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SHORT REPORT

Sarcopenia is associated with incident albuminuria in patients with type 2 diabetes: A retrospective observational study

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ABSTRACT

Sarcopenia, defined as age-related loss of skeletal muscle mass and function, increases the risk of albuminuria. However, it has still unknown whether sarcopenia could increase the risk for the progression of albuminuria. A total 238 patients with type 2 diabetes (mean age 64 ± 12 years; 39.2% women) were studied in the present retrospective observational study. The prevalence of sarcopenia was 17.6%. During the median follow-up period of 2.6 years, albuminuria was measured 5.8 ± 1.8 times, and progression of albuminuria was observed in 14.9% of patients with normoalbuminuria, as was 11.5% in those with microalbuminuria. Sarcopenia was significantly associated with both progression (hazard ratio 2.61, 95% confidence interval 1.08–6.31, $P = 0.034$) and regression (hazard ratio 0.23, 95% confidence interval 0.05–0.98, $P = 0.048$) of albuminuria by multivariate Cox regression analysis. The present data suggest that sarcopenia is an important determinant of both progression and regression of albuminuria in patients with type 2 diabetes.

INTRODUCTION

Sarcopenia, defined as the degenerative reduction of skeletal muscle mass and strength with aging, is related to functional disability, risk of falls and fracture, and mobility impairment[1,2]. Diabetes and chronic kidney disease (CKD) have been identified as important contributors to the exacerbation of sarcopenia[3,4]. Insulin resistance is thought to be implicated in the pathogenesis of diabetes[5], CKD[6] and sarcopenia[7], suggesting that CKD including albuminuria and sarcopenia could bi-directionally worsen the condition each other through the presence of insulin resistance in patients with diabetes.

Albuminuria is a major risk factor for renal and cardiovascular events, and the interventions to albuminuria have been reported to improve renal and cardiovascular outcomes in patients with type 2 diabetes[8], suggesting the importance of early identification and treatment of patients with diabetes who are at increased risk for albuminuria. Regarding the association between albuminuria and sarcopenia, it has recently been reported that individuals with sarcopenia are at increased risk of prevalent albuminuria[9]; however, there is no longitudinal survey to explore whether sarcopenia could increase the risk for the progression of albuminuria, and lower the frequency of the regression of albuminuria. In the present study, we aimed to assess the longitudinal association between sarcopenia and albuminuria in patients with type 2 diabetes.

METHODS

Study design

This was a retrospective, observational study to determine the impact of sarcopenia on the progression and regression of albuminuria in Japanese patients with type 2 diabetes. The present study was carried out according to the principles of the Declaration of Helsinki, and was approved by the ethical committee of Tokyo Medical and Dental University.

Participants

Participants were recruited from the outpatient clinic at Tokyo Medical and Dental University Hospital during the period between 1 July 2012 and 31 July 2016. Inclusion criteria were as follows: (i) type 2 diabetes patients aged ≥20 years; and (ii) those who had undergone whole-body dual-energy X-ray absorptiometry. Exclusion criteria were as follows: urinary albumin-to-creatinine ratio (ACR) ≥300 mg/g, CKD stage 5 (estimated glomerular filtration rate <15 mL/min/1.73 m^2 or receiving dialysis), pregnant women, infectious diseases or cancer.

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Clinical and biochemical analysis

Urinary albumin and creatinine excretion were measured by the turbidimetric immunoassay and enzymatic method, in a spot urine collection, and the ratio (ACR, mg/g) was used for the assessment of clinical stages of albuminuria (normoalbuminuria, ACR <30; microalbuminuria, ACR 30–299; macroalbuminruia, ACR ≥300). Glomerular filtration rate was calculated using the equation for the Japanese population[10]. We converted glycated hemoglobin values estimated by the Japan Diabetes Society method to the National Glycohemoglobin Standardization Program values[11]. Sarcopenia (reduction of muscle mass and muscle strength) was determined by the criteria for Asians[2], using height, fat-free mass in the upper and lower extremities measured by whole-body dual-energy X-ray absorptiometry (Lunar iDXA; GE Healthcare, Madison, Wisconsin, USA) and the average of bilateral grasp power, as reported previously[12]. Regarding the abdominal adiposity, visceral fat area (VFA) and subcutaneous fat area were measured by abdominal computed tomography as described previously[12].

Study end-point

The end-points were as follows: (i) the progression of albuminuria defined as worsening of clinical stages from normo- to microalbuminuria or micro- to macroalbuminuria; and (ii) the regression of albuminuria defined as the improvement of clinical stages from micro- to normoalbuminuria. The end-points were determined at least on two consecutive measurements of albuminuria.

Statistical analysis

Statistical analysis was carried out using Spss version 21.0 (IBM, Armonk, New York, USA), and the results were expressed as mean ± standard deviation, median and IQR or percentages. The *t*-test, Mann–Whitney *U*-test or χ^2-test as appropriate were used for group comparisons (patients with sarcopenia vs those without sarcopenia). Hazard ratios of the progression or regression of albuminuria were determined using the Cox proportional hazard model. In the multivariate models, age and sex were incorporated into the model irrespective of *P*-values, because these factors can strongly affect muscle strength and body composition including skeletal muscle mass. All *P*-values <0.05 were considered statistically significant.

RESULTS

Clinical characteristics

Among 258 participants screened, five were lost to follow up, 10 had no data regarding ACR and five had ACR measured only once during the follow up. Finally, a total of 238 patients with type 2 diabetes (mean age 64 ± 12 years; 39.2% female) were studied. Patients with sarcopenia were significantly older, had higher levels of urinary ACR, and had lower diastolic blood pressure, body mass index, triglycerides and transaminases than those without sarcopenia (Table 1), and tended to have longer duration of diabetes than those without sarcopenia. Patients with sarcopenia were significantly less likely to receive biguanides, and tended to have low prescription rates of angiotensin receptor blockers compared with those without sarcopenia (Table 2). Progression of albuminuria was observed in 26.3% of patients with sarcopenia, and 12.7% of those without sarcopenia. Regression of albuminuria was observed in 7.9% of patients with sarcopenia, and 12.7% of those without sarcopenia.

Table 1 | Clinical characteristics at baseline

	Sarcopenia (–) (n = 196)	Sarcopenia (+) (n = 42)	*P*-value
Age (years)	61 ± 11	73 ± 9	<0.001
Sex (% male)	63	57	0.735
Systolic blood pressure (mmHg)	127 ± 13	128 ± 20	0.935
Diastolic blood pressure (mmHg)	77 ± 13	70 ± 16	0.003
Body mass index (kg/m^2)	25.7 ± 4.5	22.3 ± 3.6	<0.001
History of CVD (%)	11	11	1.000
Duration of diabetes (years)	4 (1–10)	8 (3–14)	0.055
HbA1c (mmol/mol)	56 ± 18	52 ± 10	0.155
HbA1c (%)	7.3 ± 1.6	6.9 ± 1.0	0.155
TG (mmol/L)	1.39 (0.99–2.42)	1.24 (0.95–1.83)	<0.001
HDL cholesterol (mmol/L)	1.52 ± 0.44	1.56 ± 0.44	0.528
TG/HDL-C ratio	0.94 (0.57–1.85)	0.79 (0.53–1.48)	0.081
LDL cholesterol (mmol/L)	2.90 (2.40–3.47)	2.68 (2.18–3.10)	0.534
AST (U/L)	23 (19–31)	25 (19–28)	0.436
ALT (U/L)	21 (17–33)	18 (13–28)	0.003
γ-GTP (U/L)	35 (22–62)	27 (17–56)	0.338
Uric acid (μmol/L)	315 ± 74	290 ± 78	0.056
eGFR (mL/min/1.73 m^2)	75.6 ± 18.7	74.6 ± 28.4	0.765
Urinary ACR (mg/g)	21 (12–67)	36 (21–88)	0.004
PDR (%)	4	10	0.496
C-reactive protein (mg/L)	0.80 (0.30–1.70)	0.85 (0.30–2.4)	0.501
A/G ratio	0.69 ± 0.18	0.61 ± 0.22	0.028
Body fat (%)	34.1 ± 8.0	33.0 ± 9.5	0.493
Skeletal muscle index	6.86 (6.15–7.69)	5.73 (5.00–6.34)	<0.001
Grasp power (kg)	29.9 (20.9–36.0)	17.2 (14.5–23.2)	<0.001

ACR, albumin-to-creatinine ratio; A/G, android-to-gynoid; ALT, alanine transaminase; AST, aspartate transaminase; CVD, cardiovascular disease; eGFR, estimated glomerular filtration ratio; GTP, glutamyl transpeptidase; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein; PDR, proliferative diabetic retinopathy; TG, triglycerides.

Progression of albuminuria

During the median follow-up period of 2.6 years (IQR 2.0–3.0 years), albuminuria was measured 5.8 ± 1.8 times. Progression of albuminuria was observed in 14.9% of patients with normoalbuminuria, as was 11.5% in those with microalbuminuria. As shown in Table 3, sarcopenia was significantly associated with the progression of albuminuria in the univariate model. After adjusting for age and sex, its association remained

Table 2 | Medications at baseline

	Sarcopenia (–) (n = 196)	Sarcopenia (+) (n = 42)	P-value
Insulin (%)	24	31	0.356
Sulfonylureas (%)	24	33	0.223
Biguanides (%)	54	19	0.001
Alpha-GIs (%)	7	19	0.082
Glinides (%)	5	11	0.389
TZDs (%)	10	7	1.000
DPP4 inhibitors (%)	60	52	0.831
SGLT2 inhibitors (%)	3	0	1.000
GLP1 receptor agonists (%)	5	0	0.583
ACEIs (%)	4	7	0.246
ARBs (%)	34	21	0.058
Calcium channel blockers (%)	29	38	0.294
Beta-blockers (%)	11	12	1.000
Alpha-blockers (%)	2	0	0.592
Diuretics (%)	8	10	0.779
Statins (%)	32	26	0.482
Fibrates (%)	2	5	0.270
Antiplatelet agents (%)	12	14	0.623

ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; DPP4, dipeptidyl peptidase 4; GIs, glycosidase inhibitors; SGLT2, sodium-glucose cotransporter 2; TZDs, thiazolidinediones.

significant. Considering the covariates that could account for the risk for albuminuria progression, glycated hemoglobin (multivariate model 1) was a significant predictor of the progression of albuminuria, and the significant association of sarcopenia with albuminuria remained unchanged. Patients with sarcopenia were at significantly high risk for the progression of albuminuria, even after adjusting for body mass index (multivariate model 2) or visceral fat area by computed tomography (multivariate model 3; n = 213). When the triglycerides/high-density lipoprotein cholesterol ratio, a surrogate marker for insulin resistance[13], was forced into the multivariate model (model 4), the impact of sarcopenia on the progression of albuminuria was slightly attenuated, but its statistical significance remained.

Regression of albuminuria

Among patients with microalbuminuria (n = 91), 11.0% of the patients experienced the regression of albuminuria during the median follow-up period of 2.5 years (interquartile range [IQR] 2.0–3.0 years). As shown in Table 4, sarcopenia was significantly and inversely associated with the remission of albuminuria in univariate Cox regression mode, and the statistical significance remained unchanged even after adjusting for covariates including age, sex, duration of diabetes and body mass index (multivariate model 1). Further adjustment for triglycerides/high-density lipoprotein cholesterol ratio, instead of high-density lipoprotein cholesterol, slightly attenuated the statistical significance (multivariate model 2).

Table 3 | Hazard ratios and 95% confidence intervals for the association between sarcopenia and the progression of albuminuria in patients with type 2 diabetes

	Crude		Age- and sex-adjusted		Multivariate model 1		Multivariate model 2		Multivariate model 3		Multivariate model 4	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Sarcopenia	2.18 (1.02–4.66)	0.043	2.56 (1.09–5.99)	0.031	2.68 (1.13–6.32)	0.025	2.61 (1.08–6.31)	0.034	2.39 (1.01–6.06)	0.048	2.39 (1.01–5.67)	0.047
Age (years)			0.99 (0.96–1.02)	0.414	1.00 (0.97–1.03)	0.949	1.00 (0.96–1.03)	0.891	0.99 (0.96–1.03)	0.768	0.99 (0.96–1.03)	0.763
Sex			0.81 (0.40–1.66)	0.567	0.80 (0.38–1.68)	0.548	0.80 (0.38–1.68)	0.550	0.80 (0.39–2.01)	0.763	0.80 (0.26–1.51)	0.560
HbA1c (%)					1.32 (1.09–1.61)	0.005	1.32 (1.09–1.61)	0.005	1.27 (1.00–1.63)	0.050	1.38 (1.10–1.72)	0.005
BMI (kg/m^2)							0.99 (0.89–1.09)	0.795	NA		0.96 (0.87–1.07)	0.453
Insulin use									2.45 (1.06–5.67)	0.036	NA	
VFA (cm^2)									1.00 (1.00–1.01)	0.715	NA	
TG/HDL-C ratio											0.86 (0.59–1.26)	0.439

Model 3 includes 213 patients whose visceral fat area (VFA) was able to be evaluated by abdominal computed tomography. BMI, body mass index; CI, confidence interval; HR, hazard ratio; NA, not available; TG/HDL-C, triglycerides/high-density lipoprotein cholesterol.

Table 4 | Hazard ratios and 95% confidence intervals for the association between sarcopenia and the regression of albuminuria in patients with type 2 diabetes

	Hazard ratio	95% CI	*P*-value
Univariate			
Sarcopenia	0.27	(0.07–0.97)	0.047
Multivariate model 1			
Sarcopenia	0.20	(0.04–0.99)	0.048
Age (years)	0.95	(0.91–1.00)	0.046
HDL cholesterol (mmol/L)	3.72	(1.07–12.92)	0.038
Duration of diabetes (years)	0.91	(0.74–0.98)	0.019
Body mass index (kg/m^2)	0.82	(0.71–0.94)	0.006
Multivariate model 2			
Sarcopenia	0.26	(0.05–1.23)	0.088
Age (years)	0.96	(0.92–1.01)	0.066
Duration of diabetes (years)	0.93	(0.87–1.00)	0.074
Body mass index (kg/m^2)	0.84	(0.74–0.98)	0.022
TG/HDL-C ratio	0.75	(0.44–1.27)	0.279

CI, confidence interval; HDL, high-density lipoprotein; TG/HDL-C, triglycerides/high-density lipoprotein cholesterol.

DISCUSSION

In the present study, we showed that sarcopenia increases the risk for the progression of albuminuria, and is inversely associated with the regression of albuminuria in patients with type 2 diabetes. Albuminuria is a significant predictor for cardiovascular events and death[14]. A recent cross-sectional study showed that sarcopenia is also associated with atherosclerosis[15], but the relationship between sarcopenia and cardiovascular events has been unknown so far. In the present study, diabetes patients with sarcopenia were at significantly increased risk for the progression of albuminuria. Considering the present findings and the results of previous studies[14,15], patients with sarcopenia, especially those with diabetes, might have a high risk for cardiovascular events through the progression of albuminuria. Conversely, regression of albuminuria was reported to be associated with low cardiovascular events in patients with type 2 diabetes[8]. In the present study, diabetes patients with sarcopenia were less likely to experience a regression of albuminuria. Therefore, sarcopenia could attenuate the beneficial effects of drugs aimed at improving albuminuria. By contrast, antisarcopenic intervention might have a favorable influence on the regression of albuminuria, presumably leading to the reduction of future cardiovascular events.

Although the mechanisms linking increased albuminuria with sarcopenia are not fully understood, several explanations are speculated. Insulin resistance might be a candidate that could explain the association between sarcopenia and albuminuria. Peripheral insulin resistance in skeletal muscle is increased by aging[16], which could stimulate autophagy[17], muscle protein degradation[18] and mitochondrial dysfunction[19], leading to the loss of muscle mass and strength, eventually to sarcopenia[3]. Glucose disposal rate, measured by a hyperinsulinemic-euglycemic clamp, has been reported to be independently associated with microalbuminuria in patients with diabetes[20]. We showed that the addition of the triglycerides/high-density lipoprotein cholesterol ratio into the multivariate models slightly attenuated the association of sarcopenia with both progression (Table 3) and regression (Table 4) of albuminuria in patients with diabetes. These findings could imply that sarcopenia worsens albuminuria partly by insulin resistance. Oxidative stress, micro-inflammation and decreased myokines might also be involved in the common pathogenesis of sarcopenia and albuminuria[21–23].

The limitations of the current study might include a relatively short follow-up period and small sample size. Second, we were unable to assess the association between sarcopenia and change in glomerular filtration rate. Third, we were unable to longitudinally evaluate the association between changes in muscle mass and/or strength, and that in albuminuria. Finally, the study population was relatively homogeneous, because patients were recruited in a single university hospital, so there were limitations to generalizing the results in the present study.

In conclusion, we showed that sarcopenia is a risk factor for the progression of albuminuria, and a negative predictor of the albuminuria remission in patients with type 2 diabetes. It should be clarified in future studies whether amelioration of sarcopenia could prevent the progression of albuminuria.

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DISCLOSURE

The authors declare no conflict of interest.

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