

Research Article

Effects of Low Muscle Mass on Albuminuria and Chronic Kidney Disease in Patients With Type 2 Diabetes: The Korean Sarcopenic Obesity Study (KSOS)

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Abstract

Background: Previous studies have shown that chronic kidney disease (CKD) is associated with accelerated loss of skeletal muscle in patients on dialysis. However, the relationships of sarcopenia with albuminuria and early-stage CKD in patients with type 2 diabetes have not been examined.

Methods: We analyzed diabetic subgroup data from 409 patients with type 2 diabetes from the Korean Sarcopenic Obesity Study (KSOS). Sarcopenia was defined as a skeletal muscle mass index (SMI; $\text{SMI} [\%] = \text{total skeletal muscle mass} [\text{kg}] / \text{weight} [\text{kg}] \times 100$) less than 2 *SD* below the sex-specific mean for a younger reference group. The estimated glomerular filtration rates and urinary albumin-to-creatinine ratios were used to assess renal function and albuminuria.

Results: The prevalence of sarcopenia was significantly increased in the albuminuria group compared with the normo-albuminuria group (26.7% vs 12.6%, $p = .001$), as well as in CKD 3 group compared with the CKD 1–2 group (46.7% vs 15.1%, $p = .005$). After adjusting for age, SMI was negatively correlated with urinary albumin-to-creatinine ratios and positively correlated with aspartate aminotransferase, alanine aminotransferase, total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol levels. Multiple logistic regression analysis revealed that the odds ratio for albuminuria association was 3.02 (95% CI 1.37–6.67) in the lowest tertile of SMI compared with the highest tertile after adjusting for various confounding factors.

Conclusions: Sarcopenia is more prevalent in individuals with albuminuria than in those without albuminuria. Furthermore, increased albuminuria is independently associated with low muscle mass in patients with type 2 diabetes.

Keywords: Chronic kidney disease—Albuminuria—Sarcopenia—Skeletal muscle mass index—Type 2 diabetes

Like many other countries around the world, Korea is facing the challenge of a rapidly increasing aging population. One conspicuous change in the human body composition related to aging is a progressive loss of muscle mass and strength, called sarcopenia (1). Sarcopenia causes physical disability, functional impairment, metabolic derangement, decreased survival, and increased health care costs (2).

Moreover, the prevalence of chronic kidney disease (CKD) is steadily rising, particularly in the elderly population (3). Diabetic

kidney disease is the leading cause of end-stage renal disease (ESRD) and is also linked with cardiovascular and all-cause mortality (4,5). A low creatinine excretion rate has also been associated with increased all-cause mortality in patients with type 2 diabetes with nephropathy (6). In particular, albuminuria is regarded as an independent risk factor for progression to ESRD and for cardiovascular disease (7). Interestingly, albuminuria shares certain pathophysiological mechanisms, such as insulin resistance, inflammation,

endothelial dysfunction, and oxidative stress, with sarcopenia (8,9). Recently, we and other groups observed that sarcopenia is independently associated with type 2 diabetes, which is a critical risk factor for CKD and cardiovascular disease (10,11).

Several studies have examined the relationship between muscle mass and kidney function. Muscle wasting has been increasingly reported in patients on dialysis (12). Moreover, patients with ESRD exhibit more severe and earlier loss of muscle mass than control patients (13). However, to the best of our knowledge, no study has yet explored the relationships of sarcopenia with albuminuria and early-stage CKD in patients with type 2 diabetes mellitus after comprehensive adjustment for confounding factors including medications. Therefore, here, we examined the association between albuminuria and skeletal muscle mass index (SMI) in patients with type 2 diabetes mellitus. Furthermore, we compared the SMI with estimated glomerular filtration rate (eGFR) values calculated by the CKD-Epidemiology Collaboration (CKD-EPI) equation.

Methods

Study Subjects

We analyzed baseline cross-sectional data of the diabetic subgroup from the Korean Sarcopenic Obesity Study (diabetic KSOS), an ongoing epidemiological study. This prospective observational cohort was designed to examine the prevalence of sarcopenia and sarcopenic obesity in Korean adults with or without diabetes and to evaluate the effects of these conditions on metabolic disorders and diabetic microvascular and macrovascular complications. Details of this study have been previously published (10,14). Participants were enrolled in the KSOS cohort between September 2007 and August 2009. The study participants consisted of 428 patients with diabetes who were treated at the Diabetes Center of Korea University Guro Hospital. We excluded the participants who had a history of cardiovascular disease (myocardial infarction, unstable angina, stroke, or cardiovascular revascularization), stage 2 hypertension (resting blood pressure \geq 160/100 mmHg), acute infectious disease, malignant disease, or severe renal or hepatic disease. A total of 409 subjects for whom complete data regarding body composition were available were included in the final analysis. We investigated smoking status, alcohol status, and medication history including the use of insulin, statins, fibrates, angiotensin receptor blockers, and angiotensin-converting enzyme (ACE) inhibitors. Physical activity was classified into two categories, none or regular, with regular exercise defined as exercising at least three times a week for a minimum of 30 minutes each. Written informed consent was obtained from all parents and the Korea University Institutional Review Board approved this study protocol in accordance with the Declaration of Helsinki of the World Medical Association.

Laboratory Measurements

All blood and random spot urine samples were obtained in the morning after a 12-hour overnight fast. Blood samples were immediately stored at -80°C for subsequent assays. Serum total cholesterol, triglyceride, and high-density lipoprotein cholesterol levels were determined enzymatically using a chemistry analyzer (Hitachi 747; Tokyo, Japan). Aspartate aminotransferase and alanine aminotransferase levels were determined enzymatically with the aid of an auto-analyzer (TBA-200FR; Toshiba, Tokyo, Japan). The glucose oxidase method was used to measure fasting plasma glucose. HbA1C levels were measured using high performance liquid chromatography on a Bio-Rad Variant II instrument.

Definition of Urinary Albumin and Kidney Function

Urinary albumin and creatinine levels were used to calculate the urine albumin: creatinine ratio (ACR, expressed in $\mu\text{g}/\text{mg}$). Albuminuria was defined as a urinary ACR concentration \geq 30 $\mu\text{g}/\text{mg}$. Kidney function was assessed by estimating the eGFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (15). eGFR levels were classified according to the system recommended by the Kidney Disease Outcome Quality Initiative (K-DOQI) (16). No patient had an eGFR under 30 ml/min/1.73 m² in the present study.

Assessment of Body Composition

Body mass index (BMI) was computed as weight (kg)/height (m). Waist circumference was measured at the midpoint between the lower border of the rib cage and the top of the lateral border of the iliac crest. A whole-body dual-energy x-ray absorptiometry scan was performed on each patient to measure total and regional lean mass (kg) using fan-beam technology (Discovery A, Hologic, Bedford, MA). The appendicular skeletal muscle mass (ASM [kg]) and SMI (SMI [%] = total skeletal muscle mass [kg]/weight [kg] \times 100) were obtained as previously described (10). Sarcopenia was defined as an SMI of 2 *SD* below the sex-specific mean value for a younger reference group (14). The cutoff point for sarcopenia was 35.9% in men and 30.6% in women. Bioelectrical impedance analysis (MC 780MA, Tanita Corporation, Tokyo, Japan) was performed to determine percent body fat. Fat mass (kg) was calculated as body weight (kg) \times percent body fat (%).

Statistical Analysis

Continuous variables with normal distributions are expressed as means \pm *SD*, whereas continuous variables with skewed distributions are expressed as medians and interquartile ranges. All the continuous variables were evaluated using the Shapiro–Wilk test for normality. Selection of parametric and nonparametric analysis was performed according to the distribution and characteristic of variables. Baseline demographic and biochemical characteristics of the study population were compared by albuminuria or chronic renal disease status using an independent *t* test or the Mann–Whitney *U* test for continuous variables. Pearson's Chi-square test or Fisher's exact test was used to test for differences in the distribution of categorical variables. Analysis of covariance was used to compare urinary ACR and eGFR values between the sarcopenia and non-sarcopenia groups before and after adjusting for sex and age. All statistical results were based on two-sided tests. To evaluate correlations between SMI and metabolic variables, Spearman partial correlation analysis was used after adjusting for age. Odds ratios (ORs) and 95% confidence intervals (CIs) for the prediction of CKD based on eGFR and albuminuria values were obtained from logistic regression models after controlling for potential covariates such as sex and age. Data were analyzed by a professional statistician (S.Y. Hwang) using SAS 9.2 (SAS Institute, Cary, NC); a *p* value less than .05 was assumed to indicate statistical significance.

Results

Study Subject Characteristics

The characteristics of the study subjects with or without albuminuria are presented in Table 1. The subjects in the albuminuria group were significantly older than those in the normo-albuminuria group. The two groups also exhibited significant differences in creatinine

Table 1. Anthropometric and Clinical Characteristics of the Study Subjects With or Without Albuminuria

	Normal (<i>n</i> = 304)	Albuminuria (<i>n</i> = 105)	<i>p</i>
Male (%)	52.6	54.3	.770
Age (years)	58 (52, 65)	62 (53, 69)	.015
Height (m)	1.6 ± 0.1	1.6 ± 0.1	.699
Body weight (kg)	64.0 (57.6, 70.2)	67.0 (59.0, 73.2)	.078
Body mass index (kg/m ²)	24.8 (22.9, 27.0)	24.4 (22.1, 26.7)	.164
Waist circumference (cm)	86 (82, 91)	85 (80, 91)	.088
SBP (mmHg)	127 (118, 136)	126 (114, 134)	.163
DBP (mmHg)	79.7 ± 10.2	80.2 ± 11.1	.683
Total cholesterol (mmol/L)	3.4 (2.7, 4.1)	3.4 (2.8, 4.1)	.972
LDL cholesterol (mmol/L)	1.7 (1.2, 2.3)	1.7 (1.2, 2.3)	.872
HDL cholesterol (mmol/L)	1.0 (0.8, 1.2)	1.0 (0.8, 1.3)	.192
Triglyceride (mmol/L)	1.3 (0.9, 1.9)	1.0 (0.8, 1.6)	.014
AST (U/L)	15 (10, 21)	13 (8, 20)	.099
ALT (U/L)	18 (15, 23)	18 (14, 23)	.806
Urinary ACR (μg/mg)	6.5 (4.2, 11.4)	101.2 (55.1, 239.7)	<.001
Creatinine (μmol/l)	51.3 (40.7, 63.6)	56.6 (47.7, 75.1)	<.001
eGFR (ml/min/1.73 m ²)	106.9 (99.0, 117.8)	98.7 (86.3, 112.2)	<.001
FPG (mmol/L)	5.9 (5.0, 7.2)	5.7 (4.6, 6.8)	.205
HbA1C (% [mmol/mol])	7.1 (6.6, 7.7)	7.1 (6.6, 7.7)	.930
Duration of diabetes (years)	54 (49, 61)	54 (49, 61)	
	7.0 (3.0, 11.5)	7.0 (3.0, 13.0)	.886
Body composition			
ASM (kg)	21.2 (17.6, 24.6)	20.4 (17.8, 23.9)	.670
ASM/height ² (kg/m ²)	8.0 (7.3, 8.9)	8.0 (7.4, 8.7)	.619
SMI (%)	37.5 (33.5, 41.0)	36.2 (32.8, 39.2)	.015
BIA FM (kg)	17.1 (13.8, 21.3)	15.9 (12.5, 20.0)	.102
BIA PBF (%)	25.9 (21.3, 31.7)	25.2 (19.5, 30.8)	.129
Physical activity (%)	50.0	48.6	.801
Current smokers (%)	22.0	20.0	.661
Alcohol users (%)	52.0	53.3	.810

Note: Data are expressed as means ± SD, medians (inter-quartile ranges), or *n* (%). *p* Values were calculated using an independent two-sample *t* test, the Mann-Whitney *U* test, or the χ^2 test. Albuminuria was defined as a urinary ACR ≥ 30 μg/mg Cr. ACR = albumin to creatinine ratio; ALT = alanine aminotransferase; ASM = appendicular skeletal muscle; AST = aspartate aminotransferase; BIA FM = bioelectrical impedance analysis fat mass; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; FPG = fasting plasma glucose; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PBF = percent body fat; SMI = skeletal muscle mass index; SBP = systolic blood pressure.

and eGFR levels, two markers for kidney function. However, blood pressure, body mass index, physical activity, and laboratory measurements (lipid profile, fasting plasma glucose, and HbA1c level) were similar between the two groups, with the exception of triglycerides. The subjects in CKD 3 group were significantly older than those in CKD 1–2 group (Supplementary Table 1). In particular, the SMI values were significantly lower in the albuminuria group than in the normo-albuminuria group (36.2 [32.8, 39.2] vs 37.5 [33.5, 41.0] %, *p* = .015), as well as in the CKD 3 group compared to the CKD 1–2 group (35.4 [29.8, 37.7] vs 37.3 [33.4, 40.8] %, *p* = .046). Furthermore, the prevalence of sarcopenia was significantly higher in the albuminuria group than in the normo-albuminuria group (26.7% vs 12.6%, *p* = .001), as well as in the CKD 3 group compared to the CKD 1–2 group (46.7% vs 15.1%, *p* = .005; Figure 1). Also, as the CKD stage increased, the prevalence of sarcopenia increased (CKD stage 1, 2, and 3: 14.4%, 20.0%, and 46.7%, *p* = .003). In addition, the urinary ACR (*p* = .013) and eGFR (*p* = .003) values were significantly different between the sarcopenia group and the nonsarcopenia group. Specifically, the log-transformed urinary ACR level was significantly higher in the sarcopenia group than in the nonsarcopenia group (*p* = .003) and the log-transformed eGFR level of the sarcopenia group was significantly lower than that of the nonsarcopenia group (*p* = .014).

Correlation of SMI With Cardiovascular Risk Factors

Table 2 shows the results of partial correlation analysis of SMI with other major metabolic variables in the study populations. After adjusting for age, SMI was negatively correlated with urinary ACR (*p* = .004) and positively correlated with aspartate aminotransferase (*p* = .031), alanine aminotransferase (*p* = .017), total cholesterol (*p* = .006), high-density lipoprotein cholesterol (*p* = .039), and low-density lipoprotein cholesterol (*p* = .048) in the overall group. In the male subgroup, SMI was negatively correlated with urinary ACR (*p* = .001).

Multiple Logistic Regression Analysis for CKD and Albuminuria

Multiple logistic regression analysis was performed using stage 3 CKD and albuminuria as the dependent variables; the ORs and 95% CIs were calculated for each SMI tertile. As shown in Table 3, the SMI tertile was not significantly associated with stage 3 CKD, although increasing trends of ORs of having stage 3 CKD by SMI tertile were observed. However, multiple logistic regression analysis for albuminuria after adjusting for sex and age revealed that subjects in the second (OR = 2.13, 95% CI = 1.16–3.92) and first (OR = 2.69, 95% CI = 1.26–5.75) SMI tertiles had significantly higher risks compared with subjects in the third tertile (*p* for trend = .010; Table 4).

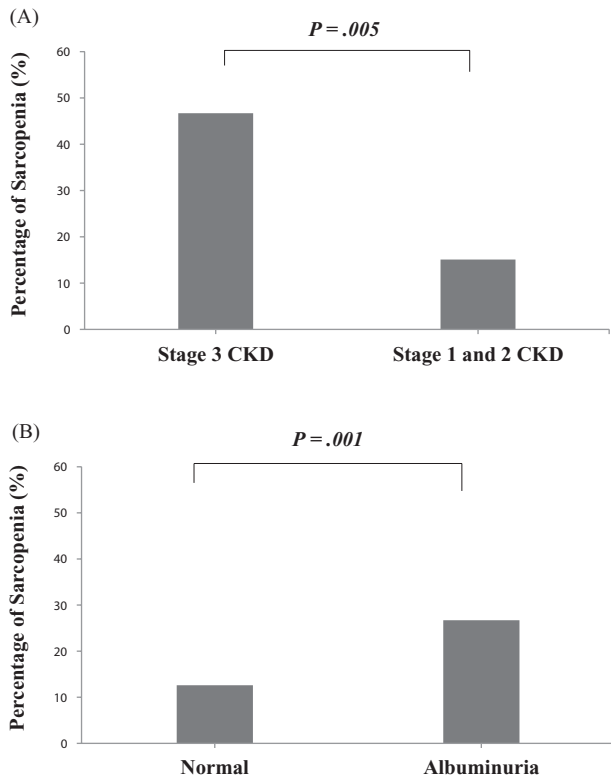


Figure 1. Prevalence of sarcopenia according to (A) chronic kidney disease (CKD) (stage 3 CKD vs stage 1 and 2 CKD; 46.7% vs 15.1%, $p = .005$) and (B) albuminuria (normal vs albuminuria; 12.6% vs 26.7%, $p = .001$) status.

Table 2. Spearman Partial Correlation Analysis of SMI and Various Parameters After Adjusting for Age

	Total		Female		Male	
	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
eGFR	-.001	.991	.028	.699	.032	.643
Urinary ACR	-.141	.004	-.070	.338	-.234	.001
SBP	.062	.213	.080	.271	-.008	.909
DBP	.016	.745	.006	.929	-.053	.444
AST	.107	.031	-.001	.994	-.049	.476
ALT	.118	.017	-.013	.857	.024	.730
Total cholesterol	.136	.006	.031	.675	.062	.366
HDL cholesterol	.103	.039	-.030	.680	.035	.614
Triglyceride	.093	.061	.018	.802	.106	.121
LDL cholesterol	.099	.048	.016	.824	.028	.686
FPG	.071	.156	-.072	.322	-.045	.509
HbA1C	-.001	.988	.131	.072	-.069	.315

Note: ACR = albumin to creatinine ratio; ALT = alanine aminotransferase; AST = aspartate aminotransferase; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; FPG = fasting plasma glucose; HDL = high-density lipoprotein; SBP = systolic blood pressure; SMI = skeletal muscle mass index.

This relationship persisted even after adjusting for percent body fat, smoking status, alcohol status, physical activity, duration of diabetes, HbA1c, systolic blood pressure, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride, and medication history (ie, renin-angiotensin system [RAS] antagonists, statins, fibrates, and insulin) (p for trend = .006).

Discussion

This study found a higher prevalence of sarcopenia in patients with type 2 diabetes with albuminuria compared with patients with type 2 diabetes with normo-albuminuria. Similarly, a higher prevalence of sarcopenia was found in the CKD 3 group compared with the CKD 1–2 group. Furthermore, the higher risk of albuminuria in patients with type 2 diabetes mellitus was significantly associated with low muscle mass independent of demographic and clinical adjustment variables. These findings suggest that the possibility of sarcopenia should be considered when albuminuria is detected in patients with type 2 diabetes.

The pathophysiological mechanisms of sarcopenia and albuminuria are multifactorial and highly similar to one another. Their shared underlying mechanisms, including insulin resistance, endothelial dysfunction, inflammation, oxidative stress, and activation of the RAS may explain the observed relationship between sarcopenia and albuminuria. Skeletal muscle is the largest organ responsible for insulin-mediated glucose disposal in humans. Moon and colleagues reported that sarcopenia is associated with insulin resistance, diabetes, and metabolic syndrome in the Korean population (17). The progressive loss of skeletal muscle might lead to insulin resistance, which could in turn promote albuminuria and cardiovascular disease. Insulin resistance has been shown to induce endothelial dysfunction, glomerular hyperfiltration, and increased vascular permeability, which result in albuminuria (18,19). In patients with type 2 diabetes, insulin resistance is independently associated with microalbuminuria (20). Loss of podocytes by apoptosis is a representative characteristic of the early stages of diabetic kidney disease. One recent study in an animal model reported that podocyte insulin resistance induces susceptibility to cell death, which may contribute to albuminuria (21). Additionally, kidney endothelial dysfunction has been shown to play an important role in the development of albuminuria by reducing vascular relaxation and inflammatory cell infiltration (22). Moreover, endothelial dysfunction and insulin resistance influence the regulation of skeletal muscle protein balance, which may contribute to the development of sarcopenia (23). Decreased nitric oxide and increased endothelin-1 levels lead to impaired endothelium-dependent vasodilatation and potentially induce inflammation through increased leukocyte-endothelium interactions (23). Albuminuria is also known to reflect endothelial dysfunction and subclinical inflammation (24). In addition, an accumulating body of evidence suggests that sarcopenia is an inflammatory state driven by cytokines and oxidative stress (25). The age-related low-grade inflammatory profile (CLIP) is related to decreased muscle mass and strength in elderly persons (26). CLIP disrupts protein kinase B (Akt) signaling and mitochondrial oxidative capacity, in addition to upregulating nuclear factor κ B (NF- κ B) and heat shock protein (Hsp) expression, all of which are linked to sarcopenia (26). Interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) are frequently reported as circulating inflammatory parameters that may explain the link between inflammation and sarcopenia (26). In addition, the RAS has been suggested to play a critical role in the connection between sarcopenia and albuminuria. ACE is expressed in the vascular endothelial cells of skeletal muscle (27). Recently, ACE inhibition was suggested to play a major role in counteracting sarcopenia (28). RAS-blocking drugs have been reported to ameliorate endothelial dysfunction, increase skeletal muscle blood flow, and enhance glucose uptake by skeletal muscle, supporting the hypothesis that RAS inhibition may protect against sarcopenia (28). ACE inhibitors (ACEIs) and angiotensin 1 receptor blockers, two

Table 3. Unadjusted and Adjusted ORs With 95% CIs of Having stage 3 CKD by SMI Tertile

	SMI Tertile (%)			<i>p</i>	<i>p</i> for Trend
	Q3	Q2	Q1		
Unadjusted	1	1.69 (0.40, 7.23)	2.42 (0.61, 9.58)	.445	.199
Model 1	1	1.89 (0.43, 8.37)	3.65 (0.67, 19.91)	.325	.134
Model 2	1	1.99 (0.43, 9.16)	5.10 (0.82, 31.56)	.211	.082
Model 3	1	1.99 (0.42, 9.54)	5.24 (0.81, 34.04)	.216	.085
Model 4	1	2.01 (0.41, 10.01)	5.30 (0.77, 36.42)	.231	.092

Note: Model 1: adjusted for sex and age. Model 2: adjusted for sex, age, percent body fat, smoking status, alcohol status, and physical activity. Model 3: adjusted for sex, age, percent body fat, smoking status, alcohol status, physical activity, duration of diabetes, HbA1c, SBP, LDL cholesterol, HDL cholesterol, and triglyceride. Model 4: adjusted for sex, age, percent body fat (PBF), smoking status, alcohol status, physical activity, duration of diabetes, HbA1c, SBP, LDL cholesterol, HDL cholesterol, triglyceride, use of RAS blockers, use of statins, use of fibrates, and use of insulin. CI = confidence interval; CKD = chronic kidney disease; OR = odds ratio; HDL = high-density lipoprotein; LDL = low-density lipoprotein; RAS = renin-angiotensin system; SBP = systolic blood pressure; SMI = skeletal muscle mass index.

Table 4. Unadjusted and Adjusted ORs With 95% CIs of Having Albuminuria by SMI Tertile

	SMI Tertile (%)			<i>p</i>	<i>p</i> for trend
	Q3	Q2	Q1		
Unadjusted	1	1.85 (1.05, 3.27)	1.87 (1.06, 3.31)	.056	.035
Model 1	1	2.13 (1.16, 3.92)	2.69 (1.26, 5.75)	.022	.010
Model 2	1	2.29 (1.23, 4.26)	2.92 (1.33, 6.39)	.014	.007
Model 3	1	2.31 (1.23, 4.34)	2.92 (1.33, 6.43)	.014	.007
Model 4	1	2.38 (1.26, 4.49)	3.02 (1.37, 6.67)	.011	.006

Note: Model 1: adjusted for sex and age. Model 2: adjusted for sex, age, percent body fat, smoking status, alcohol status, and physical activity. Model 3: adjusted for sex, age, percent body fat, smoking status, alcohol status, physical activity, duration of diabetes, HbA1c, SBP, LDL cholesterol, HDL cholesterol, and triglyceride. Model 4: adjusted for sex, age, percent body fat (PBF), smoking status, alcohol status, physical activity, duration of diabetes, HbA1c, SBP, LDL cholesterol, HDL cholesterol, triglyceride, use of RAS blockers, use of statins, use of fibrates, and use of insulin. CI = confidence interval; OR = odds ratio; HDL = high-density lipoprotein; LDL = low-density lipoprotein; SBP = systolic blood pressure; RAS = renin-angiotensin system; SMI = skeletal muscle mass index.

major classes of drug that target the RAS, have been established to reduce the risk of renal and cardiovascular events (29). Moreover, RAS blockers have shown a protective effect on the kidney against the development of albuminuria and progression to ESRD (30). Previous studies have identified advanced age, male sex, elevated BP, elevated HbA1c, elevated cholesterol, smoking status (smoker), and ethnicity (Afro-Caribbean, Asian, or Native American) as factors that contribute to the development of diabetic kidney disease (31,32). In this study, multiple logistic regression analysis revealed that low muscle mass has stepwise relationship with albuminuria, even after adjusting for possible risk factors related to medication history, such as use of RAS blockers, statins, fibrates, etc.

Previous studies have reported loss of skeletal muscle mass and strength in patients with ESRD. Moreover, the incidence of sarcopenia in patients undergoing maintenance hemodialysis (MHD) was found to be high and to increase gradually with age (33); similarly, the risk of mortality in patients with sarcopenia was higher than in patients without sarcopenia (33). Noori and colleagues also demonstrated that high mid-arm muscle circumference (MAMC), a surrogate measurement of lean body mass (LBM), is an independent predictor of improved survival and mental health in patients undergoing MHD. In patients with ESRD, the most significant predictor of LBM loss is the presence of diabetes mellitus (34). In nondiabetic patients on chronic hemodialysis, insulin resistance has been shown to be associated with the breakdown of skeletal muscle protein (35). A few recent studies investigated the associations between the early stages of CKD and sarcopenia in the general population without ESRD. Foley and

colleagues first reported an association between decreased glomerular filtration rate and increased sarcopenia prevalence in the Third National Health and Nutrition Examination Survey (NHANES III) (36). The prevalences of sarcopenia were reported to be 3.8%, 5.3%, and 9.4% in patients with CKD 1, 2, and 3–5, respectively. In the study by Foley and colleagues, most (76.9%) participants were Caucasian and skeletal muscle mass was calculated using the bioelectrical impedance analysis equation. In a different study using data from the 2008–2011 Korean National Health and Nutrition Examination Surveys (KNHANES), Moon and colleagues showed that CKD stage was significantly related to an increased prevalence of sarcopenia in men but not in women (37). Moon and colleagues proposed that elderly Korean women may retain muscle mass better than elderly Korean men because of household labor. Even more recently, Kim and colleagues demonstrated that the prevalence of albuminuria in the KNHANES 2011 survey was higher in participants with sarcopenia than in patients with a normal SMI (38). In addition, Han and colleagues reported that the overall prevalence of albuminuria was 16.5% in the general population from the KNHANES 2008–2011 (39). They found that increased risk of albuminuria was associated with sarcopenia independent of comorbidities (ORs 1.76–2.88, all $p < .05$). In our study including patients with type 2 diabetes, age-adjusted partial correlation analysis revealed that SMI values were correlated with albuminuria in men but not in women, which is in agreement with the findings of Moon and colleagues (37).

The present study did have some limitations. First, because of the inherent limitations of the cross-sectional study design, we could not

determine whether a causal relationship exists between sarcopenia and albuminuria. Second, the sample size may not have been sufficiently large to detect a significant relationship between sarcopenia and CKD, although the ORs of CKD risk tended to progressively increase with SMI tertile. Additionally, as we only investigated this relationship in Asian diabetic patients without cardiovascular disease, the results should be confirmed in other ethnic and general diabetic populations. Third, serum creatinine has typically been used to calculate eGFR and urine creatinine has typically been used to calculate urinary ACR. Creatinine levels are known to deviate according to non-GFR factors, such as muscle mass, diet, use of fibrates, age, sex, and ethnicity (40). Current guidelines recommend that initial assessment of albuminuria includes measuring the albumin-to-creatinine ratio in an untimed spot urine collection and reporting the estimated GFR (eGFR) based on serum creatinine calculated using the CKD-EPI equation (40). In contrast, eGFR based on cystatin C might be desirable in cases of extreme muscle mass (40). With regard to eGFR, which uses a variable derived from muscle breakdown (creatinine), this method might tend to underestimate the association between muscle wasting and declining kidney function (36). Lastly, physical activity, which has anti-inflammatory and vascular protective effects, was only assessed based on questionnaire.

However, the present study also has several strengths. First, this study was a well-designed epidemiological study designed to examine the impact of sarcopenia on patients with type 2 diabetes. Second, we assessed muscle mass using dual-energy x-ray absorptiometry, which is regarded as the standard method for defining sarcopenia. Third, we performed extensive adjustment for confounding variables, including age, sex, lifestyle, medication use, and anthropometric and laboratory measurements.

In conclusion, this is the first study to show that low muscle mass is independently associated with increment of albuminuria, a known surrogate marker of adverse renal and cardiovascular outcomes, in patients with type 2 diabetes after adjusting for confounding factors. Further long-term studies in other ethnic groups and with larger study populations are needed to confirm our results.

Supplementary Material

Supplementary data is available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Conflict of Interest

The authors have no conflicts of interest.

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