Sarcopenic obesity is associated with macroalbuminuria in patients with type 2 diabetes: a cross-sectional study

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Abstract. Sarcopenia is associated with the risk of albuminuria in patients with type 2 diabetes mellitus (T2DM), and obesity is a risk factor for proteinuria. However, the association between sarcopenic obesity and diabetic nephropathy, including albuminuria, in patients with T2DM has not been reported. The study included 206 men and 163 women with T2DM who participated in the KAMOGAWA-DM cohort, which investigating the natural history of diabetes since 2014. Sarcopenia was defined as having both low skeletal muscle mass index (SMI, kg/m²) (<7.0 kg/m² for men and <5.7 kg/m² for women) and low handgrip strength (<28 kg for men and <18 kg for women). Obesity was diagnosed by the percentage of body fat (>30% for men and >35% for women). The patient was said to have sarcopenic obesity if he/she had both sarcopenia and obesity. Urinary albumin excretion of patients with sarcopenic obesity was higher than that of patients without sarcopenic obesity (median [interquartile range]: 342.0 [41.8–467.5] vs. 21.0 [9.0–75.4] mg/g Cr, $p = 0.016$). Additionally, sarcopenic obesity was associated with the presence of macroalbuminuria, compared with non-sarcopenic obesity (adjusted odds ratio 6.92 [95% confidence interval: 1.63–29.4], $p = 0.009$). Adjusted odds ratios of sarcopenic obesity, sarcopenia only, and obesity only for the presence of macroalbuminuria were 6.52 (1.47–28.8, $p = 0.014$), 1.29 (0.45–3.71, $p = 0.638$), and 0.78 (0.38–1.58, $p = 0.482$), respectively, compared with neither sarcopenia nor obesity. This study indicated that sarcopenic obesity is associated with albuminuria, especially macroalbuminuria, in Japanese patients with T2DM.

Key words: Muscle, Nephropathy, Obese, Sarcopenia, Type 2 diabetes

NUMBER OF PATIENTS, especially elderly patients, with type 2 diabetes mellitus (T2DM) is increasing globally and they often develop sarcopenia [1]. Sarcopenia is defined as the age-associated decline of muscle strength, mass, and function [2]. Sarcopenia is now known as a risk factor for cardiovascular disease (CVD) and mortality [3–5]. Additionally, it has been reported that the presence of obesity in combination with sarcopenia, called as sarcopenic obesity, is a greater risk factor for mortality than the sarcopenia alone [6, 7]. It has been reported that there is a possibility that T2DM has a high risk of sarcopenic obesity [8, 9].

The prevalence of diabetic nephropathy, which is the major cause of end stage renal disease (ESRD), is also globally increasing [10]. Albuminuria, especially macro-

albuminuria, is an independent risk factor not only for incident ESRD, [11–13] but also for mortality [14], particularly in patients with diabetes. Recent studies have showed that sarcopenia is associated with the risk of albuminuria in patients with T2DM [15, 16], and obesity is a risk factor for proteinuria [17]. Thus, there is a possibility that sarcopenic obesity is associated with albuminuria in patients with T2DM. However, there has not been a study that explored this association. Therefore, the present cross-sectional study researched the relationship between sarcopenic obesity and diabetic nephropathy, including the presence of macroalbuminuria, in patients with T2DM.

Materials and Methods

Study participants

The KAMOGAWA-DM cohort study is an ongoing cohort study to elucidate the natural history of diabetes [18]. This study has been carried out since 2014. Patients enrolled in this study provided written informed consent. The present study is a part of KAMOGAWA-DM study.

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It includes the outpatients visiting the Department of Endocrinology and Metabolism, Kyoto Prefectural University of Medicine (KPUM) Hospital (Kyoto, Japan), and the Department of Diabetology, Kameoka Municipal Hospital (Kameoka, Japan). The present study included patients with T2DM who underwent bioimpedance analysis (BIA) between 15 January 2016 and 17 April 2018 [19]. The patients with unreliable BIA data, lacking urinary albumin excretion, and with poor handgrip strength were excluded from the study. This study was approved by the KPUM Ethics Committee (approval number RBMR-E-466-6) and has been conducted in accordance with the principles of Declaration of Helsinki.

Data collection

We gave a standardized questionnaire to all participants, and categorized them as smokers or non-smokers, and non-exercisers or regular exercisers based on their responses in the questionnaire. Further, venous blood was gathered from the participants who had fasted overnight and the levels of triglycerides, high-density lipoprotein (HDL) cholesterol, creatinine (Cr), uric acid, and fasting plasma glucose were measured. Estimated glomerular filtration rate (eGFR) was calculated using the equation of the Japanese Society of Nephrology, *i.e.*, $\text{eGFR} = 194 \times \text{Cr}^{-1.094} \times \text{age}^{-0.287}$ (mL/min/1.73 m²) ($\times 0.739$, if woman) [20]. The hemoglobin A1c (HbA1c) level was estimated using high-performance liquid chromatography and was expressed as a National Glycohemoglobin Standardization Program unit. Further, the immunoturbidimetric method was used for the evaluation of urinary albumin excretion (UAE), which was calculated using the formula: $\text{UAE (mg/g Cr)} = \text{urinary albumin concentration (mg/L)} / \text{urinary Cr concentration (g/L)}$. The mean UAE value was estimated from three independent readings. The stage of diabetic nephropathy was defined as follows: stage 1, $\text{eGFR} \geq 30$ mL/min/1.73 m² and normoalbuminuria ($\text{UAE} < 30$ mg/g Cr); stage 2, $\text{eGFR} \geq 30$ mL/min/1.73 m² and microalbuminuria ($\text{UAE } 30\text{--}300$ mg/g Cr); stage 3, $\text{eGFR} \geq 30$ mL/min/1.73 m² and macroalbuminuria ($\text{UAE} > 300$ mg/g Cr); and stage 4, $\text{eGFR} < 30$ mL/min/1.73 m² [21]. None of the patients required maintenance dialysis during this study. Additionally, the data for medications, including those for diabetes and hypertension (renin-angiotensin-aldosterone [RAS] inhibitor), and dyslipidemia (statin) were obtained. Data for medications were obtained from the patients' medical records.

Body composition was evaluated using a multifrequency impedance body composition analyzer, InBody 720 (InBody Japan, Tokyo, Japan) [19]. The data for body weight (kg), appendicular muscle mass (kg), and body fat mass (kg) were obtained. Body mass index

(BMI, kg/m²) and skeletal muscle mass index (SMI, kg/m²) were calculated by dividing body weight (kg) and appendicular muscle mass (kg), respectively, with the square of height (m). The percent body fat mass (%) was calculated by dividing body fat mass (kg) ($\times 100$) with body weight (kg). The handgrip strength was measured twice for each hand using a handgrip dynamometer (Smedley, Takei Scientific Instruments Co., Ltd., Niigata, Japan) and the maximum value was included in the analyses [19]. Sarcopenia was diagnosed by low SMI and low handgrip strength [22]. The cut-off values for low handgrip strength were < 28 kg/m² for men and < 18 kg/m² for women, and those for low SMI were < 7.0 kg/m² for men and < 5.7 kg/m² for women [22]. Obesity was defined by the percentage of body fat, *i.e.*, $> 30\%$ for men and $> 35\%$ for women [23]. The patient was said to have sarcopenic obesity if he/she had both sarcopenia and obesity [23].

Statistical analyses

The data are showed as median (1st quartile–3rd quartile median), mean (standard deviation [SD]), or frequencies of potential confounding variables. Patients were divided into the following four groups based on the absence or presence of sarcopenia and obesity: absence of both sarcopenia and obesity (–/–), sarcopenia only (+/–), obesity only (–/+), and sarcopenic obesity (+/+). The differences in the continuous variables were evaluated by the Mann-Whitney *U* test, Kruskal-Wallis test and Steel-Dwass test, and one-way analysis of variance (ANOVA) and the Tukey-Kramer test, and those in the categorical variables were evaluated by the Chi-square test and the Holm test.

Further, we evaluated the association between sarcopenia and/or obesity, and albuminuria. Because UAE was a skewed variable, logarithmic transformation was done before performing multivariable linear regression analyses, which were performed to evaluate the association of combined effect of sarcopenia and/or obesity with $\log_e (\text{UAE} + 1)$. Sex, age, smoking habit, exercise, BMI, systolic blood pressure, levels of HbA1c, uric acid, creatinine, duration of diabetes, consumption of RAS inhibitor, insulin, SGLT2 inhibitors, GLP-1 receptor agonists and statin were used for covariates.

Furthermore, we evaluated the effect of the presence of sarcopenia, obesity, and sarcopenic obesity on the presence of macroalbuminuria. Since the number of patients with macroalbuminuria was less, the propensity score, which preserves the statistical power by reducing covariates into a single variable, was used. The propensity score was calculated from multivariable logistic regression models that included age, sex, exercise, RAS inhibitor, insulin, SGLT2 inhibitors, GLP-1 receptor

agonists, statin, duration of diabetes, family history of diabetes, smoking, systolic blood pressure, BMI, HbA1c, uric acid and creatinine. The c-statistic for propensity score model was 0.89, which indicates an acceptable discrimination between the presence or absence of macroalbuminuria. Further, the odds ratios of sarcopenia, obesity, and sarcopenic obesity for the presence of macroalbuminuria were calculated using the propensity score. The odds ratios of the presence or absence of sarcopenia or obesity for the presence of macroalbuminuria were also calculated.

In addition, we also performed sub-analyses of using the cut-off of obesity of BMI ≥ 25 kg/m² [24] and evaluated the association between sarcopenia and/or obesity, and albuminuria, and the effect of the presence of sarcopenic obesity on the presence of macroalbuminuria.

The statistical analyses were conducted using JMP software ver. 13.2 (SAS Institute Inc., Cary, NC, USA) and EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [25], which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). The differences with p value < 0.05 were considered statistically significant.

Results

In the present study, 383 patients (212 men and 171 women) with T2DM were extracted. Among them, 8 patients (5 men and 3 women) who had not undergone the multifrequency impedance body composition analyzer test, 4 patients (women) who had not undergone the handgrip strength test, and 2 patients with no date of UAE (1 man and 1 woman) were excluded from the study (Fig. 1). Finally, the study population comprised 369 patients.

The clinical characteristics of the participants based on the absence or presence of sarcopenia and/or obesity are shown in Table 1. Mean age of patients with non-sarcopenia/non-obesity, sarcopenia only, obesity only, and sarcopenic obesity was 67.0 (8.9), 75.0 (8.4), 63.2 (12.3), and 75.4 (10.0) years, respectively. The percentage of patients with sarcopenia only, obesity only, and sarcopenic obesity was 7.9% ($n = 29/369$), 33.1% ($n = 122/369$), and 2.7% ($n = 10/369$), respectively. The patients with sarcopenic obesity were significantly older than those with obesity only. The BMI of patients with sarcopenic obesity was higher than those with sarcopenia alone, and lower than those with obesity alone. The proportion of patients using SGLT2 inhibitors or GLP-1 receptor agonists was lower in patients with sarcopenia only than those with neither sarcopenia nor obesity. Fig. 2 shows the proportion of diabetic nephropathy based on the stages according to the absence or presence of sarcopenia and/or obesity. The sarcopenic obesity was associated with the higher stage of diabetic nephropathy ($p < 0.001$).

Urinary albumin excretion of patients with sarcopenic obesity was higher than that of patients without sarcopenic obesity (median [interquartile range]: 342.0 [41.8–467.5] vs. 21.0 [9.0–75.4] mg/g Cr, $p = 0.016$). Table 2 shows the association of combined effect of sarcopenia and/or obesity with log_e (UAE + 1). The patients with sarcopenic obesity had significantly higher log_e (UAE + 1) than those with neither sarcopenia nor obesity.

Furthermore, the sarcopenic obesity was associated with the presence of macroalbuminuria after adjusting for covariates (odds ratio 6.92 [95% confidence interval: 1.63–29.4], $p = 0.009$). Compared to the non-sarcopenia/non-obesity patients, the patients with sarcopenic obesity had the highest risk for macroalbuminuria (OR 6.52

Fig. 1 Study flow diagram for the registration of patients.

UAE, urinary albumin excretion.

Table 1 Clinical characteristics of study participants according to the presence or absence of sarcopenia or obesity

Sarcopenia/obesity	(-/-)	(+/-)	(-/+))	(+/+)	<i>p</i>
Men/Women	132/76	22/7	45/77	7/3	<0.001
Age, years	67.0 (8.9)	75.0 (8.4)*	63.2 (12.3)*†	75.4 (10.0)‡	<0.001
Duration of diabetes, years	14.5 (10.1)	23.7 (10.8)*	10.6 (8.0)*†	15.0 (10.5)	<0.001
Family history of diabetes (-/+)	109/99	20/9	65/57	8/2	0.138
Height, cm	163.0 (8.8)	159.2 (6.4)	158.3 (9.5)*	157.5 (7.8)	<0.001
Body weight, kg	60.5 (10.1)	51.8 (6.6)*	72.0 (13.7)*†	62.5 (6.7)†	<0.001
Body mass index, kg/m ²	22.7 (2.5)	20.4 (1.8)*	28.7 (4.5)*†	25.3 (2.6)*‡	<0.001
Systolic blood pressure, mmHg	133.5 (19.7)	132.2 (15.2)	135.3 (16.7)	132.1 (25.0)	0.781
Diastolic blood pressure, mmHg	78.4 (11.1)	72.0 (11.1)*	81.8 (10.1)*†	74.8 (14.0)	<0.001
Insulin (-/+)	153/55	18/11	101/21	9/1	0.047
SGLT2 inhibitors (-/+)	184/24	27/2*	87/35	9/1	<0.001
GLP-1 receptor agonists (-/+)	185/23	26/3*	90/32	8/2	0.003
RAS inhibitor (-/+)	119/89	13/16	66/56	6/4	0.625
Statin (-/+)	129/79	18/11	75/47	7/3	0.963
Smoking (-/+)	173/35	26/3	106/16	10/0	0.367
Habitual alcohol consumption (-/+)	181/27	27/2	112/10	10/0	0.308
Habit of exercise (-/+)	108/100	15/14	65/57	4/6	0.883
Hemoglobin A1c, %	7.3 (1.2)	7.4 (1.0)	7.5 (1.5)	7.3 (0.7)	0.757
Hemoglobin A1c, mmol/mol	56.4 (13.4)	57.7 (11.1)	58.2 (16.1)	56.7 (7.8)	0.757
Plasma glucose, mmol/L	8.2 (2.7)	8.6 (2.2)	8.3 (3.0)	7.6 (1.8)	0.811
Creatinine, umol/L	74.8 (31.9)	69.6 (19.4)	69.2 (26.4)	88.1 (47.5)	0.128
eGFR, mL/min/1.73 m ²	68.6 (17.2)	73.6 (22.1)	71.5 (20.3)	63.2 (28.5)	0.255
Uric acid, mmol/L	301.5 (76.3)	300.5 (76.7)	311.6 (69.4)	362.2 (85.2)	0.064
TG, mmol/L	1.4 (0.9)	1.1 (0.6)	1.8 (1.0)*†	1.5 (0.7)	<0.001
HDL cholesterol, mmol/L	1.6 (0.5)	1.7 (0.5)	1.5 (0.4)	1.4 (0.3)	0.029
Urinary albumin excretion, mg/gCr	20.0 (8.0–70.0)	19.8 (12.0–110.9)	27.1 (11.0–79.2)	342.0 (41.8–467.5)	0.028
Diabetic nephropathy stage (1/2/3/4)	125/56/24/3	16/8/5/0	68/40/10/4	2/1/5/2*†‡	<0.001
Handgrip strength, kg	29.8 (9.0)	21.8 (5.6)*	27.2 (9.5)†	19.6 (5.2)*‡	<0.001
Appendicular muscle mass, kg	18.9 (4.1)	15.7 (2.8)*	18.1 (4.3)†	15.5 (2.7)*	<0.001
Body fat mass, kg	14.8 (4.3)	12.4 (3.6)	28.3 (8.0)*†	23.6 (4.6)*†	<0.001
Percent body fat mass, %	24.4 (5.9)	23.6 (5.4)	39.1 (6.0)*†	37.8 (6.3)*†	<0.001
SMI, kg/m ²	7.0 (1.0)	6.2 (0.7)*	7.1 (1.1)†	6.2 (0.6)*‡	<0.001

Data was expressed as mean (standard deviation), median (interquartile range) or number. The difference between group was evaluated by ANOVA, Kruskal-Wallis test or chi-square test. RAS, renin-angiotensin system; eGFR, estimated glomerular filtration rate; TG, triglycerides; HDL, high-density lipoprotein; SMI, skeletal muscle mass index. *, $p < 0.05$ vs. (-/-); †, $p < 0.05$ vs. (-/+); and ‡, $p < 0.05$ vs. (+/+).

[95% CI: 1.47–28.80], $p = 0.014$; Table 3). Further, the adjusted odds ratios of sarcopenic obesity, sarcopenia only, and obesity only for the presence of macroalbuminuria were 6.52 (95% CI: 1.47–28.8, $p = 0.014$), 1.29 (95% CI: 0.45–3.71, $p = 0.638$), and 0.78 (95% CI: 0.38–1.58, $p = 0.482$), respectively. Additionally, the patients

with sarcopenic obesity were at higher risk of macroalbuminuria compared to the patients with sarcopenia only (OR 5.06 [95% CI: 0.94–27.2], $p = 0.059$) and obesity only (OR 8.41 [95% CI: 1.85–38.2], $p = 0.006$).

The results of sub-analysis of the association between sarcopenia and/or obesity, and log_e (UAE + 1), using the

Table 2 The association of sarcopenic obesity with log_e (urinary albumin excretion + 1)

Sarcopenia/obesity	(-/-)	(+/-)	(-/ +)	(+/ +)	<i>p</i>
Model 1	3.36 (3.14–3.59)	3.68 (3.08–4.28)	3.56 (3.27–3.85)	4.99 (3.97–6.01)*†	0.018
Model 2	3.31 (3.09–3.54)	3.40 (2.78–4.01)	3.68 (3.38–3.98)	4.72 (3.70–5.74)*	0.022
Model 3	3.63 (3.28–3.98)	3.85 (3.22–4.48)	3.88 (3.53–4.23)	5.03 (4.09–5.97)*	<0.001

Values for outcome variables are geometric means and 95% CI. Log, logarithms.

Model 1 was unadjusted model, model 2 was adjusted for age and sex and model 3 was adjusted for age, sex, smoking, exercise, duration of diabetes, renin-angiotensin system inhibitor, insulin, SGLT2 inhibitors, GLP-1 receptor agonists, statin, systolic blood pressure, body mass index, HbA1c, uric acid, creatinine. *, $p < 0.05$ vs. (-/-); and †, $p < 0.05$ vs. (-/+).

Fig. 2 Proportion of diabetic nephropathy stage according to the presence/absence of sarcopenia and obesity

cut-off of obesity of BMI ≥ 25 kg/m², are shown in Table 4. The proportion of sarcopenia alone, obesity alone and sarcopenic obesity were 9.2% ($n = 34$), 36.3% ($n = 134$) and 1.4% ($n = 5$), respectively. The patients with sarcopenic obesity had significantly higher log_e (UAE + 1) than those with neither sarcopenia nor obesity. Moreover, the sarcopenic obesity, using the cut-off of obesity of BMI ≥ 25 kg/m², was associated with the presence of macroalbuminuria after adjusting for covariates (OR 19.90 [95% CI: 2.03–194.00], $p = 0.010$) (Table 5).

Discussion

The present study researched the relationship between sarcopenic obesity and albuminuria in patients with T2DM. The proportion of patients with sarcopenia only and sarcopenic obesity were 7.9% and 2.7%, respectively. These proportions were similar to the previous studies reported [26, 27]. The UAE of patients with sarcopenic obesity was higher than that of patients neither with sarcopenia and obesity. Additionally, sarcopenic obesity was associated with the presence of macroalbuminuria in patients with T2DM.

Sarcopenia has been established as a risk factor for CVD and mortality [3–5]. Additionally, it is known to be

Table 3 Odds ratio of the presence or absence of sarcopenia or obesity for presence of macroalbuminuria

	OR (95%CI)	<i>p</i>
Absence of sarcopenia	ref	—
Presence of sarcopenia	2.23 (0.97–5.09)	0.058
Absence of obesity	ref	—
Presence of obesity	0.94 (0.50–1.78)	0.894
Absence of sarcopenic obesity	ref	—
Presence of sarcopenic obesity	6.92 (1.63–29.4)	0.009
Presence/absence of sarcopenia and obesity		
(-/-)	ref	—
(+/-)	1.29 (0.45–3.71)	0.638
(-/ +)	0.78 (0.38–1.58)	0.482
(+/ +)	6.52 (1.47–28.8)	0.014

Since the cases of macroalbuminuria is not enough. Propensity score was used for covariates. Propensity score was evaluated by multivariable logistic regression models that include the age, sex, duration of diabetes, family history of diabetes, smoking, exercise, renin-angiotensin system inhibitor, insulin, SGLT2 inhibitors, GLP-1 receptor agonists, statin, systolic blood pressure, body mass index, HbA1c, uric acid, and creatinine. The c-statistic for propensity score model was 0.89.

a risk of albuminuria [15, 16]. Sarcopenic obesity, which more likely causes lifestyle-related morbidities than obesity without sarcopenia, may lead to a further reduction in mobility and is associated with higher mortality rates than sarcopenia alone [6, 7]. Moreover, a recent study showed that sarcopenic obesity had a higher risk of albuminuria than sarcopenia [28]. However, the definition of sarcopenia used in that study was SMI (%), which is the appendicular muscle mass (kg) divided by body weight (kg) $\times 100$, which was different from SMI (kg/m²) used in our study. In fact, SMI (%) and SMI (kg/m²) are clinically different markers [29]. In the present study, the risk of albuminuria was the highest in the patients with sarcopenic obesity. Previous studies showed that both sarcopenia and obesity were the risk of macroalbuminuria [15–17]. On the other hand, in this study, we revealed

Table 4 The association of sarcopenic obesity, using BMI cut-off, with log_e (urinary albumin excretion + 1)

Sarcopenia/obesity	(--)	(+/-)	(-/+)	(+/+)	<i>p</i>
Model 1	3.31 (3.08–3.54)	3.79 (3.24–4.34)	3.62 (3.35–3.90)	5.53 (4.09–6.96)*	0.007
Model 2	3.25 (3.03–3.48)	3.49 (2.92–4.06)	3.75 (3.46–4.03)*	5.28 (3.85–6.70)*	0.004
Model 3	3.57 (3.21–3.92)	3.91 (3.32–4.51)	3.88 (3.55–4.22)	5.44 (4.17–6.71)*	<0.001

Values for outcome variables are geometric means and 95% CI. Log, logarithms. Obesity was defined as BMI ≥ 25 kg/m².

Model 1 was unadjusted model, model 2 was adjusted for age and sex and model 3 was adjusted for age, sex, smoking, exercise, duration of diabetes, renin-angiotensin system inhibitor, insulin, SGLT2 inhibitors, GLP-1 receptor agonists, statin, systolic blood pressure, body mass index, HbA1c, uric acid, creatinine. *, $p < 0.05$ vs. (–/–).

that not the presence of sarcopenia only or obesity only but the sarcopenic obesity was a higher risk of macroalbuminuria. Thus, we should focus on sarcopenic obesity for a higher risk of macroalbuminuria, which are higher risk of renal dysfunction progression.

The diagnostic criteria for sarcopenic obesity, especially regarding obesity, are not unified yet [30, 31]. Percentage of body fat, BMI, and waist circumference has been used for definitions and diagnose for obesity [31]. In the present study, we used the cut-off values for percentage of body fat $>35\%$ in women and $>30\%$ in men for obesity [23]. A recent study has suggested that this criterion is suitable for the Japanese [23]. On the other hand, in the sub-analysis using the cut-off of obesity of BMI ≥ 25 kg/m², sarcopenic obesity was associated with albuminuria. Therefore, regardless of which definition is used, sarcopenic obesity was associated with albuminuria.

To prevent muscle mass loss, exercise and protein intake are important [32]. On the other hand, in obesity, it is important to reduce total calorie intake for weight loss [33]. Thus, there is a possibility that limiting carbohydrates and fats, but not reducing protein, might be needed in patients sarcopenic obesity [34]. A previous study revealed that protein intake was not associated with progression of albuminuria in patients with T2DM without macroalbuminuria [35]. However, it remained to be unclear regarding protein intake in diabetic nephropathy; and thus, further research on the prevention and improvement of sarcopenic obesity is needed.

The possible link between sarcopenic obesity and albuminuria can be explained as follows. The loss of skeletal muscle has a close association with insulin resistance, reactive oxygen species, and chronic inflammation, which can, in turn, promote albuminuria. Sarcopenia has been reported to be associated with an inflammatory state driven by cytokines and oxidative stress [36]. In fact, sarcopenia has been reported to be associated with nuclear factor κ B (NF- κ B) and protein kinase B (Akt) signaling through secretion of interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), and transforming growth factor- β (TGF- β) [37]. Addi-

Table 5 Odds ratio of the presence or absence of sarcopenia or obesity, using BMI cut-off, for presence of macroalbuminuria

Presence/absence of sarcopenia and obesity	OR (95%CI)	<i>p</i>
(--)	ref	—
(+/-)	1.41 (0.52–3.78)	0.498
(-/+)	0.85 (0.43–1.68)	0.632
(+/+)	19.90 (2.03–194.00)	0.010

Since the cases of macroalbuminuria is not enough. Propensity score was used for covariates. Propensity score was evaluated by multivariable logistic regression models that include the age, sex, duration of diabetes, family history of diabetes, smoking, exercise, renin-angiotensin system inhibitor, insulin, SGLT2 inhibitors, GLP-1 receptor agonists, statin, systolic blood pressure, body mass index, HbA1c, uric acid, and creatinine. The c-statistic for propensity score model was 0.89.

tionally, a previous study has revealed that obesity, like sarcopenia, increases albuminuria by triggering cascades of events including insulin resistance, increased reactive oxygen species, and chronic inflammation [38]. Obesity is also associated with Akt and NF- κ B signaling through secretion of IL-6, TNF- α , and TGF- β . Insulin resistance, reactive oxygen species, and chronic inflammation have been reported to induce albuminuria [39]. Therefore, having both sarcopenia and obesity accelerates these insulin resistance and chronic inflammation through fat accumulation in the muscles and insufficient working of insulin. Taken together, the aforementioned mechanisms suggest that the synergistic effect of sarcopenia and obesity is associated with albuminuria.

This study has a few limitations. First, the study design was cross-sectional. Therefore, the causal relationship between the sarcopenic obesity and albuminuria is unclear. Second, the generalizability of the results of the present study in non-Japanese T2DM patients is unclear. Third, we did not have the data of insulin resistance, reactive oxygen species, and inflammation, which might be link the sarcopenic obesity and albuminuria.

Fourth, the sample size of this study was relatively small. The future prospects are to examine longitudinal albuminuria changes in patients with T2DM with sarcopenic obesity, and to clarify the association between sarcopenic obesity and albuminuria.

In conclusion, the findings of the present study suggest an association between sarcopenic obesity and albuminuria, including macroalbuminuria, in Japanese patients with T2DM. Preventing sarcopenic obesity would reduce the risk of diabetic nephropathy, which is a major cause of ESRD in T2DM.

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Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Author Contributions

FT analyzed and interpreted the data, and wrote the manuscript. YH originated and designed the study, researched, analyzed and interpreted the data, and drafted the manuscript. AK and RS originated the study, researched and interpreted the data, and reviewed the manuscript. TO researched the data, and reviewed the manuscript. MH originated and designed the study, researched the data, and reviewed the manuscript. MF originated the study, researched and interpreted the data, and drafted the manuscript. All authors were involved in the writing of the manuscript and approved the final version of this article.

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