ORIGINAL RESEARCH

Relationship Between Low Handgrip Strength and Chronic Kidney Disease: KNHANES 2014-2017

Yae Lim Lee, MD[⋆] *Heejin Jin, MS*[†] *Jae-Young Lim, MD, PhD*[‡] *and Sang Yoon Lee, MD, PhD*[§]

Objective: Accelerated loss of muscle mass is common in patients with chronic kidney disease (CKD). Various factors associated with CKD, such as nutritional deficiencies, metabolic acidosis, and chronic inflammation, contribute to muscle wasting. This study aimed to investigate the relationship between CKD and handgrip strength (HGS) in the Korean population.

Design and Methods: This is a population-based, cross-sectional study of a nationally representative sample of 18,765 patients aged ≥19 years from the Korea National Health and Nutrition Examination Survey in 2014–2017. We measured HGS using a digital hand dynamometer and determined the cutoff for low HGS by deriving -2 standard deviation values of sex-matched healthy young adults (19-39 years old). We defined CKD as eGFR <60 mL/min/1.73 m^2 or the presence of CKD based on a self-reported questionnaire.

Results: The prevalence of CKD was 4.0% in the total population. The cutoff values for the low HGS were 29.5 kg for men and 16.8 kg for women. The prevalence of low HGS was 6.2% in patients without CKD, and 25.2% in patients with CKD. There was a significant correlation between HGS and eGFR in both men and women. In multivariate logistic regression adjusted by age group, diabetes, hypertension, and obesity, CKD showed an independent relationship with low HGS in both men (odds ratio [OR] 1.910, 95% confidence interval [CI] 1.468-2.485) and women (OR 1.570, 95% CI 1.202-2.052).

Conclusions: The prevalence of low HGS was higher in patients with CKD. We suggest that the sarcopenia should be evaluated in patients with CKD.

Introduction

MUSCLE WASTING IS commonly observed in patients with chronic kidney disease (CKD), markedly affecting approximately 40% of patients undergoing dialysis.[1,2] It has also been reported that the CKD stage is associated with an increased prevalence of sarcopenia even in patients not requiring dialysis.[2,3] The pathophysiologic changes associated with CKD directly induce muscle degradation and prevent muscle regeneration, as well as reduced appetite, low protein diet, and decreased exercise contribute to muscle wasting.[4,5] Low-grade inflammation, commonly observed in patients with CKD with increased levels of circulating cytokines, induces protein degradation via the NFkb pathway.[6–8] Metabolic acidosis upregulates ubiquitin-proteasome proteolysis, and activation of the renin-angiotensin system induces skeletal muscle apoptosis.[9] Impaired myogenic progenitor or satellite cells, myostatin overexpression, and combined insulin resistance also aggravate muscle wasting in CKD.[5] These various mechanisms can induce sarcopenia in patients with CKD.

The presence of sarcopenia in patients with CKD is associated with poor clinical outcomes. Sarcopenia is an independent predictor of mortality in patients with CKD without[10] or with dialysis.[11,12] Low skeletal muscle mass is associated with major adverse cardiovascular events in patients with CKD.[13] A recent study has shown that a simple screening test for sarcopenia using age, handgrip strength (HGS), and calf circumference predicts future cardiovascular events in patients with CKD.[14]

HGS is a simple and easily measured parameter for evaluating maximum voluntary muscle power and is mainly used as a single indicator of overall muscle strength in diagnosing sarcopenia.[15] The European Working Group on Sarcopenia in Older People (EWGSOP) recommends using both low muscle mass and low muscle function in the diagnosis of sarcopenia; however, measurement of

[⋆]*Department of Rehabilitation Medicine, Seoul National University College of Medicine, Seoul National University Hospital, Seoul, Republic of Korea.*

[†]*Medical Research Collaborating Center, SMG-SNU Boramae Medical Center, Seoul, Republic of Korea.*

[‡]*Department of Rehabilitation Medicine, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam-si, Gyeonggi-do, Republic of Korea.*

[§]*Department of Rehabilitation Medicine, Seoul National University College of Medicine, SMG-SNU Boramae Medical Center, Seoul, Republic of Korea.*

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Address correspondence to Sang Yoon Lee, MD, PhD, Department of Rehabilitation Medicine, Seoul National University College of Medicine, SMG-SNU Boramae Medical Center, 20 Boramae-ro 5-gil, Dongjak-gu, Seoul 07061, Republic of Korea. E-mail: rehabilee@gmail.com

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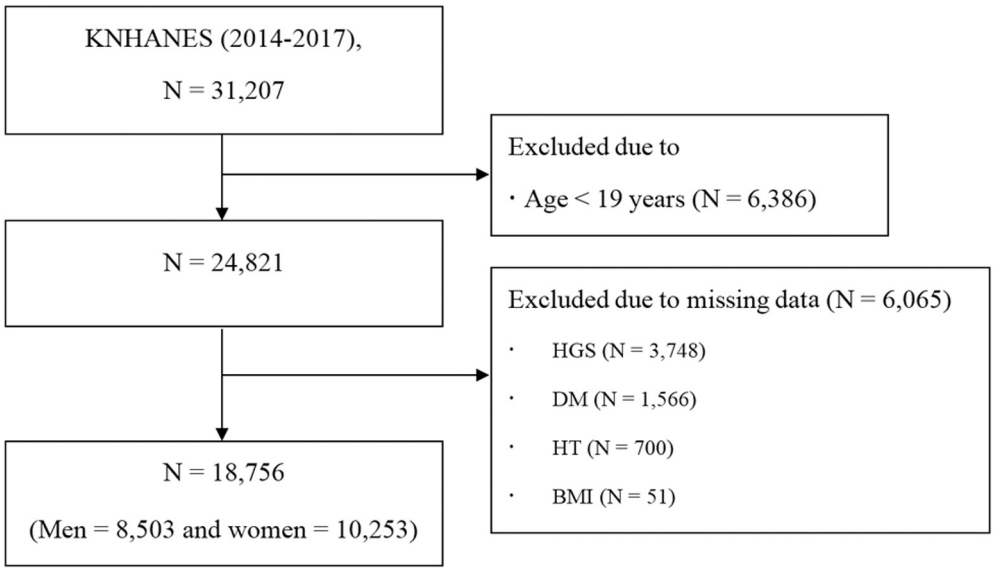

Figure 1. Flow diagram of study participants. HGS, handgrip strength; DM, diabetes mellitus; HT, hypertension; BMI, body mass index.

muscle mass using imaging techniques such as computed tomography, magnetic resonance imaging, and dual-energy X-ray absorptiometry is difficult to incorporate into daily clinical practice owing to their high cost and limited accessibility.[16] HGS is not only a simple index of overall muscle strength but also a good predictor of muscle mass and walking performance.[17-22]

The relationship between renal function and HGS, a simple and powerful index of sarcopenia, has not been fully investigated. A previous study has shown that HGS in patients with CKD is a predictor of composite renal outcomes defined by predialysis mortality or progression to dialysis-dependent end-stage renal disease (ESRD).[23] However, the study was based on a small sample size of 128 patients with CKD not undergoing dialysis, and there is a need to investigate the association between HGS and renal function in a larger population that includes healthy adults. Therefore, we aimed to investigate the relationship between CKD and HGS in the Korean population by using a nationally representative sample of community-dwelling adults.

Methods

Data Source and Study Population

We obtained the data for this study from the Korea National Health and Nutrition Examination Survey (KNHANES) conducted from 2014 to 2017 by the Korea Centers for Disease Control and Prevention. The KNHANES is a population-based cross-sectional survey designed to assess health-related behavior, health conditions, and the nutritional state of Koreans (http://knhanes.cdc.go.kr/).[24] The study used a stratified, multistage, probability sampling method to select the study patients. Sampling weights were used to represent the entire Korean population. From this pool of data, we included patients aged ≥19 years who had completed surveys on body weight and height, serum tests (blood urea nitrogen/creatinine), medical history (hypertension and diabetes mellitus), and HGS test. We finally included 18,756 patients (8503 men and 10,253 women) in this study (Figure 1). All patients provided written informed consent, and the Korea Centers for Disease Control and Prevention Institutional Review Board (ethical review committee for health survey data) approved the study protocol (IRB No. 2015-01-02-6C).

Clinical and Laboratory Examinations

Systolic blood pressure (BP) and diastolic BP were measured by standard methods using a sphygmomanometer. Three BP measurements were made for all patients at 5-minute intervals. The final reported BP value for the study patients was the average of the second and third measurements. Blood samples were obtained from each patient after fasted overnight for at least 8 h. A central and certified laboratory measured the serum glucose levels using a Hitachi Automatic Analyzer 7600 (Hitachi, Tokyo, Japan). We defined diabetes as fasting blood glucose ≥126 mg/dL that was first detected in this survey, use of an antidiabetes medication, or a previous diagnosis of diabetes by a doctor. We defined hypertension as systolic BP ≥ 140 mm Hg, diastolic BP ≥ 90 mm Hg, or use of an antihypertensive medication. We calculated body mass index (BMI [kg/m^2]) as weight (kg) divided by the square of height (m^2). We defined obesity according to the criteria recommended by the Korean Society for the Study of Obesity, in which BMI ≥18.5 and < 25.0 kg/m^2 is

categorized as normal and BMI ≥25.0 kg/m^2 is categorized as obesity.[25]

eGFR and CKD Definitions

We determined the estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration formula, as follows: eGFR (mL/min/1.73 m^2) = 141 × min(SCr/k, 1)^a × max (SCr/k, 1)$^{-1.209}$ × 0.993^{age} [1.018 if woman] × [1.159 if black] (SCr: serum creatinine [mg/dL], k: 0.7 for women and 0.9 for men, a: −0.329 for women and −0.411 for men, min: minimum value of SCr/k or 1, and max: maximum value of SCr/k or 1).[26] Patients were categorized into six groups according to the value of eGFR. Patients with eGFR ≥90 mL/min/1.73 m^2 were classified as group 1, eGFR between 60 and 89 mL/min/1.73 m^2 as group 2, eGFR between 45 and 59 mL/min/1.73 m^2 as group 3a, eGFR between 30 and 44 mL/min/1.73 m^2 as group 3b, eGFR between 15-29 mL/min/1.73 m^2 as group 4, and eGFR <15 mL/min/1.73 m^2 as group 5. In this study, we defined CKD as eGFR <60 mL/min/1.73 m^2 or the presence of CKD based on a self-reported questionnaire. As discussed later in the study, CKD was defined using eGFR of only one time point because the cross-sectional study did not measure the duration of reduced eGFR. Patients of groups 3a, 3b, 4, and 5 were classified as CKD (eGFR <60 mL/min/1.73 m^2) according to the aforementioned definition.

HGS Measurement

HGS was measured using a digital hand dynamometer (T.K.K 5401; Takei, Tokyo, Japan). With the patient in a standing position and the forearm fully extended in a sideways position away from the body at the level of the thigh, participants were asked to exert maximum grip strength three times each with the left and right hands. A resting interval of at least 30 s was allowed between each measurement.[27] We determined the cutoffs for the low HGS by deriving -2 standard deviation values of sex-matched healthy young adults (19-39 years old) in this population, respectively.

Statistical Analysis

Statistical analyses were implemented using SAS software, version 9.4 (SAS Institute, Cary, NC). We compared the patients' characteristics according to the grade of HGS by using PROC SURVEYREG procedure for continuous variables and PROC SURVEYFREQ procedure for categorical variables. We performed post hoc analysis to compare the characteristics between grade I and II low HGS. To evaluate the association between HGS and CKD, we performed univariable and multivariable logistic regression analyses using PROC SURVEYLOGISTIC procedure after taking into account stratification (kstrata), clustering (psu), and swe used the health examination survey (wt_itvex) as the sampling weights from the KNHANES. A sex-stratified logistic regression was fitted using three kinds of model: (1) unadjusted, (2) adjusted for age group, and (3) adjusted for age group, diabetes mellitus, hypertension, and obesity, and $P < .05$ was considered statistically significant.

Results

Demographic and Clinical Characteristics of the Study Population

A total of 18,765 patients (8,503 men and 10,253 women) were included in this study (Figure 1). Patients were classified into six groups according to the values of eGFR, and the number of patients in each group was 11,727 (62.5%), 6,270 (33.4%), 573 (3.1%), 130 (0.7%), 38 (0.2%), and 18 (0.1%), respectively (Table 1). The prevalence of CKD was 4.0% in the total population.

The cutoff values for the low HGS were 29.5 kg for men and 16.8 kg for women, respectively. The prevalence of low HGS was 7.0% in the total population. The prevalence of low HGS in each group was 4.2%, 9.9%, 23.7%, 30.8%, 39.5%, and 16.7%, respectively (Table 1). Patients with CKD showed a higher prevalence of low HGS (25.2%) than those without CKD (6.2%). Patients with CKD also showed a higher prevalence of diabetes and hypertension than those without CKD, which was considered in multivariable models as confounders.

Comparing to the group 1, odds ratios (ORs) of low HGS were 3.371 (95% confidence interval [CI] 2.784-4.081; group 2), 9.404 (95% CI 6.899-12.820; group 3a), 12.091 (95% CI 6.809-21.471; group 3b), 30.777 (95% CI 13.378-70.808; group 4), and 7.053 (95% CI 1.486-33.480; group 5) in men. ORs were 1.969 (95% CI 1.662-2.332), 5.789 (95% CI 4.293-7.807), 9.163 (95% CI 5.467-15.356), 4.998 (95% CI 1.404-17.794), and 2.856 (95% CI 0.350-23.278) in women, respectively.

Prevalence of CKD According to HGS

In multivariate logistic regression adjusted by age group (model 2), CKD group showed higher ORs to the prevalence of low HGS than the normal group in both men (OR 1.896, 95% CI 1.467-2.450) and women (OR 1.684, 95% CI 1.294-2.191). When adjusted by age group, diabetes, hypertension, and obesity (model 3), CKD group showed an independent relationship to low HGS in both men (OR 1.910, 95% CI 1.468-2.485) and women (OR 1.570, 95% CI 1.202-2.052) (Table 2).

The association between HGS and eGFR as continuous variables was assessed by estimating the trendline using logarithmic functions in the scatterplot between eGFR and HGS. There was a significant positive correlation between HGS and eGFR in both men (R^2 = 0.069, F = 633.5, $P < .001$) and women (R^2 = 0.045, F = 483.1, $P < .001$) (Figure 2).

Table 1. Demographic and Clinical Characteristics of a Total Population According to Kidney Function

Variables	Group 1 (n = 11,727)	Group 2 (n = 6,270)	Group 3a (n = 573)	Group 3b (n = 130)	Group 4 (n = 38)	Group 5 (n = 18)	*P* value
Age (years), mean (SE)	44.7 (0.1)	60.4 (0.2)	71.9 (0.4)	72.5 (0.8)	69.1 (1.7)	60.9 (2.7)	<.001*
Sex (male), N (%)	39.9	55.0	50.3	46.2	60.5	55.6	<.001†
Body mass index (kg/m^2), mean (SE)	24.0 (0.0)	24.4 (0.0)	24.8 (0.1)	25.4 (0.3)	25.0 (0.5)	25.4 (0.6)	<.001*
Fasting plasma glucose (mg/dL), mean (SE)	98.7 (0.2)	103.7 (0.3)	111.0 (1.2)	117.1 (4.3)	112.3 (4.8)	120.2 (11.0)	<.001*
HbA1c (%), mean (SE)	5.6 (0.0)	5.9 (0.0)	6.2 (0.0)	6.4 (0.1)	6.5 (0.2)	6.3 (0.3)	<.001*
Diabetes (%)	8.7	16.2	36.0	47.7	60.5	50.0	<.001†
Hypertension (%)	21.8	44.7	75.7	76.9	81.6	77.8	<.001†
Serum BUN (mg/dL), mean (SE)	13.4 (0.0)	15.8 (0.1)	19.5 (0.2)	24.7 (0.7)	34.8 (1.9)	60.2 (5.7)	<.001*
Serum creatinine (mg/dL), mean (SE)	0.8 (0.0)	0.9 (0.0)	1.2 (0.0)	1.5 (0.0)	2.4 (0.1)	7.3 (0.7)	<.001*
eGFR (mL/min/1.73 m^2), mean (SE)	107.2 (0.1)	78.9 (0.1)	54.2 (0.2)	39.5 (0.4)	24.8 (0.6)	7.7 (0.9)	<.001*
HGS (kg)	32.2 (0.1)	32.7 (0.1)	27.8 (0.4)	25.9 (0.8)	28.0 (1.6)	28.6 (2.2)	<.001*
Low HGS (%)	4.2	9.9	23.7	30.8	39.5	16.7	<.001†

HbA1c, hemoglobin $A1_C$; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; HGS, handgrip strength.
*Calculated using analysis of variance.
†Calculated using Pearson's chi-squared test.

Discussion

The most important finding of this study was that CKD showed an independent and positive association with the prevalence of low HGS in both men and women after adjusting for age, diabetes, hypertension, and obesity. In addition, we found a significant positive correlation between HGS and eGFR. To our knowledge, this is the first study to reveal the relationship between CKD and low HGS prevalence in a nationally representative sample.

Several animal studies have investigated the possible mechanisms that might explain the significant association between sarcopenia and CKD. Wang et al. reported that in mice with CKD, the expression of MyoD protein and myogenin decreased after muscle injury. This result suggests the impaired function of satellite cells in CKD. Resistance exercise ameliorated these impairments in mice with CKD.[28] May et al. investigated the influence of metabolic acidosis on muscle wasting in partially nephrectomized rats. In rats with CKD, muscle proteolysis was accelerated by metabolic acidosis and corrected by dietary bicarbonate.[29] Other studies have shown that metabolic acidosis of CKD stimulates muscle proteolysis in rats via the ATP-dependent ubiquitin-proteasome pathway[30] and a glucocorticoid-dependent mechanism.[31] Infusion of angiotensin II in rats led to increased muscle proteolysis, and administration of angiotensin II type 1 receptor blocker attenuated transforming growth factor–beta-induced failure of muscle regeneration in mouse models.[32-34] These studies suggested that the activation of the renin-angiotensin system in CKD might play a role in muscle wasting.

Previous clinical studies also attempted to elucidate the mechanism of sarcopenia development in patients with CKD. Boivin et al. reported increased caspase-3 activity and interleukin (IL)-6 level with augmented apoptosis proven by skeletal muscle biopsies in patients with ESRD after hemodialysis.[35] This result suggests that IL-6-induced activation of caspase-3 resulting in apoptosis may induce muscle atrophy in patients with ESRD during hemodialysis. One study also suggested the contribution of insulin resistance to the loss of muscle mass in patients with CKD.[36] In this study, insulin was infused at both high and low rates in the control group and in patients with CKD. In patients with CKD, forearm glucose uptake was increased to a lesser extent than in controls. In the

Table 2. Low Handgrip Strength Prevalence According to CKD

Model	Normal	CKD (+) OR (95% CI)	*P*-value
Men			
Model 1	1.000	5.281 (4.148-6.724)	<.001
Model 2	1.000	1.896 (1.467-2.450)	<.001
Model 3	1.000	1.910 (1.468-2.485)	<.001
Women			
Model 1	1.000	4.840 (3.768-6.218)	<.001
Model 2	1.000	1.684 (1.294-2.191)	<.001
Model 3	1.000	1.570 (1.202-2.052)	.001

OR, odds ratio; CI, confidence interval.
Data are expressed as unadjusted and adjusted odds ratios with 95% confidence intervals for low handgrip strength prevalence in different models.
Model 1 was unadjusted.
Model 2 was adjusted for age group.
Model 3 was adjusted for age group, DM, HT, and obesity.

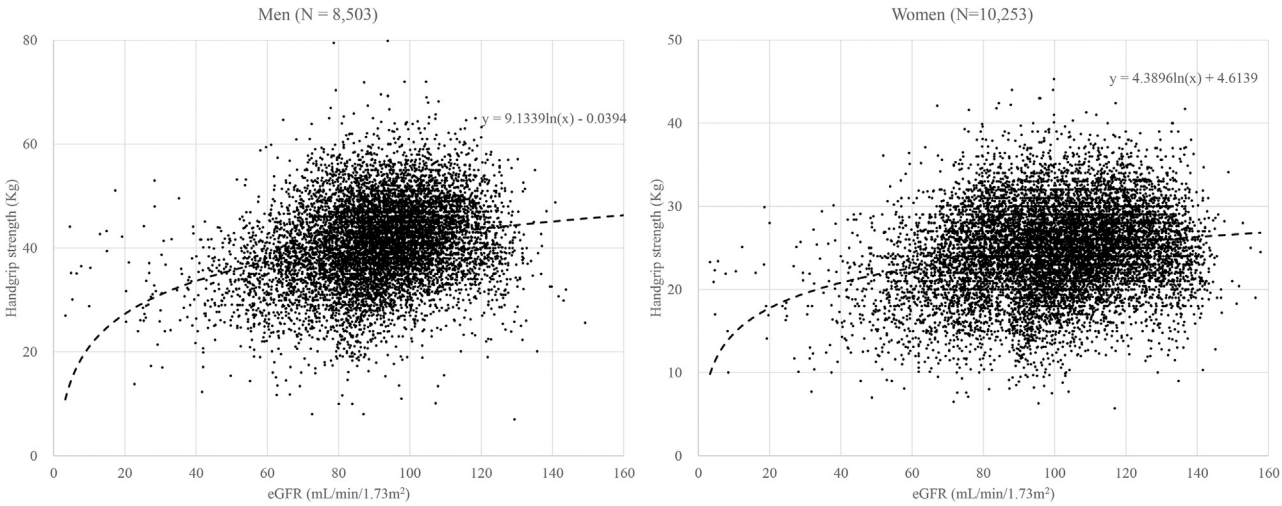

Figure 2. Scatterplot between estimated glomerular filtration rate and handgrip strength. eGFR, estimated glomerular filtration rate.

control group, protein degradation was decreased by both rates of insulin infusion; however, in patients with CKD, protein degradation was suppressed by the high rate of insulin infusion but not by the low rate of infusion. This study suggests that blunting of muscle glucose uptake and suppression of protein degradation may lead to muscle wasting in patients with CKD. Other studies demonstrated that correction of chronic metabolic acidosis in patients with CKD reduced the whole-body protein degradation.[37,38]

Recent studies have already demonstrated a positive relationship between sarcopenia and the prevalence of CKD. In the general population of the United States, a study using the Third National Health Nutrition Screening Survey showed that the prevalence of sarcopenia, defined by skeletal muscle mass measured using systemic bioelectrical impedance analysis, markedly increased with declining kidney function, although not statistically independent of clinical adjustment variables.[39] One study also reported that loss of lean body mass measured using dual-energy X-ray absorptiometry was significantly associated with a decline in glomerular filtration rate in patients with CKD stages 3-5.[40] In the Korean population, a study has shown that the CKD stage was associated with an increased prevalence of sarcopenia defined by skeletal muscle mass.[3] However, unlike our study, these studies defined sarcopenia based on only muscle mass, not muscle strength.

Although it is worthwhile to investigate the relationship between muscle mass and CKD, it would ultimately be more meaningful to evaluate muscle strength because muscle strength or performance can be reduced even when the muscle mass is maintained. One study also supported these concepts. Isoyama et al. reported that among patients undergoing dialysis, those with low muscle mass alone were not at an increased risk of mortality, but those with low muscle strength, defined by HGS, were at an increased risk.[41] Our study also successfully showed the positive relationship between low HGS and kidney function (Figure 2). As our study was based on a nationally representative sample, we could minimize the bias and include patients with preclinical CKD who are not hospitalized or followed by outpatient clinics.

In our study, the cutoff values for the low HGS were 29.5 kg for men and 16.8 kg for women. Numerous prior studies have attempted to recommend accurate cutoff values for low HGS. The revised EWGSOP2 guideline defined low HGS as $<$ 27 kg for men and $<$16 kg for women, using cutoff values at -2.5 standard deviations below the mean reference of young adults.[42] The Asian Working Group for Sarcopenia (AWGS) defined low HGS as $<$ 26 kg for men and $<$18 kg for women, or the lower 20th percentile of the HGS of the study population before outcome-based data are available.[43] An update from the AWGS in 2016 suggested that muscle strength measured by HGS should be stratified by BMI, and the AWGS consensus cutoff points of HGS might need further revision.[44] In an effort to suggest the formal statistics of HGS in the Korean population, Yoo et al. analyzed the HGS data of 4553 Koreans in 2015 KNHANES and suggested the cutoff values of 28.6 and 16.4 kg for men and women, respectively, defined as the lower 20th percentile of the HGS of the study population.[45] Kim et al. analyzed the HGS data of 7969 Koreans from the 2014-2015 KNHANES and suggested the cutoff values of 28.9 kg for men and 16.8 kg for women, deriving 2 standard deviations below the values of healthy young adults.[46] We believe that our cutoff values are more reliable than previously reported data because we analyzed the largest number of participants (18,756 Koreans from 2014 to 2017 KNHANES) thus far. As HGS varies according to race and ethnicity,[47] our data may be useful for future research

on sarcopenia in the Korean population or other Asian populations.

Our study has several limitations. First, the cross-sectional design precludes the establishment of a causal relationship. Prospective studies should be designed to establish the temporal relationship between sarcopenia and CKD. Second, eGFR calculated using creatinine tend to underestimate the association between sarcopenia and kidney function because creatinine is produced from muscle breakdown and is thus dependent on muscle composition. Other variables that are independent of muscle mass and can accurately estimate kidney function, such as cystatin C, should be considered in future studies. Third, as only HGS was analyzed, the study omitted other indices of sarcopenia, such as muscle mass or gait speed. Fourth, we defined CKD using creatinine levels measured at only one time point; however, previous studies based on national data or cohort studies also defined CKD based on the glomerular filtration rate measured at one time point. In addition, the proportion of patients with acute kidney injury among participants of a community-based research is expected to be negligible.

In conclusion, the prevalence of low HGS was higher in patients with CKD in this large population study based on national data. This study suggests that the sarcopenia should be assessed when CKD is diagnosed and that the possibility of renal function impairment should be taken into account when a weak handgrip power is detected.

Practical Application

Accelerated loss of muscle mass is common in patients with CKD. Identifying the presence of sarcopenia in patients with CKD is crucial because sarcopenia is an independent predictor of poor clinical outcomes, such as mortality and disability. We demonstrated that CKD showed an independent and positive association with the prevalence of low HGS in both men and women after adjusting for age, diabetes, hypertension, and obesity.

Credit Authorship Contribution Statement

Yae Lim Lee: Conceptualization, Methodology, Formal analysis, Writing - original draft. **Heejin Jin:** Formal analysis, Writing - original draft. **Jae-Young Lim:** Formal analysis, Writing - original draft. **Sang Yoon Lee:** Conceptualization, Methodology, Data curation, Formal analysis, Writing - original draft.

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Authors' contributions: Study concept and design were carried out by Yae Lim Lee and Sang Yoon Lee. Acquisition of patients and data was carried out by Sang Yoon Lee. Analysis and interpretation of data were carried out by Yae Lim Lee, Heejin Jin, Jae-Young Lim, and Sang Yoon Lee. Preparation of manuscript was done by Yae Lim Lee, Heejin Jin, Jae-Young Lim, and Sang Yoon Lee.

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