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Relationship Between Sarcopenia and Albuminuria

The 2011 Korea National Health and Nutrition Examination Survey

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Abstract: Studies have shown that albuminuria, obesity, and sarcopenia may share pathophysiological processes related to cardiovascular disease risk. Their direct relationships, however, have not been examined. This study investigated the association between albuminuria and sarcopenia in a representative fraction of the Korean population.

Of the 10,589 people who participated in the 2011 Korea National Health and Nutrition Examination Survey, 2158 participants aged over 19 years had been tested for albumin-to-creatinine ratio and for body composition data using dual-energy x-ray absorptiometry. Albuminuria was defined as an albumin-to-creatinine ratio ≥30 mg/g. Sarcopenia was defined as a skeletal muscle index (SMI) (SMI (%) = total appendicular skeletal muscle mass [kg]/weight [kg] × 100) of less than 1 standard deviation (SD) (grade 1) or 2 SD (grade 2) below the sex-specific mean for a younger reference group.

The prevalence of albuminuria was higher in those with grade 2 sarcopenia than in those with a normal SMI or grade 1 sarcopenia (33.3% versus 8.4% and 8.9%; $P < 0.001$). Conversely, grade 2 sarcopenia was also more prevalent in participants with albuminuria than in those with the upper tertile of normoalbuminuria. In addition, multiple logistic regression analysis showed the odds ratio for albuminuria risk in the grade 2 sarcopenia group was 2.93 (95% confidence interval [CI], 1.46–5.88), compared with normal SMI after adjusting for potential confounding factors, including the presence of obesity, diabetes, and hypertension. Moreover, individuals with albuminuria had an odds ratio of 3.39 (95% [confidence interval], 1.38–8.37) for grade 2 sarcopenia compared with those in the lowest tertile of normoalbuminuria.

This is the first study to demonstrate that individuals with sarcopenia exhibited increased risk of albuminuria and vice versa.

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Abbreviations: ACE = angiotensin-converting enzyme, ACR = albumin-to-creatinine ratio, ALT = serum alanine aminotransferase, ANCOVA = analysis of covariance, ASM = appendicular skeletal muscle mass, BMI = body mass index, BP = blood pressure, CI = confidence interval, CKD = chronic kidney disease, CVD = cardiovascular disease, DXA = dual-energy x-ray absorptiometry, eGFR = estimation of glomerular filtration rate, KNHANES = Korea National Health and Nutrition Examination Survey, KSSO = Korean Society for the Study of Obesity, OR = odds ratio, RAAS = renin–angiotensin–aldosterone system, SCr = serum creatinine, SD = standard deviation, SEM = standard error of the mean, SMI = skeletal muscle index, WBC = white blood cell.

INTRODUCTION

Albuminuria is associated with an increased risk of all-cause mortality and cardiovascular morbidity and mortality in patients with type 2 diabetes or hypertension as well as in the general population.[1,2] Even microalbuminuria is regarded as a risk factor for the progression of chronic kidney disease (CKD) and for cardiovascular disease (CVD).[1] In addition, several clinical trials showed that interventions to reduce albuminuria are often accompanied by improvements in cardiovascular endpoints.[3,4]

Sarcopenia, the age-associated loss of muscle mass, is related to physical disability, metabolic impairments, and increased mortality.[5–7] Although the etiology of sarcopenia or low muscle mass is still poorly understood, the cellular and molecular mechanisms responsible for sarcopenia, such as insulin resistance, inflammation, and oxidative stress, are associated with albuminuria. Moreover, sarcopenia is independently associated with type 2 diabetes, which is an important risk factor for CKD and CVD.[8]

Based on these findings, we hypothesized that sarcopenia and albuminuria share common pathophysiological processes and interact with each other to increase the risk of disease. Previous studies have found a significant association between albuminuria and either general or abdominal obesity or visceral fat.[9–11] To the best of our knowledge, no previous studies, however, have explored whether individuals with albuminuria have a higher risk of sarcopenia than those without albuminuria and vice versa. Therefore, we designed this study to evaluate the association of albuminuria and sarcopenia or sarcopenic obesity.

METHODS

Study Population and Data Collection

We used data from the Korea National Health and Nutrition Examination Survey (KNHANES) V-2, a national program

designed to assess the health and nutritional status of Koreans,[12] which has been conducted in 1998, 2001, 2005, 2007 to 2009, and 2010 to 2012.[13] Korea National Health and Nutrition Examination Survey has collected data on demographic, social, nutritional and health status via health interviews, and medical examinations. Urine albumin was measured starting in the 2011 study.[12] Of a total of 10,589 people who participated in KNHANES V-2, 2011 2,158 participants aged over 19 years had the measurement of albumin-to-creatinine ratio (ACR) and complete data available on body composition using dual-energy x-ray absorptiometry (DXA) (QDR 4500A, Hologic Inc, Waltham, MA). Of these subjects, a younger subgroup (aged 19–39; 620 subjects; 226 men, 334 women) was used as a sex-specific young reference group. This study was approved by the institutional review board of Ilsan Paik Hospital, South Korea (IRB-2015–09–002).

Clinical and Laboratory Examinations

Systolic and diastolic blood pressure (BP) was measured by standard methods using a sphygmomanometer. Three BP measurements were made for all subjects at 5-minute intervals; the final BP value for study subjects was reported by average of the second and third measurements. Blood samples were obtained from each subject after fasting overnight for at least 8 hours. Total cholesterol, triglycerides, and glucose levels were measured in a central and certified laboratory using a Hitachi Automatic Analyzer 7600 (Hitachi, Tokyo, Japan). Diabetes was defined as fasting blood glucose $\geq$7.0 mmol/L that was first detected in this survey, use of an antidiabetes medication, or a previous diagnosis of diabetes by a doctor. Hypertension was defined as systolic BP $\geq$ 140 mm Hg, diastolic BP $\geq$ 90 mm Hg, or use of an antihypertensive medication.

Assessment and Definition of Microalbuminuria and Estimation of Glomerular Filtration Rate

Serum and urinary creatinine (Cr) concentrations were measured using a colorimetric method (Hitachi Automatic Analyzer 7600, Hitachi, Tokyo, Japan). Urinary albumin was measured in random urine samples using a turbidimetric immunoassay (Hitachi Automatic Analyzer 7600, Hitachi, Tokyo, Japan). A detailed explanation of these assays as well as the validity and reproducibility of them in KNHANES V-2 have been provided elsewhere.[12,14] The ratio of urinary albumin to urinary Cr was reported as ACR in milligrams per gram of Cr.[12,14] Normoalbuminuria was defined as ACR $<$ 30 mg/g Cr and albuminuria as ACR $\geq$ 30 mg/g Cr.[14] The eGFR was determined using the Chronic Kidney Disease Epidemiology Collaboration formula: eGFR (mL/min/1.73 m^2) = 141 $\times$ min (SCr/k, 1)^a $\times$ max (SCr/k, 1)$^{-1.209}$ $\times$ 0.993^{Age} [1.018 if woman] $\times$ [1.159 if black] (SCr: serum creatinine [mg/dL], k: 0.7 for women and 0.9 for men, a: −0.329 for women and −0.411 for men, min: minimum of SCr/k or 1, and max: maximum of SCr/k or 1).[15] Chronic kidney disease was defined as $<$60 mL/min per 1.73 m^2 in this study.

Definition of Obesity and Sarcopenia

Body mass index (BMI, [kg/m^2]) was calculated as weight (kg) divided by the square of height (m^2). Obesity was defined according to the criteria recommended by the Korean Society for the Study of Obesity, defining normal as BMI $\geq$ 18.5 and $<$25.0 kg/m^2 and obese as BMI $\geq$ 25.0 kg/m^2.[16] As previous described,[17] a whole-body DXA was performed for each individual to obtain total and regional lean mass (kg) and total body fat (kg). Appendicular skeletal muscle mass (ASM [kg]) was calculated as the sum of the lean soft-tissue masses of the arms and legs, following the method of Heymsfield et al.[18] Sarcopenia was defined as a skeletal muscle index (SMI) (SMI (%) = total ASM [kg]/weight [kg] $\times$ 100) of between 1 and 2 standard deviations (SD) (grade 1) or more than 2 SDs (grade 2) below the sex-specific mean for a younger reference group aged 19 to 39 years.[19] Participants were classified as having a normal muscle mass (men $>$29.6%, women $>$22.8%), grade 1 sarcopenia (men 26.9%–29.6%, women 20.0%–22.8%), or grade 2 sarcopenia (men $<$26.9%, women $<$20.0%).

Health-related Behaviors

Regular exercise was categorized as ''yes'' when participants performed moderate exercise on a regular basis (exercising $\geq$20 minutes at a time $\geq$5 times a week). Alcohol intake was assessed by questions about drinking behavior during the month before the interview. Heavy alcohol drinking was defined as drinking 4 or more times per week. Smoking status was defined based on self-reported cigarette use: current smoker, exsmoker, and nonsmoker.

Statistical Analyses

Clinical and biochemical characteristics were presented according to presence and degree of sarcopenia (Table 1). Data were expressed as mean $\pm$ standard error of the mean or number (percentages). Differences in continuous variables between the 3 groups were evaluated using analysis of covariance (Table 1, Tables 2–4). The Bonferroni method was also used to determine significant differences between the 2 groups as a post hoc test. Persons with normoalbuminuria were further divided into tertiles, giving us 4 ordered categories of albuminuria (Table 3 and Table 5). The normoalbuminuric population was not neatly divisible into tertiles because of the large numbers within each 0.01-mg/g Cr increment of ACR. Multiple logistic regression analysis for the presence of albuminuria (Table 6) or grade 2 sarcopenia (Table 5) was performed using age, sex, diabetes, hypertension, CKD, and obesity as covariates. Two-tailed analyses were conducted, and $P < 0.05$ was deemed to indicate statistical significance. All statistical analyses were conducted using SPSS (ver. 21.0 for Windows, SPSS, Chicago, IL).

RESULTS

Demographic and Clinical Characteristics of the Study Population

The descriptive characteristics of the 2158 participants, categorized by SMI, are shown in Table 1. There were no significant differences across the 3 categories in sex, heavy alcohol drinking, current smoking, regular exercise, systolic and diastolic blood pressure, total cholesterol levels, and eGFR (Table 1). Subjects with normal SMI had lower BMI than those with grade 1 sarcopenia ($P < 0.001$), who in turn had lower BMI than those with grade 2 sarcopenia ($P = 0.007$). Subjects with normal SMI had higher ASM than those with grade 1 sarcopenia ($P < 0.001$), who in turn had slightly higher ASM than those with grade 2 sarcopenia ($P = 0.013$).

Prevalence of Albuminuria According to Skeletal Muscle Index Category

The prevalence of albuminuria was higher in those with grade 2 sarcopenia than in those with normal SMI and grade 1

TABLE 1. Age, Sex, and Age- and Sex-adjusted Clinical Characteristics of Participants by Skeletal Muscle Index

	Normal (n = 1815)	Grade 1 Sarcopenia (n = 297)	Grade 2 Sarcopenia (n = 46)	*P*
Age, y	50.0 ± 0.4	57.9 ± 0.8*,†	64.1 ± 2.0*	<0.001
Men (%)	44.6	41.1	50.0	0.380
College graduate (%)	29.5 ± 1.0	29.4 ± 2.4	31.6 ± 6.1	0.940
Heavy alcohol drinking (%)	7.9 ± 0.6	7.0 ± 1.5	6.4 ± 3.9	0.804
Current smoking (%)	21.6 ± 0.9	20.0 ± 2.2	23.8 ± 5.5	0.717
Regular exercise (%)	9.7 ± 0.7	10.4 ± 1.7	2.0 ± 4.4	0.199
BMI (kg/m^2)	23.3 ± 0.1	26.3 ± 0.2*,†	27.6 ± 0.5*	<0.001
Waist circumference (cm)	80.8 ± 0.2	88.1 ± 0.5*,†	91.8 ± 1.3*	<0.001
Obesity (%)	26.9 ± 1.1	62.1 ± 2.6*	68.9 ± 6.7*	<0.001
Whole body fat mass (kg)	16.4 ± 0.1	23.4 ± 0.3*,†	27.3 ± 0.7*	<0.001
ASM (kg)	18.0 ± 0.1	17.1 ± 0.1*,†	16.1 ± 0.4*	<0.001
Systolic BP (mm Hg)	120.2 ± 0.4	121.9 ± 0.9	123.8 ± 2.3	0.091
Diastolic BP (mm Hg)	75.8 ± 0.2	77.1 ± 0.6	77.0 ± 1.5	0.113
Antihypertensive drug (%)	18.8 ± 0.8	36.6 ± 2.1*	47.1 ± 5.3*	<0.001
Hypertension (%)	31.9 ± 1.0	43.3 ± 2.4*	54.5 ± 6.1*	<0.001
Serum total cholesterol (mg/dL)	190.8 ± 0.8	192.1 ± 2.1	197.2 ± 5.5	0.466
Serum triglyceride (mg/dL)	132.0 ± 2.5	148.4 ± 6.2*,†	208.2 ± 15.9*	<0.001
Antilipid drug (%)	5.4 ± 0.6	12.7 ± 1.4*	19.1 ± 3.6*	<0.001
Fasting plasma glucose (mg/dL)	97.1 ± 0.5	102.5 ± 1.3*,†	119.4 ± 3.4*	<0.001
Antidiabetes drug (%)	7.0 ± 0.6	9.4 ± 1.5†	21.3 ± 3.8*	<0.001
Diabetes (%)	10.7 ± 0.7	20.2 ± 1.9*,†	39.5 ± 4.7*	<0.001
ACR (mg/g Cr)	30.6 ± 5.9	12.2 ± 14.8†	159.6 ± 37.4*	0.001
Albuminuria (%)	8.4 ± 0.7	8.9 ± 1.6†	33.3 ± 4.2*	<0.001
eGFR (mL/min/1.73 m^2)	94.1 ± 0.3	95.6 ± 0.7*	93.1 ± 1.7	0.070
CKD (%)	2.7 ± 0.4	3.2 ± 1.0*,†	12.1 ± 2.4*	0.001
Daily total energy intake (cal)	1994 ± 19	1888 ± 47*	1684 ± 120*	0.007
Daily total protein intake (g/d)	71.1 ± 0.9	67.8 ± 2.3	57.6 ± 5.8*	0.040
WBC (/mm^3)	6018 ± 40	6552 ± 101*,†	7484 ± 262*	<0.001
AST (U/L)	22.0 ± 0.3	25.2 ± 0.6*	23.4 ± 1.6	<0.001
ALT (U/L)	20.7 ± 0.4	26.7 ± 1.0*	25.8 ± 2.4	<0.001
Cancer history (%)	2.9 ± 0.4	5.2 ± 1.0	7.8 ± 2.7*	0.037

Data, mean ± standard error of the mean.
ASM = appendicular skeletal muscle mass, eGFR = glomerular filtration rate, BP = blood pressure.
* $P < 0.05$ versus normal.
† $P < 0.05$ versus grade 2 sarcopenia.

sarcopenia (33.3% versus 8.4% and 8.9%; $P < 0.001$). Albuminuria was approximately 3 times as likely in the group with grade 2 sarcopenia as in the groups with normal and grade 1 sarcopenia even after adjusting for age, sex, diabetes, hypertension, obesity, serum triglyceride, daily total energy intake, white blood cell (WBC), and serum alanine aminotransferase (ALT) (Table 2).

Prevalence of Grade 2 Sarcopenia by the Degree of Albuminuria

Table 3 shows the prevalence of grade 2 sarcopenia according to the degree of albuminuria. Age- and sex-adjusted prevalences of grade 2 sarcopenia in the normoalbuminuric and albuminuric populations were 1.6% ± 0.6% and 8.0% ± 1.0%,

TABLE 2. Prevalence of Albuminuria According to Skeletal Muscle Mass Index Classification

	Normal SMI	Grade 1 Sarcopenia	Grade 2 Sarcopenia	*P*
Model 1	8.8 ± 0.7	7.4 ± 1.7	27.8 ± 4.2*	<0.001
Model 2	8.8 ± 0.7	5.6 ± 1.7	23.5 ± 4.5*	0.001
Model 3	8.5 ± 0.7	6.4 ± 1.8	21.7 ± 4.7*	0.007

Model 1: age, sex, diabetes, hypertension, obesity, regular exercise, and CKD adjusted.
Model 2: model 1 + serum triglyceride, daily total energy intake, white blood cell (WBC) count, and serum alanine aminotransferase (ALT) adjusted.
Model 3: model 2 after exclusion of subjects with cancer history (n = 2085).
SMI = skeletal muscle index.
* $P < 0.05$ versus normal.

TABLE 3. Prevalence of Grade 2 Low Muscle Mass by the Degree of Albuminuria

	Normoalbuminuria				
	Tertile 1	Tertile 2	Tertile 3	Albuminuria	
Range of ACR (mg/g Cr)	0–1.61 (n = 784)	1.62–4.01 (n = 674)	4.02–29.90 (n = 505)	>30.00 (n = 195)	*P*
Model 1	1.3 ± 0.5	1.5 ± 0.6	2.0 ± 0.6	8.0 ± 1.0*	<0.001
Model 2	1.7 ± 0.5	1.7 ± 0.5	1.6 ± 0.6	6.8 ± 1.0*	<0.001
Model 3	1.5 ± 0.5	1.5 ± 0.5	1.8 ± 0.6	6.2 ± 1.0*	0.001

Model 1: age and sex adjusted.
Model 2: age, sex, diabetes, hypertension, obesity, regular exercise, and CKD adjusted.
Model 3: model 2 after exclusion of subjects with cancer history (n = 2085).
ACR = albumin-to-creatinine ratio.
* $P < 0.001$ versus tertile 1.

respectively. There were no significant differences in the prevalence of grade 2 sarcopenia among the tertile groups in subjects with normoalbuminuria. Grade 2 sarcopenia was more prevalent in participants with albuminuria than those with the upper tertile of normoalbuminuria. Even with further adjustment for potential confounding factors, including age, sex, diabetes, hypertension, obesity, and CKD, the associations remained statistically significant ($P < 0.001$).

Prevalence of and Risk for Albuminuria According to Sarcopenia and/or Obesity Defined by Skeletal Muscle Index and Body Mass Index

The unadjusted prevalence of albuminuria according to the 4 sarcopenia/obesity groups defined by SMI and BMI were 7.6% in the normal group, 10.1% in the obesity-only group, 42.9% in the grade 2 sarcopenia-only group, and 34.4% in the obesity and grade 2 sarcopenia group. The prevalence of albuminuria was higher in both the grade 2 sarcopenia only and the combined obesity and grade 2 sarcopenia groups than in the normal group even after adjustment for age, sex, diabetes, hypertension, obesity, CKD, serum triglyceride, daily total energy intake, WBC, and ALT. The results remained significant after excluding data for subjects with cancer history (Table 4).

The odds ratios (ORs) of albuminuria across the SMI tertile groups and the 4 groups based on obesity and sarcopenia were evaluated using multiple logistic regression analysis (Table 5). After adjusting for confounding variables, including age, sex, diabetes, hypertension, CKD, and obesity, the ORs for albuminuria in individuals with grade 2 sarcopenia were 2.93 (95% confidence interval [CI], 1.46–5.88) when compared with individuals with normal SMI. Albuminuria was more prevalent in the grade 2 sarcopenia group than the normal group regardless of the presence of obesity.

Multiple Logistic Regression Analysis for Grade 2 Low Muscle Mass Across the 4 Groups Based on Albuminuria Status

Multivariate logistic regression analysis to determine the predictors of grade 2 sarcopenia in the 4 groups (normoalbuminuric tertile groups and albuminuric group) is shown in Table 6. Data revealed that presence of diabetes (OR 2.46, 95% CI, 1.26−4.79), obesity (OR 3.89, 95% CI 2.01−7.53), and albuminuria (OR 3.41, 95% CI, 1.38−8.41) had independently significant associations with grade 2 sarcopenia. There, however, was no significant difference in risk of grade 2 sarcopenia among the normoalbuminuric tertile groups.

TABLE 4. Prevalence of Albuminuria Among 4 Low Muscle Mass/Obesity Groups as Defined by Skeletal Muscle Index and Body Mass Index

	Normal (n = 1440)	Obese Only (n = 672)	Grade 2 Sarcopenia Only (n = 14)	Obesity/Grade 2 Sarcopenia (n = 32)	*P*
Model 1	7.6 ± 0.7	10.1 ± 1.1	42.9 ± 7.6*	34.4 ± 5.0*	<0.001
Model 2	7.9 ± 0.7	9.8 ± 1.1	38.6 ± 7.5*	31.0 ± 5.0*	<0.001
Model 3	8.6 ± 0.7	8.6 ± 1.1	35.2 ± 7.4†	24.7 ± 4.9†	<0.001
Model 4	8.4 ± 0.8	8.1 ± 1.1	23.7 ± 9.6	24.0 ± 4.9†	0.007
Model 5	8.3 ± 0.8	7.9 ± 1.1	32.9 ± 11.0†	19.7 ± 5.1†	0.019

Model 1: unadjusted.
Model 2: age and sex adjusted.
Model 3: age, sex, diabetes, hypertension, regular exercise, and CKD adjusted.
Model 4: model 3 + serum triglyceride, daily total energy intake, WBC, and serum ALT adjusted.
Model 5: model 4 after exclusion of cancer history (n = 2085).
* $P < 0.001$ versus normal.
† $P < 0.05$ versus normal.

TABLE 5. Logistic Regression Analysis for Grade 2 Sarcopenia

	Odds Ratio (95% CI)	*P*
Age, y		0.025
19–39	Reference	
40–64	1.15 (0.36–3.71)	0.811
>65	2.89 (0.87–9.60)	0.083
Women	0.81 (0.44–1.52)	0.514
Diabetes	2.46 (1.26–4.79)	0.008
Hypertension	1.72 (0.81–3.65)	0.155
CKD	1.41 (0.54–3.70)	0.483
Obesity	3.90 (2.02–7.55)	<0.001
Regular exercise	0.23 (0.03–1.70)	0.149
Albuminuria		0.011
Normal tertile 1	Reference	
Normal tertile 2	0.95 (0.36–2.54)	0.923
Normal tertile 3	1.24 (0.50–3.08)	0.648
Albuminuria	3.39 (1.38–8.37)	0.008

CI = confidence interval, CKD = chronic kidney disease.

DISCUSSION

This nationally representative, population-based study demonstrates a higher risk of albuminuria in individuals with grade 2 sarcopenia compared with those with normal SMI. Moreover, individuals with combined obesity and grade 2 sarcopenia are more than 2 times more likely to have albuminuria than nonsarcopenic and nonobese subjects, whereas there is no significant difference in risk of albuminuria between the nonsarcopenic obese group and the nonobese group with normal mass. Furthermore, although association between low-grade albuminuria within the normal range and grade 2 sarcopenia was not significant, albuminuria is independently associated with grade 2 sarcopenia. Unlikely grade 2 sarcopenia, grade 1 sarcopenia was not independently associated with an increased likelihood of albuminuria in this study. These results suggest that modest reductions in skeletal muscle mass with aging do not cause albuminuria. If muscle loss, however, progresses to the point where the skeletal muscle mass relative to body weight is 2 SDs below the mean for young adults, there is an increased likelihood that albuminuria will occur.

The positive relationships of albuminuria with central obesity, metabolic syndrome and CVD have been well elucidated,[10,20,21] but it was not until recently that the association of albuminuria with sarcopenia and sarcopenic obesity was paid much attention. Although studies showed that both low muscle mass and albuminuria are associated with CVD, most prior studies on the association between low muscle mass and albuminuria showed greater concern over the tendency of low muscle mass to bias urine ACR to higher levels than the investigation of interconnected relationships between the 2 disorders. These studies demonstrated that urine Cr excretion rate is highly and positively correlated with muscle mass,[22,23] and that ACR tended to be underestimated in severely obese ($BMI > 35\,kg/m^2$) individuals as a consequence of the large creatininuria that is proportional to total body skeletal muscle mass.[24] By contrast, among community-living individuals with 24-hour urinary albumin excretion (24-hour UAE) of less than 30 mg/d, ACR is higher in women and older people than could be explained by lower body weight alone, independently of 24-hour UAE.[25] In the current study, sex and obesity, however, were not independently associated with albuminuria. Our study showed that ACR within the normal range is not associated with grade 2 sarcopenia. In addition, because there are very few severely obese individuals in this study, albuminuria may be a more important factor in the association of ACR with presence of grade 2 sarcopenia than urinary Cr. Furthermore, lower levels of timed urine Cr excretion rate and muscle mass are known to be related to CVD and total mortality.[25,26] Therefore, ACR might be more strongly associated with sarcopenia-related metabolic disorders, such as metabolic syndrome, type 2 diabetes, and CVD than is 24-hour UAE.

The pathophysiological mechanisms that result in albuminuria and sarcopenia are considered multifactorial. In this context, the common underlying mechanisms, including endothelial dysfunction, inflammation, insulin resistance, and renin–angiotensin–aldosterone system (RAAS) activation

TABLE 6. Logistic Regression Analysis for Albuminuria

	Odds Ratio (95% CI)	*P*		Odds Ratio (95% CI)	*P*
Age, y		0.076	Age, y		0.081
19–39	Reference		19–39	Reference	
40–64	1.78 (1.06–2.97)	0.028	40–64	1.77 (1.06–2.95)	0.029
>65	1.83 (1.04–3.24)	0.038	>65	1.81 (1.02–3.19)	0.042
Women	1.12 (0.82–1.53)	0.485	Women	1.12 (0.82–1.53)	0.480
Diabetes	2.11 (1.45–3.05)	<0.001	Diabetes	2.09 (1.44–3.02)	<0.001
Hypertension	2.80 (1.96–4.02)	<0.001	Hypertension	2.78 (1.94–3.99)	<0.001
CKD	2.26 (1.23–4.15)	0.008	CKD	2.26 (1.23–4.15)	0.008
Obesity	0.98 (0.71–1.40)	0.984	Obesity	–	
Regular exercise	0.72 (0.40–1.31)	0.282	Regular exercise	0.72 (0.40–1.31)	0.280
Presence of sarcopenia		0.005	Body composition		0.009
Normal SMI	Reference		Nonobese and normal SMI	Reference	
Grade 1 sarcopenia	0.88 (0.56–1.36)	0.557	Obese and normal SMI	1.00 (0.72–1.40)	0.986
Grade 2 sarcopenia	2.93 (1.46–5.88)	0.003	Nonobese and grade 2 sarcopenia	4.81 (1.46–15.80)	0.010
			Obese and grade 2 sarcopenia	2.48 (1.09–5.62)	0.030

CI = confidence interval, CKD = chronic kidney disease, SMI = skeletal muscle index.

between albuminuria and sarcopenia, could largely explain why albuminuria might be an independent indicator for sarcopenia. Endothelial dysfunction plays a crucial role in the development of albuminuria with a shift toward reduced vascular relaxation and inflammatory cell infiltration and slight inflammation in blood vessels.[27] In addition, recent evidence has emerged suggesting that endothelial dysfunction and inflammation of muscle protein metabolism may considerably contribute to the initiation and progression of sarcopenia.[28] The current study has reported that individuals with sarcopenia had increased white blood cell counts, a marker of inflammation, compared with those without sarcopenia. Moreover, both endothelial dysfunction and inflammation have been reported to increase with advancing age, which is a major risk factor for sarcopenia as well as CVD.[29,30] Age-related increases in inflammatory cytokines can disrupt endothelial-dependent dilation by disturbing cell-to-cell communication through gap junctions. Although inflammation exacerbates endothelial dysfunction, elevated endothelin-1 and decreased nitric oxide, causes of impaired endothelial-dependent vasodilation, can lead to increased leukocyte–endothelium interaction, potentially increasing inflammation.[28] Therefore, endothelial dysfunction and inflammation may be a promising mechanism linking CKD, sarcopenia, and CVD.

Skeletal muscle is the major tissue responsible for insulin-mediated glucose disposal in humans. Therefore, the loss of skeletal muscle as the largest insulin-sensitive tissue might cause insulin resistance, which promotes albuminuria and CVD. Various mechanisms may hypothetically mediate the association of insulin resistance and albuminuria. Podocytes of the glomerular filtration barrier are known insulin-sensitive cells. In animal studies, insulin resistance of podocytes increases their susceptibility to cell death and may contribute to albuminuria.[31] Insulin resistance even in nondiabetic states is known to induce glomerular hyperfiltration, endothelial dysfunction, and increased vascular permeability, which all lead to albuminuria.[32,33] Studies on patients with type 2 diabetes have also suggested that insulin resistance is independently associated with microalbuminuria.[34] Although indices of insulin resistance were not measured in this study, the presences of hypertension and diabetes, as insulin-resistance clinical phenotypes, are independently associated with albuminuria. Moreover, presence of diabetes is also significantly associated with sarcopenia, which suggests that insulin resistance may be an important underlying factor associated with both sarcopenia and albuminuria.

In addition to endothelial dysfunction, inflammation and insulin resistance, the RAAS system is also believed to play a role in the link between sarcopenia and albuminuria. Renin–angiotensin–aldosterone system is locally expressed in tissue. From the view of sarcopenia, angiotensin-converting enzyme (ACE) is present on the membrane of vascular endothelial cells in muscle as well as in blood.[35,36] Over half of the angiotensin II in the venous drainage of skeletal muscle is because of local synthesis and this angiotensin II might be more important for vasoconstriction than circulating angiotensin II.[37] Furthermore, ACE inhibitors are known to ameliorate endothelial dysfunction, improve skeletal muscle blood flow, and enhance glucose uptake by skeletal muscle, suggesting that altering the RAAS may counter sarcopenia.[36,38] On the contrary, although little is known about the mechanisms causing the reduced albuminuria by ACE inhibitor, the antialbuminuric effect of ACE inhibitors is relatively well established. In this context, ACE inhibitors might be mediating direct effects on both sarcopenia and albuminuria. Taken together, these mechanisms, such as endothelial dysfunction, inflammation, insulin resistance, and RAAS activation enhance our understanding of a close relationship between sarcopenia and albuminuria.

There are several limitations to this study. First, its cross-sectional study design did not allow us to identify causal relationships between albuminuria and sarcopenia. Our study, however, suggested that albuminuria could be the cause of sarcopenia or vice versa based on our results and the shared mechanisms of albuminuria and sarcopenia. Second, a consensus of standardized diagnostic criteria for sarcopenia has not been entirely established, and potentially relevant muscle quality measurements, such as voluntary muscle strength and muscle fiber size and number, were not performed as part of this study. Finally, only a single urine ACR result was used in the current study, which might result in misleading classifications of albuminuria. Repeated or direct measurement of these parameters, however, is costly in time and money and is therefore highly impracticable and almost impossible in nationwide studies.

On the contrary, the current study had several strengths. First, this was a large population-based analysis using well-examined national data, which strengthens the statistical reliability of the results and generalizability of the data. Furthermore, we assessed muscle mass using DXA, which enabled us to more precisely evaluate individuals with sarcopenia.

In conclusion, we showed that individuals with sarcopenia had an increased risk of albuminuria and vice versa after adjusting for confounding factors, including age, sex, and obesity-related metabolic disease, such as diabetes, hypertension, and CKD. The current study may be a stimulant to provoke further research about the novel relationship between sarcopenia and albuminuria.

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