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■ **Original Article**

Relationship between Decreased Estimated Glomerular Filtration Rate and Sarcopenic Obesity among Postmenopausal Women: Korea National Health and Nutrition Examination Survey (2008–2011)

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Background: Previous studies have shown that body composition is associated with chronic kidney disease (CKD), and perimenopause is associated with increased fat mass and decreased lean body mass. Muscle wasting is common among patients with CKD. Sarcopenic obesity (SO) refers to excess adiposity with decreased muscle mass. However, little is known about the relationship between SO and renal function decline. Here, we identified the relationship between SO and decreased estimated glomerular filtration rate (eGFR) in postmenopausal women.

Methods: We conducted a cross-sectional study based on the data from the Korea National Health and Nutrition Examination Survey (2008–2011). We analyzed 4,560 postmenopausal women who underwent dual energy X-ray absorptiometry. Sarcopenia was defined based on weight-adjusted appendicular skeletal muscle mass. Obesity was defined based on body mass index. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation. Subjects were classified into four groups: normal, obese, sarcopenic, and sarcopenic obese. Logistic regression analysis was performed to examine the association between SO and decreased eGFR. The results were adjusted for variable confounders.

Results: In the unadjusted model, the odds ratio (OR) of decreased eGFR for SO was 1.67 (95% confidence interval [CI], 1.23–2.26). The obese and sarcopenic groups had ORs of 0.67 (95% CI, 0.44–1.03) and 0.70 (95% CI, 0.44–1.10), respectively. After controlling for confounding variables, there was also a significant association between SO and decreased eGFR (adjusted OR, 1.48; 95% Cl, 1.05–2.07).

Conclusion: SO was independently associated with decreased eGFR in postmenopausal Korean women.

Keywords: Sarcopenia; Obesity; Chronic Renal Insufficiency; Postmenopause

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INTRODUCTION

The decreased glomerular filtration rate (GFR) is a characteristic of chronic kidney disease (CKD) and is associated with clinical prognosis such as metabolic disease and cardiovascular mortality.[1,2] Recently, the prevalence of CKD has been increasing due to the high numbers of individuals with obesity, hypertension (HTN), and diabetes mellitus (DM), placing a financial burden on the public economy.[3,4] Common health conditions related to CKD include high blood pressure (BP), malnutrition, and heart and vessel diseases. In addition, CKD is frequently associated with adverse changes to body composition and musculoskeletal health. Protein-energy or muscle wasting syndrome that appears to be an accelerated form of sarcopenia is also one of the conditions related to CKD.[5] Several previous studies have suggested that there might be an association between sarcopenia and kidney dysfunction.[6-8]

Sarcopenia, a term proposed by Rosenberg[9] in 1989, is a syndrome characterized by the progressive loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life, and mortality.[10] In patients with sarcopenia, the loss of muscle tissue is accompanied by infiltration with fat and connective tissue, a condition known as myosteatosis in which sarcopenia is combined with obesity, so-called sarcopenic obesity (SO), causing chronic inflammation and catabolic cytokine production.[11] Sarcopenia and obesity share several pathophysiological mechanisms and may potentiate each other. Patients with SO have a higher risk of insulin resistance and metabolic syndrome than those with obesity or sarcopenia alone.[12] Therefore, populations that have both obesity and sarcopenia should be considered. However, few studies have been conducted to evaluate the relationship between SO and CKD.

An aging population is an important concern around the world. The elderly population in South Korea has been increasing, and more than 30% of Korean women are older than 50 years, which is the mean age of menopause. Several studies have suggested that menopause is associated with increased visceral fat mass and decreased skeletal muscle mass because of the natural decline in estrogen.[13-15]

In this epidemiological study, we examined the association between SO and decreased GFR after adjusting for multiple confounding variables in a representative sample of the postmenopausal Korean women using data from the Korea National Health and Nutrition Examination Surveys (KNHANES).

METHODS

1. Study Participants

This cross-sectional study was based on data obtained from the 2008 to 2011 KNHANES IV and V. The KNHANES is a national surveillance system that has been assessing the nutritional and general health status of the civilian population of South Korea since 1998.[16] Among the 37,753 participants in the 2008 to 2011 KNHANES IV and V, there were 20,558 women and 17,195 men. After excluding 4,558 participants with missing menopause-related data, data from 7,127 (44.5%) postmenopausal women were collected. In addition, 2,567 participants with missing data for appendicular skeletal muscle mass (ASM), determined by dual-energy X-ray absorptiometry (DXA, QDR 4800A; Hologic Inc., Bedford, MA, USA), serum creatinine level, and body mass index (BMI) were excluded. Therefore, a total of 4,560 postmenopausal women were included in the final analysis. All the patients enrolled in the KNHANES signed an informed consent form. This was a cross-sectional study based on the KNHANES (http://knhanes.cdc.go.kr/knhanes/); therefore, ethical approval was not required.

2. Clinical and Laboratory Measurements and Data Collection

Blood samples were obtained after 8 hours of fasting from each participant. Total cholesterol, triglyceride, high-density lipoprotein cholesterol, and fasting glucose were measured by an enzymatic method, and serum creatinine using an automatic analyzer 7600 (Hitachi, Tokyo, Japan). DM was defined as fasting blood glucose ≥126 mg/dL, those who were taking anti-diabetic drugs or insulin, or those who had a previous diagnosis of DM by a health care professional. HTN was defined as systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg, or those who were taking anti-hypertensive drugs. Hyperlipidemia was defined as total cholesterol ≥240 mg/dL or triglyceride ≥200 mg/dL, or those who were taking lipid-lowering drugs. The homeostasis model assessment of insulin resistance (HOMA-IR) score was calculated using the following formula: fasting plasma glucose (mg/dL)×fasting insulin (mIU/mL)/405. We defined insulin resistance as HOMA-IR ≥2.5.

Information about lifestyle factors was obtained using a self-reported questionnaire. Regular exercise was defined as at least 20 minutes of high-intensity physical activity at least 3 times a week. Alcohol intake was defined as those who consumed more than 1 drink per month in the past 1 year. The participant's current smoking status was defined as either current smoker or non-current smoker based on their self-reported cigarette use. Daily energy and nutrient intake data were assessed by trained dieticians using the 24-hour diet recall method.

3. Definition of Obesity, Sarcopenia, and Sarcopenic Obesity in the Postmenopausal Women

In our study, menopause was defined as amenorrhea for 12 consecutive months following the final menstruation period. Thus, postmenopausal status was defined as the self-reported cessation of menstruation for >1 year.

Whole and regional body compositions were measured using whole-body DXA scans. This scan has been used to assess body muscle distribution as well as bone density. To define sarcopenia, we used ASM, calculated as the sum of lean soft tissue masses in the arms and legs, assuming that all non-fat and non-bone tissues were skeletal muscles. The skeletal muscle mass index (SMI), which was expressed as a percentage, was calculated using the following formula: ASM (kg)/weight (kg)×100, which was based on and modified from the studies of

Janssen et al.[17)] and Lim et al.[18)]

Obesity was defined as a BMI ≥25.0 kg/m^2 based on the Asian Pacific criterion. Sarcopenia was defined using SMI, as a percentage of body weight (ASM/wt), of less than 1 standard deviations (SD) below the gender-specific mean for the younger reference group aged 20–39 years (n=3,334). The cutoff value for sarcopenia was 23.76% for 1SD. SO was defined as high BMI ≥25.0 kg/m^2 and low relative skeletal muscle mass (SMI of 1SD below the value of a young reference group) in the same participants. Based on the combination of sarcopenia and obesity cutoff points, the subjects were classified into one of four groups: normal (non-sarcopenic, non-obese), obese (non-sarcopenic obese), sarcopenic (sarcopenic non-obese), and SO (sarcopenic obese).

4. Definition of the Decreased Glomerular Filtration Rate

The estimated GFR (eGFR) was calculated to estimate kidney function using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation: for females with a serum creatinine level ≤0.7 mg/dL, GFR=144×(serum creatinine/0.7)$^{-0.329}$×(0.993)^{Age}; for females with a serum creatinine level >0.7 mg/dL, GFR=144×(serum creatinine/0.7)$^{-1.209}$×(0.993)^{Age}. Decreased renal function was defined as eGFR <60 mL/min/1.73 m^2 according to the Kidney Disease Improving Global Outcomes criteria for CKD.

5. Statistical Analysis

We analyzed participant characteristics according to the four groups based on obesity and sarcopenic statuses. Continuous variables were analyzed by one-way analysis of variance and expressed as mean±SD, and categorical variables were analyzed using the chi-square test and expressed as a proportion. Logistic regression analyses were conducted to determine the odds ratio (OR) and 95% confidence interval (CI) to estimate the association between SO and decreased eGFR after adjusting for confounding variables, such as age, height, energy/protein intake, vitamin D, DM, HTN, hyperlipidemia, current smoking, alcohol intake, and regular exercise. All of the statistical analyses were conducted using the PASW SPSS ver. 18.0 for Windows (SPSS Inc., Chicago, IL, USA). The P-value <0.05 was considered statistically significant.

RESULTS

1. Clinical Characteristics of the Study Participants

The differences in various clinical characteristics of 4,560 enrolled participants according to the four groups, based on obese and sarcopenia status, are shown in Tables 1 and 2. The normal group was the most common with 2,249 subjects (49.3%), the SO group had 947 subjects (20.7%), the obese group had 748 subjects (16.4%), and the sarcopenic group was the lowest with 616 subjects (13.5%). The mean age of the normal, obese, sarcopenic, and SO group were 63.2, 61.9, 63.1, and 64.3 years, respectively; the mean ASMs were 13.9, 16.1, 12.1, and 14.3 kg, respectively; the mean total fat masses were 16.0, 21.8, 20.1, and 25.0 kg, respectively (Table 1). Furthermore, in the comorbidity category, the prevalence of DM in the normal, obese, sarcopenic, and SO groups was 12.1%, 18.6%, 14.4%, and 22.8%, respectively; the prevalence of HTN was 43.1%, 55.7%, 47.7%, and 68.6%, respectively; and

Table 1. Clinical characteristics of the participants according to body composition based on muscle mass and fat mass among the postmenopausal women

Characteristic	Normal (n=2,249)	Obese (n=748)	Sarcopenic (n=616)	Sarcopenic obese (n=947)	P-value*
Age (y)	63.2±9.9	61.9±8.6	63.1±9.4	64.3±8.7	<0.001
Menopause age (y)	54.3±2.4	55.7±4.6	48.5±0.27	50.7±1.3	<0.858
Height (cm)	153.9±0.2	154.1±0.3	152.2±0.4	152.6±0.3	<0.001
Weight (kg)	52.4±0.2	63.8±0.3	53.9±0.3	64.4±0.4	<0.001
Body mass index (kg/m^2)	22.1±0.7	26.8±0.1	23.3±0.1	27.6±0.1	<0.001
Waist circumference (cm)	76.9±0.3	88.8±0.3	81.1±0.4	91.6±0.5	<0.001
Appendicular skeletal muscle mass (kg)	13.9±0.1	16.1±0.1	12.1±0.1	14.3±0.1	<0.001
Total fat mass (kg)	16.0±0.1	21.8±0.2	20.1±0.3	25.0±0.2	<0.001
Total cholesterol (mg/dL)	198.4±1.2	197.6±2.1	207.5±2.7	206.9±2.3	<0.001
Triglyceride (mg/dL)	127.9±2.6	153.4±5.0	142.3±8.0	156.2±5.4	<0.001
High-density lipoprotein cholesterol (mg/dL)	53.4±0.4	49.0±0.6	52.0±0.9	51.1±0.7	<0.001
Fasting glucose (mg/dL)	98.2±0.7	105.1±1.7	103.5±2.2	108.3±1.5	<0.001
Homeostasis model assessment of insulin resistance	2.2±0.6	3.1±0.1	2.8±0.4	3.5±0.1	<0.001
Systolic blood pressure (mm Hg)	123.2±0.6	127.3±0.9	124.9±1.4	129.6±1.1	<0.001
Diastolic blood pressure (mm Hg)	76.5±0.4	79.3±0.6	77.9±0.8	79.7±0.6	<0.001
Caloric intake (kcal/d)	1,562.7±27.9	1,603.2±36.7	1,416.3±50.3	1,408.8±31.1	0.005
Protein intake (g/d)	52.3±1.0	53.1±1.5	49.2±2.1	47.3±1.4	0.119
Fat intake (g/d)	22.3±0.7	22.0±0.9	21.0±1.2	19.2±0.9	0.558
White blood cells (/mm^3)	5.5±0.1	5.7±0.1	5.8±0.1	6.0±0.1	<0.001
Vitamin D (ng/mL)	19.8±0.3	20.2±0.5	17.9±0.5	18.0±0.4	<0.001
Serum creatinine (mg/dL)	0.7±0.2	0.7±0.2	0.7±0.3	0.7±0.2	0.391

Values are presented as mean±standard error.
*Analyzed using one-way analysis of variance for continuous variables.

Table 2. Prevalence of co-morbidity and health-related behavior factors according to body composition based on muscle mass and fat mass among the postmenopausal women

Characteristic	Normal (n=2,249)	Obese (n=748)	Sarcopenic (n=616)	Sarcopenic obese (n=947)	P-value*
Co-morbidity					
Diabetes mellitus	272 (12.1)	139 (18.6)	88 (14.4)	215 (22.8)	<0.001
Hypertension	971 (43.1)	417 (55.7)	294 (47.7)	650 (68.6)	<0.001
Hyperlipidemia	644 (28.7)	301 (40.2)	227 (36.9)	426 (45.0)	<0.001
Myocardial infarction/angina pectoris	74 (3.3)	33 (4.4)	31 (4.9)	48 (5.1)	0.057
Decreased estimated glomerular filtration rate[†]	102 (4.5)	25 (3.3)	21 (3.4)	63 (6.7)	0.003
Health-related behavior					
Current smoker	123 (5.5)	26 (3.5)	24 (3.9)	29 (3.1)	0.008
Alcohol intake	557 (24.8)	220 (29.4)	143 (23.2)	219 (23.1)	0.015
Regular exercise	290 (12.9)	110 (14.7)	54 (8.8)	104 (11.0)	0.003

Values are presented as number of subjects (%).
*Analyzed using chi-square test for categorical variables. [†]Defined as <60 mL/min/1.73 m^2.

Table 3. Odds ratio and 95% confidence interval for decreased eGFR* according to body composition based on muscle mass and fat mass after adjusting for confounding variables[†]

	Decreased eGFR*			
	Normal	Obese	Sarcopenic	Sarcopenic obese
Unadjusted	1 (Ref)	0.67 (0.44–1.03)	0.70 (0.44–1.10)	1.67 (1.23–2.26)
Model 1	1 (Ref)	0.83 (0.61–1.48)	0.68 (0.42–1.10)	1.70 (1.23–2.34)
Model 2	1 (Ref)	0.97 (0.62–1.52)	0.65 (0.40–1.07)	1.79 (1.29–2.48)
Model 3	1 (Ref)	0.80 (0.60–1.48)	0.62 (0.38–1.03)	1.48 (1.05–2.07)

Values are presented odds ratio (95% confidence interval). Model 1: adjusted for age and height; model 2: adjusted for age, height, energy/protein intake, and vitamin D; and model 3: adjusted for age, height, energy/protein intake, vitamin D, diabetes mellitus, hypertension, hyperlipidemia, current smoking, alcohol intake, and regular exercise.
eGFR, estimated glomerular filtration rate; Ref, reference.
*Decreased eGFR was defined as <60 mL/min/1.73 m^2. [†]Data were analyzed using logistic regression analysis.

the prevalence of hyperlipidemia was 28.7%, 40.2%, 36.9%, and 45.0%, respectively (Table 2). Statistical differences were observed between the four groups for the mean age, height, BMI, waist circumference, total fat mass, caloric intake, white blood cell/vitamin D level; metabolic markers such as cholesterol level, fasting glucose, HOMA-IR score, and BP; co-morbidity such as DM, HTN, and hyperlipidemia; and health-related behaviors such as smoking/alcohol status and exercise.

2. Prevalence of Decreased Estimated Glomerular Filtration Rate according to Body Composition Based on Muscle Mass and Fat Mass among Postmenopausal Women

The proportion of postmenopausal women with decreased eGFR in the normal, obese, sarcopenic, and SO groups were 4.5% (102/2,249), 3.3% (25/748), 3.4% (21/616), and 6.7% (63/947), respectively (Table 2).

3. Logistic Regression Analysis to Evaluate the Relationship between Sarcopenic Obesity and Decreased Estimated Glomerular Filtration Rate among the Postmenopausal Women

The logistic regression analysis was performed to evaluate the independent association between SO and decreased eGFR and used to determine the OR of decreased eGFR for the four groups among the postmenopausal women controlling for confounding variables (Table

3). Compared to the normal group, the SO group had an OR of 1.48 (95% CI, 1.05–2.07) after adjusting for all confounding factors in model 3. The SO group was more likely to have decreased eGFR than the normal group. However, the obese or sarcopenic group was not statistically associated with decreased eGFR.

DISCUSSION

This study aimed to examine the association between SO and kidney function decline in postmenopausal Korean women based on data from the KNHANES. In our study, the SO group was associated with independently decreased eGFR, even after adjusting for the confounding variables. These results suggest that postmenopausal women with SO had a higher risk of CKD than those with normal BMI and SMI. However, obesity or sarcopenia alone were not significantly associated with increased CKD risk.

Body composition of fat mass and muscle mass is affected by age, ethnicity, exercise, external factors such as nutrition, and several chronic conditions such as CKD, DM, and cardiovascular disease. Obesity, defined as excess adiposity, is related to a risk factor of CKD and is highly prevalent in patients with CKD. Sarcopenia, defined as low muscle mass, is common among the elderly and patients with chronic wasting disease.[19] Previous studies have suggested an association between body composition and kidney function. Foley et al.[7] re-

ported that sarcopenia is common in community-dwelling adults with CKD in the United States. Furthermore, Zhou et al.[20] found that loss of appendicular skeletal muscle was significantly related to GFR decline. In contrast, the present study found that there was no significant association between decreased eGFR and sarcopenia or obesity. This controversial finding may be explained by different population characteristics, such as sex and ethnic differences. It is possible that women are less affected by sarcopenia relating to CKD than men in the Korean population. Moon et al.[8] suggested that sarcopenia is associated with the stage of CKD in men but not women in Korean adults. Huh et al.[21] reported that the peak muscle mass was reached at 40–59 years of age in Korean women, while it was reached at 20–39 years of age in Korean men because of the lack of physical activity and the changing body image among young Korean women. In addition, Jang et al.[22] indicated that obesity showed no clear association with CKD in the Korean population, whereas a number of studies in the United States and Iran have indicated that obesity is associated with CKD. Moreover, BMI cannot be used to accurately assess the fat distribution in Asians, who have a relatively higher proportion of body fat than other ethnic groups.[23,24] Shankar et al.[25] suggest that among Asians, there is an association in BMI and kidney disease among men, whereas among women, this association either appeared to be absent or of very low magnitude if present. Therefore, CKD risk cannot be associated with obesity based on body weight only; further evaluations concerning the appropriate index to measure obesity are required for Asian people in future studies.

Several possible mechanisms could account for the relationship between SO and decreased kidney function. Sarcopenia often coexists with an increased fat mass. SO is defined by the combination of sarcopenia and fat deposition, which refers to muscle loss associated with pathological accumulation of adipose tissue. This condition may be associated with the cumulative risk because of the double metabolic burden due to low muscle mass (sarcopenia) and high fat mass (obesity). The clinical outcome of sarcopenic obese patients with chronic diseases is worse than that of obese patients with normal muscle mass. Obesity can influence muscle strength due to lipid infiltration in muscle tissues, impairing the incorporation of amino acids and reducing the synthesis of muscle proteins.[26] Moreover, an increase in visceral fat may lead to accelerated secretion of pro-inflammatory adipokines that further promote metabolic abnormalities, insulin resistance, and systemic inflammation as well as potentially having a direct catabolic effect on muscle. In other words, muscle loss is not isolated, but is accompanied by an increase in fat mass. This mechanism leads to a vicious cycle between muscle loss and fat gain.[27,28] The combined effect of obesity and muscle mass is related to accelerated functional decline and higher risk of diseases and mortality. Risk for frailty and disability in obese subjects with low muscle mass has been reported to be significantly higher than that observed in non-obese counterparts with similar muscle alterations. This could appear as contradictory to the so-called "obesity paradox," but it means that obesity does not protect from chronic disease-related mortality when it is associated with sar-

copenia. Indeed low muscle mass is emerging as a negative prognostic factor associated with higher morbidity and mortality in obese patients with chronic diseases.[29,30] The combination of sarcopenia and obesity may potentiate each other to determine clinical adverse consequences in the elderly.[31] Therefore, we suggest that obesity, when it was accompanied by sarcopenia, might increase the risk of decreased renal function. However, it is often under-recognized whether SO is associated with kidney dysfunction. Thus, this nationally representative cross-sectional study explored the effects of obesity and sarcopenia on the renal function. We confirmed that SO is closely related to an increased CKD risk among postmenopausal Korean women.

This study also found that SO is associated with several comorbidities (dyslipidemia, HTN, DM, and myocardial infarction/angina pectoris), metabolic measurements (fasting glucose, HOMA-IR, triglyceride, BP), and inflammatory markers (white blood cell, vitamin D). Furthermore, the coexistence of obesity and sarcopenia may have had an effect on the metabolic and inflammatory conditions in our analysis.

This study has several limitations. First, because of the cross-sectional nature of the study, it is impossible to evaluate the cause-effect relationships among variables. Second, the standard definition for sarcopenia and SO is unclear internationally. The European Working Group on Sarcopenia in Older People (EWGSOP) defined sarcopenia as ASM/height^2 for 2SD below the mean of young adults. However, in the Korean population, the height-adjusted definition was observed to underestimate the prevalence of sarcopenia and SO, and the weight-adjusted definition was more closely correlated with metabolic factors compared to the height-adjusted definition. The weight-adjusted definition might be better for defining sarcopenic status in Korean individuals.[18] In addition, we did not evaluate muscle strength and physical performance for the assessment of sarcopenia, which was described by the EWGSOP, because the information of muscle function was not available. Third, we did not exclude postmenopausal women who were undergoing hormone replacement therapy or taking oral contraceptives. Forth, because the sample size of premenopausal women with decreased eGFR was small, we did not analyze differences in eGFR between pre- and postmenopausal women in this study. In addition, it was difficult to confirm the effects of estrogen levels on body composition because sex hormones were not measured. Finally, we used the CKD-EPI equation to estimate eGFR. The use of a creatinine-based eGFR equation would result in high eGFR in patients with sarcopenia, because serum creatinine is influenced by muscle mass. The cystatin-C-based eGFR formula may be more accurate than the creatinine-based eGFR formula. Despite these limitations, this study showed strong evidence for a close relationship between SO and decreased eGFR in postmenopausal women after adjusting for confounders.

In conclusion, the present study demonstrated that SO was independently associated with decreased eGFR among postmenopausal Korean women. Additionally, there was no significant association between decreased eGFR and sarcopenia or obesity. Further prospective studies with a large cohort and with adjustment for several factors related to kidney function are needed for assessing the relationship between SO

and CKD. Furthermore, public health care and interventions are required to prevent and treat SO and CKD in postmenopausal women.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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