Recent studies in Western countries have reported a significant association between glomerular filtration rate (GFR) and bone mineral density (BMD) in the absence of dialysis among the general population. However, there have been few studies regarding renal function and BMD among Korean or Asian subjects with moderate to severe (stage 3 or 4) chronic kidney disease (MS-CKD). The aim of the present study was to investigate the association between MS-CKD and BMD in the general Korean population. BMD, serum creatinine and other measures were obtained from 3,190 subjects (1,428 males and 1,762 females; the fourth Korean National Health and Nutrition Examination Survey). GFR was estimated using the Cockcroft-Gault formula, with adjustment for body surface area. After adjustment for all variables, multiple regression analysis showed that BMD in the femur neck, total femur and lumbar spine were positively associated with eGFR in both males and females. Additional analysis showed that MS-CKD was also significantly associated with osteoporosis in both males and females (odds ratio [OR] 2.20, 95% confidence interval [CI] 1.15-4.20 in males; and OR 1.96, 95% CI 1.33-2.88 in females). Individuals with MS-CKD may be at higher risk of osteoporosis even among Asians.

Key Words: Glomerular Filtration Rate; Bone Density; Osteoporosis; Renal Insufficiency; KNHANES

INTRODUCTION

End-stage renal disease (ESRD) is a well-established risk factor for reduced bone mineral density (BMD) and osteoporosis as well as for hip fracture (1-3). Since the relationship between renal function and BMD in ESRD patients has been extensively investigated (4-7), it is suggested that an association between a moderate to severe decrease in glomerular filtration rate (GFR) in the absence of dialysis (K-DOQI [Kidney Disease Outcomes Quality Initiative] 3 and 4) and BMD (or osteoporosis) may exist among the general population (6, 7). Though the values of GFR and BMD vary across ethnicity, most previous studies of the potential association between renal function and BMD among the general population with stage 3 or 4 CKD have been performed in Western countries (6, 7). There have been few studies regarding renal function and BMD among the general population with moderate to severe (stage 3 or 4) chronic kidney disease (MS-CKD) in Korea or Asia. Furthermore, former studies have been performed only in postmenopausal women (8, 9) or with small sample sizes (9).

In addition to ethnicity, previous studies concerning bone health have also been conducted mainly for women, especially postmenopausal women (8-10). Few studies have been performed on men. Given the increasing prevalence of both osteogenesis and CKD without dialysis and osteoporosis in Asian countries (11, 12), even among men, evaluating the relationship between decreased renal function and BMD in both Korean men and women is of great importance. Therefore, we investigate the association between MS-CKD and BMD in the general Korean population.

MATERIALS AND METHODS

Data source and study subjects

The present study used the BMD data subset of the Korean National Health and Nutrition Examination Survey IV (KNHANES IV) of 2008. The KNHANES collected representative data on the health, nutritional status, and BMD of the civilian, non-institutionalized Korean general population. A stratified multistage clustered probability design was used to select representative samples of non-institutionalized Korean civilians for the KNHANES (13). The survey data were publicly available. A total of 3,583 subjects were recruited in the BMD sub-dataset. We excluded the data from individuals that did not include serum creatinine levels (n = 116). The data for BMD and clinical examination findings, including serum creatinine levels, were avail-
able for a total of 3,467 individuals. Individuals with incomplete survey responses (n = 8), diagnosis and treatment of osteoporosis (n = 257), or ESRD (eGFR < 15 mL/min/1.73 m²) and dialysis (n = 12) were also excluded, leaving a total of 3,190 subjects.

**BMD and definition of osteoporosis**

In KNHANES IV, subjects were examined in a mobile examination vehicle. Licensed, trained technicians measured BMD in men and non-pregnant women aged ≥ 20 yr by using dual energy X-ray absorptiometry (DXA; HOLOGIC, DISCOVERY-W, Bedford, MA, USA). BMD was measured at several areas (whole femur, femoral neck and lumbar spine). BMD was expressed as g/cm². For the purpose of DXA quality control, daily automatic calibration was performed to maintain a precision standard of 1.5% for the total hip measurements according to the manufacturer’s instructions (13). Osteoporosis was operationally defined as a T-score of equal or below -2.5. T-score was estimated using the following equation: (measured BMD - mean of maximum BMD)/standard deviation (SD) of maximum BMD. As there is no universal consensus on maximum BMD, an Asian standard (Japanese) measured for BMD was used. The mean (± SD) values in the femur neck were 0.846 (± 0.124) for males and 0.803 (± 0.107) for females. The values in the total femur were 0.940 (± 0.137) for males and 0.851 (± 0.115) for females. The values in the lumbar spine were 1.024 (± 0.120) for males and 1.006 (± 0.115) for females (14).

**GFR estimation**

In KNHANES IV, serum creatinine was measured using the Jaffe method and a Hitachi Automatic Analyzer 7600 (Hitachi, Tokyo, Japan), and serum creatinine concentrations were calibrated to a creatinine standard. Renal function was estimated using the estimated glomerular filtration rate (eGFR). As Modification of Diet in Renal Disease (MDRD) study population had been derived from almost non-dialysis patients with CKD (15), the GFR of healthy people might be underestimated by the MDRD equation. Therefore, we estimated the GFR (mL/min/1.73 m²) following the Cockcroft-Gault (CG) formula: eGFR (mL/min/1.73 m²) = ([140-age] × weight × [0.85 if subject was female])/72 × serum creatinine, adjusted for body surface area (BSA). BSA was calculated as follows: BSA = weight (kg)⁰.⁴²⁵ × height (cm)⁰.⁷²⁵ × 0.007184 (16). With K-DOQI, MS-CKD was defined as subjects with eGFR < 60 mL/min/1.73 m² (K-DOQI stage 3 or 4).

**Covariate assessments**

Body mass index (BMI) was calculated by dividing weight (kg) by square of height (m²). BMI was classified into the following 3 groups: underweight (BMI < 18.5 kg/m²), normal weight (BMI 18.5 kg/m² to < 25 kg/m²) and obesity (BMI ≥ 25 kg/m²) (13). Daily calcium intake (mg/day) was calculated using the 24-hr recall method. Information concerning cigarette smoking (never smoked & ex-smoker/ current smoking), alcohol consumption (less than once per month/more than once per month), exercise (none/1-2 times per week/3-4 times per week/5 times or more per week), and menopause and hormone replacement therapy, and fracture-related history, such as any history of osteoporosis in family members and any history of fracture in themselves (no/yes) were assessed using survey questionnaires.

**Statistical analysis**

All statistical analyses were performed using SAS software, version 9.2 (SAS Institute Inc, Cary, NC, USA) to account for the stratified multistage clustered probability design and survey weights. The age-standardized prevalence of osteoporosis was measured by using the standardization methods for the population derived from the 2005 Korean Census as the standard population. For continuous variables (age, BMI, daily calcium intake, vitamin D level, and BMD at various sites), a univariate regression analysis was applied to evaluate the difference in means between subjects with and without MS-CKD according to statistical guidelines (13). For categorical variables (BMI, smoking status, exercise, alcohol consumption, fracture-related history, and menopause & hormonal replacement therapy), a Rao-Scott chi-square analysis was applied to account for differences in terms of the absence or presence of MS-CKD. The relationship between eGFR and BMD was determined in terms of sex by MS-CKD stratified simple and multiple regression analysis (SAS syntax: SURVEYREG); after adjustment for age and BMI, covariates were related to bone health (age, BMI, daily calcium intake, vitamin D level, alcohol consumption, cigarette smoking, exercise, and fracture-related history, as well as menopause and hormone replacement therapy in females). The association between MS-CKD and osteoporosis was estimated using a logistic regression model. For the first step, adjustments were made for age and BMI. Next, multiple logistic regression analysis included all variables. The reference category in each model was an eGFR of ≥ 60 mL/min/1.73 m².

**Ethics statement**

The design of the present study was approved by institutional review board of the Catholic University of Korea, College of Medicine (approval ID: CUMC11U1139). The Korea Center for Disease Control and Prevention received the informed consent from all participants (13). The data are publicly available in website (13).

**RESULTS**

The estimated percentages of subjects with MS-CKD were 6.4% in males and 17.0% in females. The subjects with MS-CKD were older than those with an eGFR of ≥ 60 mL/min/1.73 m². Both
males and females with MS-CKD were more likely to have lower BMD and calcium intake. The subjects who were underweight or normal weight, former smokers/non-smokers, and who had a history of fracture risks had higher prevalence of MS-CKD in all four groups. Women with MS-CKD were more likely to be taking hormone replacement therapy (Table 1).

Table 2 shows the association between eGFR (per 5 mL/min/1.73 m⁴) and BMD. Multiple regression analysis revealed that in both males and females, the BMD at femur neck, total femur, and lumbar spine area were positively associated with eGFR among those with MS-CKD. The regression coefficients of eGFR on BMD were higher in females with MS-CKD ($\beta = 0.013-0.019$) at all sites than in those with an eGFR of $\geq 60$ mL/min/1.73 m⁴ ($\beta = 0.007-0.008$). For males, the regression coefficients of eGFR on BMD were higher in males with MS-CKD ($\beta = 0.017-0.022$) at total femur ($P < 0.001$) and lumbar spine ($P = 0.014$) than in those with an eGFR of $\geq 60$ mL/min/1.73 m⁴ ($\beta = 0.010-0.011$) (Table 2).

Table 3 shows the association between MS-CKD and osteoporosis. After adjustment for all confounding factors, the MS-CKD was significantly associated with osteoporosis (odds ratio [OR] 2.20, 95% confidence interval [CI] 1.15-4.20 in males; and OR 1.96, 95% CI 1.33-2.88 in females) (Table 3).

**DISCUSSION**

Our study results revealed that there was a positive association between eGFR and BMD in the Korean population and that both men and women with MS-CKD were likely to have a higher decline in BMD than those with an eGFR of $\geq 60$ mL/min/1.73 m⁴ in multiple linear regression analysis. In ESRD patients undergoing dialysis, the bone loss resulted in...
from secondary hyperparathyroidism. However, there have been few reports of obvious mechanisms for the association between BMD and MS-CKD in terms of the degrees of CKD. Recently, some studies have suggested several possible mechanisms behind bone loss in patients with MS-CKD without dialysis (17-19). As GFR decreases below 60 mL/min/1.73 m², phosphate retention in blood triggers a rise in parathyroid hormone (PTH) and fibroblast growth factor-23 (FGF-23) as well as a decrease in serum bicarbonate may result in a gradual dissolution of bone mineral (18). Another possible mechanism is that chronic metabolic acidosis characterized by decreased eGFR (per 5 mL/min/1.73 m²) and -0.31% for the first (lowest) to fourth (highest) eGFR quartiles (calculated using a MDRD formula) was reported. The mean annualized BMD percentage changes of -0.58%, -0.39%, -0.37%, and -0.31% for the first (lowest) to fourth (highest) eGFR quartiles, respectively (P for linear trend = 0.020) were also shown in multiple regression analysis (4). As this study demonstrated a significant association between eGFR and BMD observed in the males from their cohort, its results suggested that a positive association between GFR and BMD might exist in males.

| Table 2. Univariate and multiple linear regression of glomerular filtration rate according to bone mineral density in subjects by sex and moderate to severe chronic kidney disease |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Variables       | eGFR ≥ 60 mL/min/1.73 m² | eGFR < 60 mL/min/1.73 m² | eGFR ≥ 60 mL/min/1.73 m² | eGFR < 60 mL/min/1.73 m² |
|                 | β   | SE  | P value | β   | SE  | P value | β   | SE  | P value |
| Femur neck BMD  | 0.013 | 0.001 < 0.001 | 0.011 | 0.004 < 0.001 | 0.009 | 0.001 < 0.001 | 0.023 | 0.005 < 0.001 |
| + all variables* | 0.014 | 0.001 < 0.001 | 0.011 | 0.005 < 0.001 | 0.008 | 0.001 < 0.001 | 0.015 | 0.005 0.004 |
| Total femur BMD  | 0.010 | 0.001 < 0.001 | 0.017 | 0.005 0.002 | 0.008 | 0.001 < 0.001 | 0.027 | 0.006 < 0.001 |
| + all variables* | 0.011 | 0.001 < 0.001 | 0.017 | 0.005 0.001 | 0.007 | 0.001 < 0.001 | 0.019 | 0.006 0.001 |
| Lumbar spine BMD| 0.009 | 0.001 < 0.001 | 0.018 | 0.006 0.004 | 0.010 | 0.001 < 0.001 | 0.022 | 0.006 < 0.001 |
| + all variables* | 0.010 | 0.001 < 0.001 | 0.022 | 0.006 < 0.001 | 0.008 | 0.001 < 0.001 | 0.013 | 0.005 0.014 |

*For males: adjusted for (age, BMI, daily calcium intake, blood vitamin D level, alcohol consumption, smoking, exercise, and any history of osteoporosis in family member and any history of fracture in themselves); For females: adjusted for (age, BMI, daily calcium intake, blood vitamin D level, alcohol consumption, smoking, exercise, any history of osteoporosis in family member and any history of fracture in themselves, and menopause & hormone replacement therapy).

| Table 3. Multiple logistic regression for the association between osteoporosis and moderate to severe chronic kidney disease (MS-CKD) by sex |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Kidney disease  | Prevalence of osteoporosis | Model 1* | Model 2† | Prevalence of osteoporosis | Model 1* | Model 2‡ |
|                 | Age-standardized % (95% CI) | OR (95% CI) | OR (95% CI) | Age-standardized % (95% CI) | OR (95% CI) | OR (95% CI) |
| MS-CKD No       | 6.2 (4.7-7.8) 1.0 | 1 | 1 | 14.2 (9.3-19.1) 1.0 | 1 | 1 |
| MS-CKD Yes      | 9.5 (7.0-12.9) 3.28 (1.82-5.58) 2.20 (1.15-4.20) | 18.0 (14.5-21.6) 2.66 (1.88-3.74) 1.96 (1.33-2.88) |

eGFR estimated glomerular filtration rate; OR odds ratio; CI confidence interval. Osteoporosis was defined as a T-score < -2.5 for any sites of the measured bones (total femur, femoral neck, or lumbar spine). The age-standardized prevalence of osteoporosis was measured by the standardization methods for the population derived from the 2005 Korean Census as the standard population. *Adjusted for age. †Adjusted for (age, BMI, daily calcium intake, blood vitamin D level, alcohol consumption, smoking, exercise, any history of osteoporosis in family member and any history of fracture in themselves). ‡Adjusted for (age, BMI, smoking, exercise, frequency of alcohol consumption, daily calcium intake, blood vitamin D level and any history of osteoporosis in family member and any history of fracture in themselves).
pital in Ireland, there may have been a selection bias in that older subjects or those with more co-morbid diseases related to osteoporosis or kidney disease had been referred to the hospital for DXA and assessments of renal function (24). Environmental factors and lifestyle may also affect ethnic differences in bone density. A previous study has shown that US born Japanese females may have significantly higher body fat and BMD than native Japanese females due to lifestyle differences (25). Thus, ethnic and environmental differences may play an important role in evaluating association between BMD and other factors. Further studies are needed to generalize the association between BMD and MS-CKD in the absence of dialysis in the Korean general population as well as in other ethnic groups.

In our study, serum vitamin D was higher in males with MS-CKD than in those without. Our data was not in accordance with previously described mechanism through vitamin D deficiency (17). After adjustment for potential confounding factors, such as age and smoking, multiple regression analysis was performed (not shown in Tables). Although a positive regression coefficient was found for MS-CKD (2.915; comparing to those with eGFR ≥ 60 mL/min/1.73 m²) and serum vitamin D levels (unadjusted), non significant regression coefficient of MS-CKD (-0.157; comparing to those with eGFR ≥ 60 mL/min/1.73 m²) was also seen after adjustment for age and smoking rate. Therefore, age and smoking rate might serve as confounders for serum vitamin D levels. Furthermore, with the limitation of the KNHANES survey, the authors could not check for supplement use including vitamin D or the active form of vitamin D (including 1,25(OH)₂D; calcitriol). Thus, further longitudinal studies are required to confirm this issue.

Our study had some limitations. First, the data were derived from the cross-sectional KNHANES survey, and so we could not evaluate the causal relationship between MS-CKD, BMD and osteoporosis. Second, measurement of GFR with 24-hr urine collection was not available. A 24-hr urine collection is a more precise method for measuring creatinine clearance or GFR than the CG formula and MDRD equation used in research, and this urine collection was used in a previous epidemiological study (26). However, this method is not feasible in the context of population-based studies, such as the KNHANES and the NHANES, which estimated eGFR using serum creatinine instead (6, 7, 9). Third, it was necessary to estimate the figures for patients with a family history of osteoporosis and the number of patients with ‘fragility’ fractures at the age of > 50 yr. However, due to the limitation of our questionnaire, we could not evaluate this issue.

Our study had some strengths, including the use of a large, healthy and community-based study population. To the best of our knowledge, our study is the first to evaluate the association between MS-CKD, BMD and osteoporosis in the Korean general population. In addition, we performed sex-stratification and age-standardization for the prevalence of MS-CKD as well as adjustments for known confounder, including eGFR and BMD. This point is important because the CG formula uses age, sex, weight and BSA to estimate GFR and because it would be unclear whether the observed association was a consequence of renal dysfunction or confounders, such as age or sex.

In conclusion, the results of present study provide important evidence to support an association between GFR and BMD in both males and females and suggest that osteoporosis may be highly prevalent in individuals with MS-CKD in the Korean general population. Further longitudinal studies are warranted to investigate the potential effects of MS-CKD on individuals from the general population who are vulnerable to osteoporosis. Hence, screening procedures for the early detection of such patients should be established.

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