Effect of low skeletal muscle mass and sarcopenic obesity on chronic kidney disease in patients with type 2 diabetes

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Abstract
**Objective:** This study aimed to investigate the association between low muscle mass or sarcopenic obesity and the risk of incident chronic kidney disease (CKD) in patients with type 2 diabetes mellitus (T2DM).

**Methods:** A total of 3123 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 estimated glomerular filtration rate < 60 mL/min/1.73 m². Sarcopenic obesity was defined as the coexistence of sarcopenia and abdominal obesity.

**Results:** During 8.9 years of follow-up, 530 (17.0%) patients developed incident CKD. When patients 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% CI: 1.24-2.51; \( p = 0.001 \)) compared with the other groups.

**Conclusions:** 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 age [1]. 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 CKD [9]. 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, to our knowledge, has examined the causal relationship between sarcopenic obesity and renal function decline.
SARCOPENIC OBESITY ON CHRONIC KIDNEY DISEASE

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 described [14]. We included 3123 patients 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 (eGFR) ≤ 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 (Institutional Review Board No. 2020-06-031).

Measurements of clinical and laboratory indices

Anthropometric indices, including weight, height, and waist circumference (WC), were measured in all patients 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 (HbA1c), 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 CKD

The eGFR values were calculated using the CKD Epidemiology Collaboration (CKD-EPI) creatinine equation [15] as follows: eGFR = $141 \times \min (\text{Scr}/\kappa, 1)^{\alpha} \times \max (\text{Scr}/\kappa, 1)^{-1.209} \times 0.993^{\text{age}} \times 1.018$, if female; where Scr is serum creatinine in milligrams per deciliter, $\kappa$ is 0.7 for female individuals and 0.9 for male individuals and 0.9 for male individuals, “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 to 6 months’ interval between follow-up visits.

Short insulin tolerance test

A short insulin tolerance test was performed to assess the insulin sensitivity. The rate constant for plasma glucose disappearance (KITT; percentage per minute) was used as a marker of insulin sensitivity [16]. As previously described [14], the test was performed at 8:00 AM after an 8-hour fast. Venous blood samples were collected at 0, 3, 6, 9, 12, and 15 minutes after regular insulin (Humulin; Eli Lilly and Company, Indianapolis, Indiana) 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 minutes, 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 $\text{KITT} = 0.693/t_{1/2} \times 100$ (percentage per minute). 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 version 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

Study Importance

What is already known?

- Previous studies have shown that sarcopenia is associated with renal function, especially with albuminuria, in patients with type 2 diabetes mellitus (T2DM).
- However, the causal relationship between low muscle mass and development of chronic kidney disease (CKD) is uncertain, particularly in patients with T2DM.

What does this study add?

- We have demonstrated that combination of sarcopenic obesity, but not obesity or sarcopenia alone, was independently associated with an increased risk of incident CKD.

How might these results change the direction of research?

- Future prospective trials are warranted to better understand the natural course of CKD associated with longitudinal dynamic changes in skeletal muscle mass and waist circumference in patients with T2DM.
calculated by dividing ASM by body weight (kilograms) and expressed as a percentage (SMI = ASM/body weight × 100%) [17]. Patients were divided into three groups based on sex-specific SMI tertiles: for men, lowest: T1 (18.2-24.7); middle: T2 (24.8-30.0); and highest: T3 (30.1-45.6); and, for women, lowest: T1 (13.1-25.7); middle, T2 (25.8-30.0); and highest, T3 (30.1-40.7).

Definition of sarcopenia, obesity, and sarcopenic obesity

Sarcopenia was defined as an SMI (percentage) < 2 SDs below the gender-specific mean for healthy young adults in the Korean population: SMI (percentage) < 29.0 in men and <22.9 in women was considered sarcopenia [18]. Obesity was defined as WC ≥ 90 cm in men and ≥85 cm in women [19]. Sarcopenic obesity was defined as the coexistence of sarcopenia and obesity. Individuals without sarcopenic obesity were classified as follows: reference (non-sarcopenic and nonobese), sarcopenic (sarcopenia without obesity), and obese (non-sarcopenic with obesity). Sensitivity analysis was performed using obesity defined by a BMI ≥ 25 kg/m² [19].

Statistical analysis

Continuous variables are reported as mean ± SD or median with interquartile range, whereas categorical variables are reported as numbers and percentages. To evaluate the differences in demographic

| TABLE 1 Baseline characteristics of study population according to sex-specific SMI tertiles |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                | T1 (n = 1042)   | T2 (n = 1039)   | T3 (n = 1042)   | p value for trend |
| Age (y)                        | 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 (y)       | 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/m²)                    | 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 (mm Hg)                    | 138.0 ± 18.4    | 135.3 ± 17.8    | 129.7 ± 17.0    | <0.001           |
| DBP (mm Hg)                    | 87.4 ± 11.5     | 85.9 ± 10.6     | 83.0 ± 10.6     | <0.001           |
| HbA1c (%)                      | 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           |
| 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 m²)          | 89.2 ± 15.2     | 91.3 ± 14.7     | 920.0 ± 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 inhibitor/ARB              | 232 (22.3%)     | 233 (22.4%)     | 193 (18.5%)     | 0.047            |
| Incident CKD                   | 244 (23.4%)     | 170 (16.4%)     | 116 (11.1%)     | <0.001           |

Note: Data are presented as mean ± SD, median (interquartile range), or number (percentage). Values with statistical significance are shown in bold. Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BUN, blood urea nitrogen; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; KITT, rate constant for plasma glucose disappearance; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SMI, skeletal muscle mass index; TZD, thiazolidinedione; WC, waist circumference.
characteristics based on SMI tertiles, a p value 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, obesity, and sarcopenic obesity) were evaluated using ANOVA, with Bonferroni correction for continuous variables and $\chi^2$ 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 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 HbA1c, 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% CIs. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using SPSS software (version 26.0; IBM Corp., Armonk, New York), and the graphs were plotted using GraphPad Prism version 6.0 (GraphPad, San Diego, California).

RESULTS

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

A total of 3123 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. Patients 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, HbA1c, 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.

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 patients 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 Figure 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, HbA1c, total cholesterol, and hs-CRP levels, and had lower KITT values.

To investigate the association between baseline SMI tertiles and incident CKD, Cox proportional-hazards regression analyses were performed (Table 3). In comparison with the highest SMI tertile, the lowest SMI tertile was associated with an increased risk of incident CKD, with an 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; HbA1c; 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).

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 the reference group, patients with sarcopenia alone were older; were more likely to be female; had poorer metabolic profiles, including higher BMI, SBP, DBP, total cholesterol, triglyceride, LDL-C, and hs-CRP levels; and had lower KITT values. Patients with obesity alone had poorer metabolic profiles, including higher BMI, DBP, total cholesterol, triglyceride, and hs-CRP levels compared with the reference group. The use of sulfonylurea, metformin, and ACE inhibitors or ARBs was higher in patients with obesity than in reference patients. 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 patients with sarcopenic obesity 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 group with sarcopenia, 18.3% in the group with obesity, and 25.2% in the group with sarcopenic obesity (Figure 2; \( p < 0.001 \) by log-rank test).

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
TABLE 3  Multivariable Cox regression analyses showing associations of sex-specific SMI tertiles and risk of incident CKD among adults with type 2 diabetes

| Model | T3 (reference) | T2, HR (95% CI) | T1, HR (95% CI) | p value for trend |
|-------|----------------|----------------|----------------|------------------|
| 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 |

Note: Model 1: age and sex.
Model 2: model 1 + smoking, SBP, duration of diabetes, hemoglobin A1c, LDL-C, estimated glomerular filtration rate, log high-sensitivity C-reactive protein, and rate constant for plasma glucose disappearance.
Model 3: model 2 + use of insulin, metformin, and angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers.
Model 4: model 3 + BMI and waist circumference.
Values with statistical significance are shown in bold.
Abbreviations: CKD, chronic kidney disease; HR, hazard ratio; SMI, skeletal muscle mass index.

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; HbA1c; LDL-C; eGFR; use of insulin, metformin, and ACE inhibitors or ARBs; hs-CRP; and KITT (model 3, adjusted HR = 1.51; 95% CI: 1.15-1.98). This association was augmented with an 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).

DISCUSSION

In this retrospective longitudinal cohort study of 3123 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.

Previously studies have demonstrated an association between sarcopenia and CKD in the general population. In a population study in the United States, 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 age [7]. 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 factors [8]. 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 sarcopenia [11].

Regarding the relationship between sarcopenia and eGFR, the results were inconclusive because of a 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 T2DM [13]. 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 decline [12]. However, they included patients with reduced eGFR levels at baseline and their outcome of interest was >30% annual rate of eGFR decline, whereas 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 with WC [20] but a potential error in measuring a particular region of interest due to overlapping regions in patients with obesity [21]. 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 [22, 23]. 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 sarcopenia [24]. As skeletal muscle is a major target organ for insulin, loss of muscle mass can result in decreased insulin sensitivity with subsequent hyperinsulinism [25], which is linked to low-grade inflammation, endothelial dysfunction, and imbalance in adipokines [24]. These findings have been well replicated in our study, in which 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
TABLE 4 Baseline characteristics of study population according to sex-specific sarcopenic obesity status (according to WC and SMI)

| Reference (n = 1026) | Sarcopenia (n = 1062) | Obesity (n = 630) | Sarcopenic obesity (n = 405) | p value |
|----------------------|-----------------------|-------------------|-----------------------------|---------|
| Age (y)              | 54.9 ± 9.8            | 58.9 ± 9.4        | 55.8 ± 9.5                  | 58.4 ± 11.4 | <0.001 |
| Sex/male             | 694 (67.6%)           | 352 (33.1%)       | 327 (51.9%)                 | 246 (60.7%) | <0.001 |
| Duration of diabetes (y) | 8.0 ± 7.1          | 7.5 ± 6.8         | 6.8 ± 6.3                   | 6.5 ± 6.4 | <0.001 |
| SMI (%)              |                       |                   |                             |         |
| Male                 | 33.1 ± 1.9            | 27.6 ± 2.9        | 30.8 ± 1.3                  | 26.4 ± 2.5 | <0.001 |
| Female               | 28.8 ± 1.6            | 24.0 ± 2.6        | 25.1 ± 1.6                  | 20.6 ± 2.1 | <0.001 |
| BMI (kg/m²)          | 22.4 ± 2.2            | 23.7 ± 2.1        | 26.8 ± 2.1                  | 28.2 ± 3.1 | <0.001 |
| WC (cm)              |                       |                   |                             |         |
| Male                 | 81.4 ± 5.4            | 84.2 ± 3.7        | 93.6 ± 3.3                  | 96.1 ± 5.8 | <0.001 |
| Female               | 73.6 ± 5.7            | 77.8 ± 4.8        | 89.4 ± 4.1                  | 91.6 ± 5.8 | <0.001 |
| Smoking              | 213 (22.9%)           | 93 (9.9%)         | 109 (18.8%)                 | 59 (16.5%) | <0.001 |
| SBP (mm Hg)          | 129.6 ± 16.6          | 135.9 ± 19.2      | 136.1 ± 17.5                | 139.2 ± 17.1 | <0.001 |
| DBP (mm Hg)          | 83.6 ± 10.6           | 85.2 ± 11.1       | 86.7 ± 10.5                 | 88.7 ± 11.6 | <0.001 |
| HbA1c (%)            | 8.4 ± 2.1             | 8.3 ± 1.8         | 8.3 ± 1.6                   | 8.5 ± 1.9 | 0.837 |
| FPG (mg/dL)          | 164.4 ± 63.1          | 156.2 ± 54.9      | 159.9 ± 55.2                | 163.4 ± 58.4 | 0.527 |
| KITT (%/min)         | 2.3 ± 1.0             | 2.1 ± 0.9         | 1.8 ± 0.8                   | 1.7 ± 0.8 | <0.001 |
| Total cholesterol (mg/dL) | 189.8 ± 40.6     | 198.6 ± 41.3      | 195.0 ± 41.3               | 203.1 ± 39.4 | <0.001 |
| Triglyceride (mg/dL) | 124.8 ± 92.1          | 144.9 ± 113.3     | 168.5 ± 121.3              | 171.0 ± 128.2 | <0.001 |
| HDL-C (mg/dL)        | 52.7 ± 14.2           | 51.5 ± 13.3       | 48.2 ± 11.7                 | 48.2 ± 12.8 | <0.001 |
| LDL-C (mg/dL)        | 112.6 ± 35.9          | 119.2 ± 37.5      | 113.9 ± 34.3               | 122.6 ± 36.3 | <0.001 |
| eGFR (mL/min/1.73 m²) | 92.3 ± 15.6           | 90.0 ± 14.5       | 91.2 ± 15.7                 | 88.6 ± 15.6 | <0.001 |
| hs-CRP (mg/dL)       | 0.6 (0.3; 1.1)        | 0.7 (0.4; 1.4)    | 1.0 (0.5; 2.0)              | 1.2 (0.6; 2.4) | <0.001 |
| Insulin              | 108 (10.5%)           | 100 (9.4%)        | 71 (11.3%)                  | 43 (10.6%) | 0.651 |
| Sulfonylurea         | 494 (48.1%)           | 593 (55.8%)       | 346 (54.9%)                 | 204 (50.4%) | 0.002 |
| Metformin            | 459 (44.7%)           | 446 (42.0%)       | 317 (50.3%)                 | 170 (42.0%) | 0.006 |
| TZD                  | 92 (9.0%)             | 86 (8.1%)         | 59 (9.4%)                   | 42 (10.4%) | 0.555 |
| ACE inhibitor / ARB  | 173 (16.9%)           | 198 (18.6%)       | 179 (28.4%)                 | 108 (26.7%) | <0.001 |
| Incident CKD         | 103 (10.0%)           | 210 (19.8%)       | 115 (18.3%)                 | 102 (25.2%) | <0.001 |

Note: Data are presented as mean ± SD, median (interquartile range), or number (percentage). Values with statistical significance are shown in bold. Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BUN, blood urea nitrogen; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; KITT, rate constant for plasma glucose disappearance; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SMI, skeletal muscle mass index; TZD, thiazolidinedione; WC, waist circumference.

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 [26, 27]. 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 hormones [28]. Similar findings have been reported in patients with T2DM [29]. 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 CKD [30]. 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 [31, 32]. In accordance with these findings, few studies have reported that visceral adiposity, but not general adiposity, is associated with CKD in patients with T2DM [33, 34]. In line with these observations, our study demonstrated that
general obesity defined by BMI was not significantly associated with incident CKD, whereas 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, although there was no association when sarcopenic obesity was defined by BMI [12].
CONCLUSION

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.

AUTHOR CONTRIBUTIONS

Da Hea Seo and So Hun Kim contributed to the study concept and design, data analysis and interpretation, statistical analysis, and manuscript drafting and revision. Young Ju Suh contributed to the statistical analysis. Yong-ho Lee, Seong Hee Ahn, Seongha Seo, Yongin Cho, Seongbin Hong, Young Ju Choi, and Eunjig Lee contributed to data analysis and interpretation, study discussion, and manuscript review and editing. So Hun Kim is the guarantor of this work; as such, she had full access to all study data and takes responsibility for the data’s integrity, analytical accuracy, and final approval of the version to be published.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

DATA AVAILABILITY STATEMENT

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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