Effect of Low Skeletal Muscle Mass and Sarcopenic Obesity on Chronic Kidney Disease in Patients with Type 2 Diabetes

Da Hea Seo

Inha University School of Medicine

Young Ju Suh

Inha University School of Medicine

Yongin Cho

Inha University School of Medicine

Seong Hee Ahn

Inha University School of Medicine

Seongha Seo

Inha University School of Medicine

Seongbin Hong

Inha University School of Medicine

Yong-ho Lee

Yonsei University College of Medicine

Young Ju Choi

Huh's Diabetes Center

Eunjig Lee

Yonsei University College of Medicine

So Hun Kim (✉ shoney@inha.ac.kr)

Inha University School of Medicine

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Abstract

The causal relationship between low muscle mass and development of chronic kidney disease (CKD) is uncertain in patients with type 2 diabetes mellitus (T2DM). We aimed to investigate the association between low muscle mass or sarcopenic obesity and the risk of incident CKD in patients with T2DM. A total of 3,123 patients with T2DM with preserved renal function were followed up for incident CKD. Skeletal muscle mass was estimated from bioelectrical impedance analysis. CKD was defined as an estimated glomerular filtration rate $< 60 \text{ mL/min/1.73m}^2$. Sarcopenic obesity was defined as the coexistence of sarcopenia and abdominal obesity. During 8.9 years of follow-up, 530 (17.0%) patients developed incident CKD. When subjects were divided into three groups based on sex-specific tertiles, lower muscle mass was not associated with an increased risk of incident CKD after adjustment for risk factors. However, when patients were divided into four groups according to the presence of sarcopenia and obesity, sarcopenic obesity was associated with an increased risk of incident CKD (adjusted hazard ratio 1.77; 95% confidence interval 1.24-2.51; $p=0.001$) compared to the other groups. Sarcopenic obesity, but not low muscle mass alone, may increase the risk of CKD in patients with T2DM.

Introduction

Sarcopenia is a progressive and generalized skeletal muscle disorder involving loss of muscle mass and decline in physical function with advancing age¹. Sarcopenia is associated with functional disability, risk of falls and fractures, poor quality of life, and even death, especially in elderly individuals^{2,3}. Sarcopenia has been recently recognized to be associated with cardiometabolic disorders, including type 2 diabetes mellitus (T2DM)⁴. Moreover, another phenomenon during the aging process — obesity, particularly visceral obesity in combination with sarcopenia — may exert additive deleterious effects on metabolic and cardiovascular health compared with obesity or sarcopenia alone^{5,6}.

There has been growing evidence suggesting a link between sarcopenia and chronic kidney disease (CKD)^{7,8}. Accumulation of uremic toxins, chronic inflammation, insulin resistance, hormonal imbalance, malnutrition, vitamin D deficiency, and oxidative stress contribute to the pathogenesis of sarcopenia in patients with CKD⁹. Several cross-sectional studies have shown that both sarcopenia and obesity are associated with a higher prevalence of CKD in the general population^{8,10}. Limited studies involving patients with diabetes have also indicated that sarcopenia or sarcopenic obesity is associated with CKD^{11–13}. To date, only a single longitudinal study has examined the causal relationship between sarcopenic obesity and renal function decline exclusively in patients with T2DM¹². Furthermore, no studies have assessed the association between low muscle mass and the risk of incident CKD in a large cohort of patients with T2DM and preserved renal function. Therefore, this longitudinal study aimed to evaluate whether low skeletal muscle mass (SMM) is independently associated with the development of incident CKD in a large cohort of patients with T2DM and preserved renal function. Moreover, we further explored the combined effect of sarcopenia and obesity on the risk of incident CKD.

Results

Baseline characteristics of study population according to sex-specific SMI tertiles

A total of 3,123 people were included in the study. The mean age was 56.9 ± 10.0 years and the mean duration of diabetes was 7.4 ± 6.8 years. The characteristics of the study participants according to sex-specific SMI tertiles are summarized in Table 1. Subjects in the lower SMI tertiles were older, had a shorter duration of diabetes, and had a poorer metabolic profile with higher BMI, WC, blood pressure, HbA_{1c}, hs-CRP, lipid profile, and lower KITT ($p < 0.05$). Patients in the lower SMI tertiles had a lower baseline eGFR. More patients were treated with ACE inhibitors and ARBs in the lower SMI tertiles than in the highest SMI tertile.

Table 1
Baseline characteristics of study population according to sex-specific SMI tertiles.

	T1 (N=1042)	T2 (N=1039)	T3 (N=1042)	P for trend
Age (years)	58.7 ± 10.6	56.9 ± 9.2	55.1 ± 9.8	< 0.001
Sex/Male	539 (51.7%)	539 (51.9%)	541 (51.9%)	0.996
Duration of diabetes (years)	7.0 ± 6.8	7.2 ± 6.4	8.0 ± 7.1	< 0.001
WC (cm)				
Male	90.7 ± 7.6	87.7 ± 6.0	81.7 ± 6.7	< 0.001
Female	84.4 ± 8.3	81.7 ± 6.7	75.9 ± 7.3	< 0.001
BMI (kg/m ²)	26.1 ± 3.4	24.8 ± 2.3	22.5 ± 2.4	< 0.001
SMI (%)				
Male	26.7 ± 2.6	30.7 ± 0.7	33.8 ± 1.6	< 0.001
Female	21.4 ± 2.2	25.2 ± 0.6	28.2 ± 1.7	< 0.001
Smoking	139 (15.4%)	157 (16.5%)	178 (18.8%)	0.134
SBP (mmHg)	138.0 ± 18.4	135.3 ± 17.8	129.7 ± 17.0	< 0.001
DBP (mmHg)	87.4 ± 11.5	85.9 ± 10.6	83.0 ± 10.6	< 0.001
HbA _{1c} (%)	8.5 ± 1.9	8.3 ± 1.8	8.3 ± 2.1	0.009
FPG (mg/dl)	160.9 ± 56.9	160.1 ± 56.5	160.7 ± 61.5	0.935
KITT (%/min)	1.9 ± 0.9	2.0 ± 0.9	2.3 ± 1.0	< 0.001
Total cholesterol (mg/dl)	201.0 ± 41.3	195.1 ± 39.7	190.6 ± 41.5	< 0.001
Triglyceride (mg/dl)	162.5 ± 128.0	151.8 ± 109.6	125.0 ± 92.7	< 0.001
HDL-C (mg/dl)	48.6 ± 12.6	50.4 ± 12.9	53.4 ± 14.0	< 0.001
LDL-C (mg/dl)	121.6 ± 36.7	115.4 ± 37.4	112.1 ± 34.3	< 0.001

Data are presented as mean ± standard deviation, median (interquartile range), or number (%). Values with statistical significance are shown in bold.

Abbreviations: SMI, skeletal muscle mass index; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA_{1c}, hemoglobin A1c; KITT, rate constant for plasma glucose disappearance ; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; Hs-CRP, high-sensitivity C-reactive protein; TZD, thiazolidinedione; ACE inhibitors, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease

	T1 (N=1042)	T2 (N=1039)	T3 (N=1042)	P for trend
BUN (mg/dL)	17.2 ± 6.1	17.4 ± 5.0	17.4 ± 5.0	0.266
Creatinine (mg/dL)	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	0.343
eGFR (mL/min/1.73 m ²)	89.2 ± 15.2	91.3 ± 14.7	92.0 ± 15.8	< 0.001
Hs-CRP (mg/dl)	0.97 [0.51;2.07]	0.78 [0.48;1.50]	0.55 [0.30;1.15]	< 0.001
Insulin	99 (9.5%)	88 (8.5%)	135 (13.0%)	0.002
Sulfonylurea	546 (52.4%)	572 (55.1%)	519 (49.8%)	0.057
Metformin	432 (41.5%)	479 (46.1%)	481 (46.2%)	0.046
TZD	91 (8.7%)	93 (9.0%)	95 (9.1%)	0.954
ACE inhibitors/ARBs	232 (22.3%)	233 (22.4%)	193 (18.5%)	0.047
Incident CKD	244 (23.4%)	170 (16.4%)	116 (11.1%)	< 0.001
Data are presented as mean ± standard deviation, median (interquartile range), or number (%). Values with statistical significance are shown in bold.				
Abbreviations: SMI, skeletal muscle mass index; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA _{1c} , hemoglobin A1c; KITT, rate constant for plasma glucose disappearance ; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; Hs-CRP, high-sensitivity C-reactive protein; TZD, thiazolidinedione; ACE inhibitors, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease				

Association Between Baseline Smi Tertiles And Incident Ckd

During 8.9 ± 3.5 years of follow-up, 530 (17.0%) patients developed incident CKD. The cumulative incidence of CKD was significantly higher in subjects in the lower SMI tertiles than in those in the highest SMI tertile: 258 (24.7%) in the lowest SMI tertile, 180 (17.3%) in the middle SMI tertile, and 92 (8.9%) in the highest SMI tertile (Table 1 and Fig. 1, $p < 0.001$ by log-rank test). Table 2 shows the baseline characteristics of patients with and without incident CKD. Compared with patients without incident CKD, patients with incident CKD were older, were more likely to be female, and had a longer duration of diabetes and lower baseline eGFR levels. In addition, patients with incident CKD had poorer metabolic profiles with higher blood pressure, HbA_{1c}, total cholesterol, and hs-CRP levels, and lower KITT values.

Table 2
Baseline characteristics of the study population stratified by incident CKD

	Incident CKD (-) (N=2592)	Incident CKD (+) (N=530)	p
Age (years)	55.5 ± 9.8	63.6 ± 7.7	< 0.001
Sex/Male	1420 (54.8%)	198 (37.4%)	< 0.001
Duration of diabetes (years)	6.9 ± 6.6	9.6 ± 7.2	< 0.001
SMI (%)	28.1 ± 4.3	26.1 ± 4.0	< 0.001
Male	30.6 ± 3.4	29.3 ± 3.6	< 0.001
Female	25.1 ± 3.3	24.2 ± 3.0	< 0.001
BMI (kg/m ²)	24.4 ± 3.1	24.7 ± 3.0	0.066
WC (cm)	83.7 ± 8.7	84.4 ± 7.7	0.059
Male	86.6 ± 7.8	87.1 ± 7.1	0.470
Female	80.1 ± 8.3	82.8 ± 7.6	< 0.001
Smoking	431 (18.4%)	42 (9.2%)	< 0.001
SBP (mmHg)	132.5 ± 17.4	143.5 ± 18.4	< 0.001
DBP (mmHg)	85.1 ± 10.8	86.8 ± 11.8	0.002
HbA _{1c} (%)	8.3 ± 1.9	8.6 ± 1.9	0.003
FPG (mg/dl)	160.3 ± 57.8	161.8 ± 60.8	0.592
KITT (%/min)	2.1 ± 1.0	1.9 ± 0.9	< 0.001
Total cholesterol (mg/dl)	194.9 ± 40.7	199.1 ± 42.4	0.030
Triglyceride (mg/dl)	144.9 ± 112.2	154.0 ± 111.7	0.091
HDL-C (mg/dl)	50.8 ± 13.1	50.7 ± 14.4	0.837
LDL-C (mg/dl)	116.0 ± 35.8	118.4 ± 38.8	0.196

Data are presented as mean ± standard deviation, median (interquartile range), or number (%). Values with statistical significance are shown in bold.

Abbreviations: CKD, chronic kidney disease; SMI, skeletal muscle mass index; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA_{1c}, hemoglobin A1c; FPG, fasting plasma glucose; KITT, rate constant for plasma glucose disappearance ; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; Hs-CRP, high-sensitivity C-reactive protein; TZD, thiazolidinedione; ACE inhibitors, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blocker.

	Incident CKD (-) (N=2592)	Incident CKD (+) (N=530)	p
BUN (mg/dL)	17.0 ± 5.3	18.7 ± 5.4	< 0.001
Creatinine (mg/dL)	0.8 ± 0.2	0.8 ± 0.2	< 0.001
eGFR (mL/min/1.73 m ²)	92.7 ± 14.8	81.6 ± 14.3	< 0.001
Hs-CRP (mg/dl)	0.7 [0.4; 1.5]	0.9 [0.5; 2.2]	< 0.001
Insulin	227 (8.8%)	95 (17.9%)	< 0.001
Sulfonylurea	1306 (50.4%)	330 (62.3%)	< 0.001
Metformin	1138 (43.9%)	253 (47.7%)	0.117
TZD	234 (9.0%)	45 (8.5%)	0.755
ACE inhibitors/ ARB	501 (19.3%)	157 (29.6%)	< 0.001
Data are presented as mean ± standard deviation, median (interquartile range), or number (%). Values with statistical significance are shown in bold.			
Abbreviations: CKD, chronic kidney disease; SMI, skeletal muscle mass index; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA _{1c} , hemoglobin A1c; FPG, fasting plasma glucose; KITT, rate constant for plasma glucose disappearance ; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; Hs-CRP, high-sensitivity C-reactive protein; TZD, thiazolidinedione; ACE inhibitors, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blocker.			

To investigate the association between baseline SMI tertiles and incident CKD, Cox proportional hazards regression analyses were performed (Table 3). In comparison to the highest SMI tertile, the lowest SMI tertile was associated with an increased risk of incident CKD with a HR of 1.49 (95% CI, 1.19-1.87) after adjustment for age and sex (model 1). However, these associations became insignificant after further adjustment for other clinical risk factors including smoking; SBP; duration of diabetes; HbA_{1c}; LDL-C; eGFR; hs-CRP; KITT; use of insulin, metformin, and ACE inhibitors/ARBs; BMI; and WC (model 4, adjusted HR 1.10; 95% CI 0.82-1.47).

Table 3

Multivariable Cox regression analyses showing associations of sex-specific SMI tertiles and risk of incident CKD among type 2 diabetic adults

	T3	T2	T1	P for trend
	(reference)	HR (95% CI)	HR (95% CI)	
Model 1	1	1.26(1.00-1.60)	1.49(1.19-1.87)	<0.001
Model 2	1	1.08(0.83-1.39)	1.10 (0.85-1.43)	0.467
Model 3	1	1.15 (0.89-1.50)	1.20 (0.92-1.55)	0.193
Model 4	1	1.09 (0.83 -1.43)	1.09 (0.82- 1.46)	0.600
Model 1: age and sex				
Model 2: model 1 + smoking, SBP, duration of diabetes, HbA _{1c} , LDL-C, eGFR, logHs-CRP, and KITT				
Model 3: model 2 + use of insulin, metformin and ACE inhibitors/ARBs				
Model 4: model 3 + BMI and WC,				
Abbreviations: SMI, skeletal muscle mass index; CKD, chronic kidney disease; HR, hazard ratio; CI, confidence interval; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; HbA _{1c} , hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; ACE inhibitors, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; Hs-CRP, high-sensitivity C-reactive protein; KITT, rate constant for plasma glucose disappearance.				

Association Between Sarcopenic Obesity And Incident Ckd

Next, we investigated whether sarcopenia and obesity had a combined effect on the development of CKD in patients with T2DM. Table 4 shows the baseline characteristics of the four patient groups stratified by sarcopenia and abdominal obesity using SMI and WC. Compared with reference group, subjects with sarcopenia alone were older, were more likely to be female, and had poorer metabolic profiles, including higher BMI, SBP, DBP, total cholesterol, triglyceride, LDL-C, and hs-CRP levels and lower KITT values. Subjects with obesity alone had poorer metabolic profiles, including higher BMI, DBP, total cholesterol, triglyceride, and hs-CRP levels and lower HDL-C and KITT values compared to the reference group. The use of sulfonylurea, metformin and ACE inhibitors, or ARBs was higher in obese subjects than in reference subjects. Finally, those with sarcopenic obesity were older, were more likely to be female, and had a shorter duration of diabetes than the reference group. In addition, they had poorer metabolic profiles, including higher BMI, SBP, DBP, total cholesterol, triglyceride, LDL-C, and hs-CRP levels and lower HDL-C and KITT values. The use of ACE inhibitors or ARBs was higher in sarcopenic obese subjects with a lower baseline eGFR. The cumulative incidence of CKD was significantly different among groups:

10.0% in the reference group, 19.8% in the sarcopenic group, 18.3% in the obese group, and 25.2% in the sarcopenic obese group (Fig. 2, $p < 0.001$ by log-rank test).

Table 4

Baseline characteristics of study population according to sex-specific sarcopenic obese status (according to WC and SMI).

	Reference	Sarcopenic	Obese	Sarcopenic obese	p
	(N=1026)	(N=1062)	(N=630)	(N=405)	
Age (years)	54.9 ± 9.8	58.9 ± 9.4 ^a	55.8 ± 9.5 ^b	58.4 ± 11.4 ^{a,c}	< 0.001
Sex/Male	694 (67.6%)	352 (33.1%) ^a	327 (51.9%) ^{a,b}	246 (60.7%) ^{a,b,c}	< 0.001
Duration of diabetes (years)	8.0 ± 7.1	7.5 ± 6.8	6.8 ± 6.3 ^a	6.5 ± 6.4 ^{a,b}	< 0.001
SMI (%)					
Male	33.1 ± 1.9	27.6 ± 2.9 ^a	30.8 ± 1.3 ^{a,b}	26.4 ± 2.5 ^{a,b,c}	< 0.001
Female	28.8 ± 1.6	24.0 ± 2.6 ^a	25.1 ± 1.6 ^{a,b}	20.6 ± 2.1 ^{a,b,c}	< 0.001
BMI (kg/m ²)	22.4 ± 2.2	23.7 ± 2.1 ^a	26.8 ± 2.1 ^{a,b}	28.2 ± 3.1 ^{a,b,c}	< 0.001
WC (cm)					
Male	81.4 ± 5.4	84.2 ± 3.7 ^a	93.6 ± 3.3 ^{a,b}	96.1 ± 5.8 ^{a,b,c}	< 0.001
Female	73.6 ± 5.7	77.8 ± 4.8 ^a	89.4 ± 4.1 ^{a,b}	91.6 ± 5.8 ^{a,b,c}	< 0.001
Smoking	213 (22.9%)	93 (9.9%) ^a	109 (18.8%) ^b	59 (16.5%) ^{a,b}	< 0.001

Data are presented as mean ± standard deviation, median (interquartile range), or number (%). Values with statistical significance are shown in bold.

Abbreviations: SMI, skeletal muscle mass index; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA_{1c}, hemoglobin A1c; FPG, fasting plasma glucose; KITT, rate constant for plasma glucose disappearance ; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; Hs-CRP, high-sensitivity C-reactive protein; TZD, thiazolidinedione; ACE inhibitors, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease

^aIndicates p < 0.05 vs reference

^bIndicates p < 0.05 vs sarcopenia

^cIndicates p < 0.05 vs obesity

	Reference	Sarcopenic	Obese	Sarcopenic obese	p
	(N=1026)	(N=1062)	(N=630)	(N=405)	
SBP (mmHg)	129.6 ± 16.6	135.9 ± 19.2 ^a	136.1 ± 17.5 ^a	139.2 ± 17.1 ^{a,b,c}	< 0.001
DBP (mmHg)	83.6 ± 10.6	85.2 ± 11.1 ^a	86.7 ± 10.5 ^{a,b}	88.7 ± 11.6 ^{a,b,c}	< 0.001
HbA _{1c} (%)	8.4 ± 2.1	8.3 ± 1.8	8.3 ± 1.6	8.5 ± 1.9 ^c	0.837
FPG (mg/dl)	164.4 ± 63.1	156.2 ± 54.9 ^a	159.9 ± 55.2	163.4 ± 58.4 ^b	0.527
KITT (%/min)	2.3 ± 1.0	2.1 ± 0.9 ^a	1.8 ± 0.8 ^{a,b}	1.7 ± 0.8 ^{a,b,c}	< 0.001
Total cholesterol (mg/dl)	189.8 ± 40.6	198.6 ± 41.3 ^a	195.0 ± 41.3 ^{a,b}	203.1 ± 39.4 ^{a,c}	< 0.001
Triglyceride (mg/dl)	124.8 ± 92.1	144.9 ± 113.3 ^a	168.5 ± 121.3 ^{a,b}	171.0 ± 128.2 ^{a,b}	< 0.001
HDL-C (mg/dl)	52.7 ± 14.2	51.5 ± 13.3 ^a	48.2 ± 11.7 ^{a,b}	48.2 ± 12.8 ^{a,b}	< 0.001
LDL-C (mg/dl)	112.6 ± 35.9	119.2 ± 37.5 ^a	113.9 ± 34.3 ^b	122.6 ± 36.3 ^{a,c}	< 0.001
eGFR (mL/min/1.73 m ²)	92.3 ± 15.6	90.0 ± 14.5	91.2 ± 15.7	88.6 ± 15.6 ^{a,c}	< 0.001
Hs-CRP (mg/dl)	0.6 [0.3; 1.1]	0.7 [0.4; 1.4] ^a	1.0 [0.5; 2.0] ^{a,b}	1.2 [0.6; 2.4] ^{a,b,c}	< 0.001

Data are presented as mean ± standard deviation, median (interquartile range), or number (%). Values with statistical significance are shown in bold.

Abbreviations: SMI, skeletal muscle mass index; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA_{1c}, hemoglobin A1c; FPG, fasting plasma glucose; KITT, rate constant for plasma glucose disappearance; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; Hs-CRP, high-sensitivity C-reactive protein; TZD, thiazolidinedione; ACE inhibitors, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease

^aIndicates p < 0.05 vs reference

^bIndicates p < 0.05 vs sarcopenia

^cIndicates p < 0.05 vs obesity

	Reference	Sarcopenic	Obese	Sarcopenic obese	p
	(N=1026)	(N=1062)	(N=630)	(N=405)	
Insulin	108 (10.5%)	100 (9.4%)	71 (11.3%)	43 (10.6%)	0.651
Sulfonylurea	494 (48.1%)	593 (55.8%) ^a	346 (54.9%) ^a	204 (50.4%)	0.002
Metformin	459 (44.7%)	446 (42.0%)	317 (50.3%) ^{a,b}	170 (42.0%) ^c	0.006
TZD	92 (9.0%)	86 (8.1%)	59 (9.4%)	42 (10.4%)	0.555
ACE inhibitors/ ARB	173 (16.9%)	198 (18.6%)	179 (28.4%) ^{a,b}	108 (26.7%) ^{a,b}	< 0.001
Incident CKD	103 (10.0%)	210 (19.8%) ^a	115 (18.3%) ^a	102 (25.2%) ^{a,b,c}	< 0.001
Data are presented as mean ± standard deviation, median (interquartile range), or number (%). Values with statistical significance are shown in bold.					
Abbreviations: SMI, skeletal muscle mass index; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA _{1c} , hemoglobin A1c; FPG, fasting plasma glucose; KITT, rate constant for plasma glucose disappearance ; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; Hs-CRP, high-sensitivity C-reactive protein; TZD, thiazolidinedione; ACE inhibitors, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease					
^a Indicates p < 0.05 vs reference					
^b Indicates p < 0.05 vs sarcopenia					
^c Indicates p < 0.05 vs obesity					

To further examine the relationship between body composition and incident CKD, the Cox proportional hazards model was used. Sarcopenia without obesity and obesity without sarcopenia were not associated with an increased risk of incident CKD (Table 5). However, sarcopenic obesity was associated with a significantly increased risk of incident CKD after adjustment for age; sex; smoking; SBP; duration of diabetes; HbA_{1c}; LDL-C; eGFR; use of insulin, metformin, and ACE inhibitors/ARB; hs-CRP; and KITT (model 3, adjusted HR 1.51; 95% CI 1.15-1.98). This association was augmented with a HR of 1.77 (95% CI, 1.24-2.51) after further adjustment for BMI (model 4). When sarcopenic obesity was defined using BMI and SMI, there was a similar association between sarcopenic obesity and incident CKD (model 3, adjusted HR 1.39; 95% CI 1.05-1.84); however, the association was attenuated and became insignificant after further adjustment for WC (model 4) (Table 6).

Table 5

Multivariable Cox regression analyses showing associations of sex-specific sarcopenic obese status (according to WC and SMI) and risk of incident CKD among adults with type 2 diabetes

	Reference	Sarcopenic	Obese	Sarcopenic obese	P for trend
	(reference)	HR (95% CI)	HR (95% CI)	HR (95% CI)	
Model 1	1	1.23 (0.96-1.57)	1.38 (0.87-2.19)	1.90 (1.49-2.42)	<0.001
Model 2	1	0.92 (0.70-1.22)	1.19 (0.71-1.98)	1.46 (1.11-1.91)	<0.001
Model 3	1	1.00 (0.76-1.32)	1.16 (0.70-1.94)	1.51 (1.15-1.98)	<0.001
Model 4	1	1.04 (0.78- 1.38)	1.27 (0.75- 2.14)	1.77 (1.24- 2.51)	<0.001
Model 1: age and sex					
Model 2: model 1 + smoking, SBP, duration of diabetes, HbA _{1c} , LDL-C, eGFR, logHs-CRP, and KITT					
Model 3: model 2 + use of insulin, metformin and ACE inhibitors/ARBs					
Model 4: model 3 + BMI					
Abbreviations: SMI, skeletal muscle mass index; CKD, chronic kidney disease; HR, hazard ratio; CI, confidence interval; BMI, body mass index; SBP, systolic blood pressure; HbA _{1c} , hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; ACE inhibitors, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blocker; Hs-CRP, high-sensitivity C-reactive protein; KITT, rate constant for plasma glucose disappearance.					

Table 6

Multivariable Cox regression analyses showing associations of sex-specific sarcopenic obese status (according to BMI and SMI) and risk of incident CKD among adults with type 2 diabetes

	Reference	Sarcopenic	Obese	Sarcopenic obese	P for trend
	(reference)	HR (95% CI)	HR (95% CI)	HR (95% CI)	
Model 1	1	1.40 (1.09-1.79)	1.47 (0.96-2.27)	1.66 (1.30-2.13)	<0.001
Model 2	1	1.17 (0.88-1.55)	1.46 (0.92-2.32)	1.39 (1.05-1.84)	0.014
Model 3	1	1.22 (0.92-1.63)	1.44 (0.91-2.30)	1.39 (1.05-1.84)	0.022
Model 4	1	1.17 (0.88-1.56)	1.27 (0.78-2.07)	1.17 (0.82-1.66)	0.507
Model 1: age and sex					
Model 2: model 1 + smoking, SBP, duration of diabetes, HbA _{1c} , LDL-C, eGFR, logHs-CRP, and KITT					
Model 3: model 2 + use of insulin, metformin and ACE inhibitors/ARBs					
Model 4: model 3 + WC					
Abbreviations: SMI, skeletal muscle mass index; CKD, chronic kidney disease; HR, hazard ratio; CI, confidence interval; WC, waist circumference; SBP, systolic blood pressure; HbA _{1c} , hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; ACE inhibitors, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blocker; Hs-CRP, high-sensitivity C-reactive protein; KITT, rate constant for plasma glucose disappearance.					

Discussion

In this retrospective longitudinal cohort study of 3,123 patients with T2DM, we demonstrated that sarcopenic obesity, defined by SMI and WC, was independently associated with an increased risk of incident CKD during a mean follow-up of 8.9 ± 3.5 years, even after adjustment for BMI. However, patients with obesity or sarcopenia alone did not exhibit a higher risk of CKD. Moreover, there was no significant association between the SMI and incident CKD in patients with T2DM.

Previous studies have demonstrated an association between sarcopenia and CKD in the general population. In a population study in the US, there was a stepwise increase in the prevalence of sarcopenia with declining eGFR levels; however, the association between eGFR levels and sarcopenia became insignificant after adjusting for clinical risk factors, including age⁷. Similar findings were also noted in a Korean population study in which there was an increase in the prevalence of sarcopenia with increasing stages of CKD; however, these associations remained significant in men only after adjustment for clinical risk factors⁸. This discrepancy may be due to differences in the definitions of sarcopenia, assessment modalities, and ethnicities. Only a few studies have examined the association between sarcopenia and CKD exclusively in the diabetic population. In a meta-analysis on the association between sarcopenia and renal function in patients with diabetes, the main outcome of interest was albuminuria, which was

significantly associated with sarcopenia¹¹. Regarding the relationship between sarcopenia and eGFR, the results were inconclusive due to lack of evidence in patients with T2DM. In a Chinese cross-sectional study, there was no correlation between muscle mass and eGFR in both men and women with T2DM¹³. In contrast, in a Japanese study of T2DM patients, sarcopenia was associated with rapid renal function decline in men during 3.6 years of follow-up and in agreement with our study, the combination of sarcopenia and obesity resulted in the greatest risk of rapid renal function decline¹². However, they included patients with reduced eGFR levels at baseline, and their outcome of interest was > 30% annual rate of eGFR decline, while we exclusively included those with preserved renal function with an outcome of interest of incident CKD with two consecutive eGFR < 60 mL/min/1.73 m². Moreover, they used the android/gynoid fat mass ratio to define obesity, assessed by a whole-body dual-energy X-ray absorptiometry (DEXA) scan, which may have comparable accuracy to WC¹⁴ but a potential error in measuring a particular region of interest due to overlapping regions in obese subjects¹⁵. In the present study, we observed that the risk of incident CKD did not increase in patients with either sarcopenia or obesity, but was restricted to patients with sarcopenic obesity and T2DM.

Generally, sarcopenia is considered a complication of CKD, contributing to an increased risk of major adverse cardiovascular events and mortality^{16,17}. However, when we address the issue of CKD from the point of view of sarcopenia, decreased insulin sensitivity and endothelial dysfunction due to loss of SMM may be a potential mechanism linking CKD to sarcopenia¹⁸. As skeletal muscle is a major target organ for insulin, loss of muscle mass can result in decreased insulin sensitivity with subsequent hyperinsulinism¹⁹, which is linked to low-grade inflammation, endothelial dysfunction, and imbalance in adipokines¹⁸. These findings have been well replicated in our study, where hs-CRP levels were significantly higher and KITT values were significantly lower in patients with sarcopenia and sarcopenic obesity. However, the association between sarcopenic obesity and incident CKD remained significant, even after adjusting for traditional risk factors, including hs-CRP levels and KITT values. This finding may imply that there may be other factors beyond chronic inflammation and insulin resistance underlying the relationship between sarcopenic obesity and incident CKD.

Numerous observational studies have documented a significant association between obesity and the development and progression of CKD in the general population^{20,21}. Increased adiposity may have a direct impact on kidney function by exerting unfavorable renal hemodynamic effects, such as glomerular hypertrophy and hyperfiltration, along with activation of growth factors and alteration in adipocyte-driven hormones²². Similar findings have been reported in patients with T2DM²³. These findings were further supported by the Look AHEAD (Action for Health in Diabetes) trial, which showed that 8% weight loss by intensive lifestyle intervention resulted in a 31% reduction in CKD²⁴. Recently, particular attention has been directed to regional adiposity rather than general adiposity; in addition, visceral adiposity, measured using WC, has been shown to predict various obesity-related outcomes^{25,26}. In accordance with these findings, few studies have reported that visceral adiposity, but not general adiposity, is associated with CKD in patients with T2DM^{27,28}. In line with these observations, our study demonstrated that general

obesity defined by BMI was not significantly associated with incident CKD, while visceral obesity was associated with a 1.77-fold increased risk of incident CKD in combination with sarcopenia. This relationship is similar to that observed in a recent longitudinal study, which demonstrated a strong link between sarcopenic obesity, defined by the android/gynoid percent fat ratio, and faster renal function decline in people with T2DM, while there was no association when sarcopenic obesity was defined by BMI¹².

The combination of sarcopenia and obesity, especially visceral obesity, is an age-related change in body composition and is currently one of the concerns in a growing aged society²⁹. The actual prevalence of sarcopenic obesity significantly differs among studies depending on the background of the studied population, methods used for muscle volume quantification, and cut-off values³⁰. There is accumulating evidence that obesity combined with sarcopenia further deteriorates the risk of insulin resistance and/or metabolic syndrome compared with obesity or sarcopenia alone⁵. Although it is still uncertain whether the increased risk of incident CKD is restricted to patients with sarcopenic obesity or applies to all patients with either sarcopenia or obesity, our study demonstrated that the combination of sarcopenia and obesity has a synergistic effect on the development of CKD in patients with T2DM. Therefore, it is important to identify those with sarcopenic obesity in the diabetic population as such patients also have a higher risk of developing CKD, as reported in our study.

This study had several strengths. It was a longitudinal study that involved serial measurements of kidney function to accurately identify incident CKD during 8.9 ± 3.5 years of follow-up. Our cohort consisted of a large number of participants from a homogeneous population with more than 8 years of follow-up. Moreover, we also measured the degree of insulin resistance using a standard KITT method and included a broad spectrum of clinical variables as clinical risk factors in our analysis. To our knowledge, this is the first longitudinal study to report that sarcopenic obesity is associated with an increased risk of incident CKD in Korean patients with T2DM and preserved renal function.

However, this study has several limitations. First, our estimation of SMM did not involve highly accurate modalities such as DEXA or computed tomography. However, BIA is a non-invasive method for assessing SMM and is useful in large population-based studies. Previous studies have reported a good correlation between the results of BIA and DEXA for estimating SMM³¹. Second, we did not have longitudinal data on the changes in body composition. Future prospective studies will be necessary to investigate the association between the relative changes in SMM and reduction in the incidence of CKD in patients with T2DM. Third, there is a possibility of inaccurate estimation of eGFR as a decrease in muscle mass may have led to a decrease in serum creatinine level, leading to an inaccurate reflection of renal function³². Lastly, we did not have data on albuminuria, which is an important marker of diabetic nephropathy. However, it is valuable to assess the risk factors that can lead to a reduction in renal function in patients with diabetes, as reduced eGFR in the absence of albuminuria is more commonly recognized and is a stronger predictor of cardiovascular diseases, especially coronary events and mortality^{33,34}. Therefore, our findings may have an additive role in identifying individuals at a higher risk of CKD.

In a large cohort of patients with T2DM, we demonstrated that sarcopenic obesity is associated with an increased risk of incident CKD, independent of clinical risk factors. However, low muscle mass alone was not an independent risk factor. In addition to its role as a nutritional and clinical surrogate in patients with CKD, assessment of SMM and WC in patients with diabetes may also serve as a tool to identify those at risk of CKD in patients with T2DM. Future prospective trials are warranted to better understand the natural course of CKD associated with longitudinal dynamic changes in SMM and WC in patients with T2DM.

Methods

Study population

Patients from the Seoul Metabolic Syndrome cohort were enrolled between January 2000 and December 2016 at the Huh Diabetes Center in Seoul, Korea, as previously described³⁵. We included 3,123 subjects with baseline bioelectrical impedance analysis for measurements of muscle mass and more than three annual follow-up visits with renal function assessment. The exclusion criteria were age <19 years, diagnosis of type 1 diabetes, and baseline estimated glomerular filtration rate ≤ 60 mL/min/1.73 m². The interval between visits varied among patients, and the last follow-up was conducted in December 2019. All participants provided written informed consent and the study was approved by the Institutional Review Board of Inha University Hospital (IRB No. 2020-06-031) and all methods were carried out in accordance with relevant guidelines and regulations.

Measurements of clinical and laboratory indices

Anthropometric indices, including weight, height and waist circumference (WC) were measured in all subjects by a well-trained nurse who was blinded to the patients' clinical and laboratory data. WC was measured at the midpoint between the lower ribs and the iliac crest at the end of the expiratory phase. All patients underwent renal function tests and blood tests for metabolic parameters including fasting plasma glucose, glycated hemoglobin (HbA_{1c}), C-peptide, insulin, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), and high-sensitivity C-reactive protein (hs-CRP). Each patient's social and medical histories were collected using a self-administered questionnaire.

Definition of incident chronic kidney disease

The estimated glomerular filtration rate (eGFR) values were calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation³⁶ as follows: $eGFR = 141 \times \min(Scr/\kappa, 1)^\alpha \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{age} \times 1.018$ [if female]; where, Scr is serum creatinine in mg/dL, κ is 0.7 for female and 0.9 for male, α is -0.329 for female and -0.411 for male, min is the minimum value of Scr/ κ or 1, and max is the maximum value of Scr/ κ or 1. Incident CKD was defined as two consecutive eGFR < 60 mL/min/1.73 m² during 3-6 months' interval between follow-up visits.

Short insulin tolerance test

A short insulin tolerance test (SITT) was performed to assess the insulin sensitivity. The rate constant for plasma glucose disappearance (KITT: %/min) was used as a marker of insulin sensitivity³⁷. As previously described³⁵, the test was performed at 8:00 AM after an 8-h fast. Venous blood samples were collected at 0, 3, 6, 9, 12, and 15 min after regular insulin (Humulin; Eli Lilly, Indianapolis, IN, USA) intravenous bolus injection at a dose of 0.1 U/kg. The plasma glucose disappearance rate (KITT) value was calculated from the slope of the fall in log-transformed plasma glucose from 3 to 15 min, which was used to calculate the time taken for the basal level of blood glucose concentration to decrease by half ($t_{1/2}$). The formula used was $KITT = 0.693/t_{1/2} \times 100$ (%/min). Higher KITT values indicated higher insulin sensitivity.

Measurement of body composition using bioelectrical impedance

The patients' body composition was assessed using a segmental multifrequency bioelectrical impedance analysis (BIA) system (InBody 4.0, Biospace, Korea). In this study, the appendicular skeletal mass (ASM) was calculated as the sum of the lean muscle mass in the bilateral upper and lower limbs. Skeletal muscle mass index (SMI) was calculated by dividing ASM by body weight (kg) and expressed as a percentage ($SMI = ASM/body\ weight \times 100\%$)³⁸. Subjects were divided into three groups based on sex-specific SMI tertiles: lowest, T1 (18.2-24.7), middle, T2 (25.8-30.0) and highest, T3 (30.1-45.6) for men and lowest, T1 (13.1-25.7), middle, T2 (25.8-30.0) and highest, T3 (30.1-40.7) for women.

Definition of sarcopenia, obesity and sarcopenic obesity

Sarcopenia was defined as an SMI (%) < 2 standard deviations (SDs) below the gender-specific mean for healthy young adults in the Korean population: SMI (%) < 29.0 in men and < 22.9 in women was considered sarcopenia³⁹. Obesity was defined as WC $\geq$ 90 cm in men and $\geq$ 85 cm in women⁴⁰. Sarcopenic obesity was defined as the coexistence of sarcopenia and obesity. Individuals without sarcopenic obesity were classified as follows: reference (non-sarcopenic and non-obese), sarcopenic (sarcopenia without obesity), and obese (non-sarcopenic and obese). Sensitivity analysis was performed using obesity defined by a BMI $\geq$ 25⁴⁰.

Statistical analysis

Continuous variables are reported as mean $\pm$ SD or median with interquartile range, while categorical variables are reported as numbers and percentages. To evaluate the differences in demographic characteristics based on SMI tertiles, p for trend was calculated using a contrast to test for linear trends in continuous variables and the Cochran-Armitage test for categorical variables. The differences in demographic characteristics according to body composition (reference, sarcopenic, obese, and sarcopenic obese) were evaluated using analysis of variance with Bonferroni correction for continuous variables and chi-square test for categorical variables. The cumulative CKD incidence rates by SMI tertiles or the four categories of body composition were assessed using Kaplan-Meier plots and the log-rank test. Cox's proportional hazards model was used to determine the independent association between four

categories of body composition or SMI tertiles and incident CKD after adjustment for confounding variables including age, sex, duration of diabetes, systolic blood pressure (SBP), diastolic blood pressure (DBP), baseline HbA_{1c}, LDL-C, HDL-C, eGFR, hs-CRP, KITT, use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB), smoking, and BMI. Adjusted hazard ratios (HRs) were presented with 95% confidence intervals (CIs). Statistical significance was set at $P < 0.05$. All statistical analyses were performed using SPSS software (version 26.0; IBM Corp., Armonk, NY, USA) and the graphs were plotted using GraphPad Prism version 6.0 (GraphPad, San Diego, CA, USA).

Declarations

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Competing interests

The authors declare no competing interests.

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Authors' contributions

Conception or design: DHS and SHK

Acquisition, analysis, or interpretation of data: DHS, YJS and SHK

Drafting the work or revising: DHS, YC, SHA, SS, SH, YL, YJC, and EL

Final approval of the manuscript: SHK

Data Availability

All data sets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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Figures

Figure 1.

Figure 1

Cumulative CKD incidence according to sex-specific SMI tertiles (Kaplan-Meier analysis).

CKD, chronic kidney disease; SMI, skeletal muscle mass index.

Figure 2.

Figure 2

Cumulative CKD incidence according to sex-specific sarcopenic obesity status (Kaplan-Meier analysis).

CKD, chronic kidney disease.