. This phenomenon suggested that among those of the same age, gender, duration, history of hypertension, and use of ACEI/ARB, only individuals with sarcopenic overweight may have a high risk of having LV diastolic dysfunction and LV remodeling.

The present study demonstrated that individuals of the same age, gender, diabetes duration, history of hypertension, and using ACEI/ARB, sarcopenic overweight may have a high risk of having LV diastolic dysfunction and LV remodeling. The current data also showed that ASMI, but not BMI, was associated with other cardiometabolic variables, such as heart rate, SV, and CO.

A previous study has shown the adverse effects of overweight and obesity on LV structure and diastolic and systolic functions from children and adolescents to adults. Low muscle mass and sarcopenia were independently associated with increased risk of LV diastolic dysfunction in community-dwelling subjects.[5] However, similar data from diabetic subjects were scarce. The current study provided objective evidence that those of the same age, gender, diabetes duration, and individuals with sarcopenic overweight may face the risk of LV diastolic dysfunction and LV remodeling. This finding was distinct from previous studies that either sarcopenia or overweight/obesity alone may lead to such adverse outcomes. Notably, few or no studies have been performed to match some dominant confounding factors, such as age, gender, diabetes duration, history of hypertension, and use of ACEI/ARB. The present study before PSM also showed that sarcopenia or overweight adversely affects LV diastolic function and LV remodeling regardless of other confounding factors in addition to the deleterious effects of sarcopenia and overweight. Intriguingly, only sarcopenic overweight was addressed to link to the adverse outcome after matching the abovementioned dominant confounding factors. Second, the research on overweight and obesity defined only by BMI has paradoxically reported a protective effect against the cardiometabolic disease, reflecting the limitations of BMI while distinguishing fat mass and lean mass. Strikingly, adipose tissue, but not lean tissue, has a biological feature of unhealthy and dysfunctional. The pathological fat accumulated, which becomes dysfunctional, insulin-resistant, and inflamed, leading to an "unhealthy" phenotype that is strongly associated with unfavorable cardiometabolic disease outcomes. This phenomenon might account for a negative finding in overweight subjects without sarcopenia after PSM. However, the deleterious effects of sarcopenia may be diluted in diabetic patients with normal weight, which could be at least partially attributed to the complete adjustment for confounders, such as age, sex, diabetes duration, and better management of metabolic diseases.

A few studies have focused on SV, CO, and Q-Tc and their effect on the lean tissue. Also, another interesting finding should be clarified. ASMI, but not BMI, was associated with other cardiometabolic variables, such as heart rate, SV, and CO. Some plausible pathophysiologic processes explain the underlying association. Increasing muscles induce powerful muscle contraction, leading to a high level of SV and CO, without a compensatory increasing heart rate; an association of ASMI and BMI with EF and Q-Tc was not observed in the present study. Thus, it could be speculated that the recruited patients had non-severe T2DM with a normal range of EF and Q-Tc.

This study has several strengths. First, the echocardiogram was assessed by an experienced ultrasound expert, and the lean tissue was screened using DEXA, providing objective and robust evidence. Furthermore, the sample size was large and PSM was performed, thus enhancing the credibility of the results.

The current study suggested that the deleterious effects of sarcopenia and overweight are additive. For those of the same age, gender, diabetes duration, and sarcopenic overweight may have a high risk of LV diastolic dysfunction and LV remodeling. Sarcopenia could be a primary target for preventing LV diastolic dysfunction and LV remodeling in diabetic patients with overweight.

Funding

Conflicts of interest

None.

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