

A Decline in Renal Function is Associated With Loss of Bone Mass in Korean Postmenopausal Women With Mild Renal Dysfunction

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This study was conducted to assess the relationship between estimated glomerular filtration rate (eGFR) and bone mineral density (BMD) in Korean postmenopausal women with mild renal dysfunction. A total of 328 postmenopausal women who underwent BMD measurement during health check-up was investigated. BMD was measured in lumbar spine (L1-L4), femoral neck, total proximal femur and femoral trochanteric areas by dual energy radiography absorptiometry and renal function was estimated by eGFR using Cockcroft-Gault equation. Of the 328 subjects, 317 (96.6%) had an eGFR ≥ 60 mL/min/1.73 m². By using simple linear regression analysis, age, height, weight and eGFR were significantly associated with BMD for the 4 aforementioned anatomic sites, while serum levels of creatinine and blood urea nitrogen did not influence BMD. When multiple regression analyses were applied, age and body weight still had significant associations with BMD at 4 different anatomic sites ($P < 0.001$). A significant association of eGFR with BMD remained in the lumbar spine, femoral neck and proximal total femur ($P < 0.05$) but not in the trochanteric area ($P = 0.300$). Our study suggests that a decline of renal function is associated with lower BMD in the lumbar spine, femoral neck and total proximal femur areas in Korean menopausal women with mild renal dysfunction.

Key Words: Association; Bone Density; Koreans; Postmenopause; Renal Insufficiency

INTRODUCTION

It has been well established that patients with end stage renal disease (ESRD) have reduced bone mineral density (BMD) and are at risk of osteoporosis and fragility fractures (1, 2). Multiple mechanisms including dysregulation of bone mineral metabolism, vitamin D deficiency, hyperparathyroidism and chronic acidosis are involved in the development of uremic bone disease (3). Accumulating evidence suggests that abnormal phosphate retention and subsequent elevation in parathyroid hormone (PTH) may occur from the early stage of renal impairment and negatively affect BMD (3-5). However, data on BMD in the population with mild renal dysfunction are scarce. Although several studies have demonstrated the association between renal function and BMD in the population without significant renal disease, their results are inconsistent and even conflicting (6-16). Some studies showed that decreased renal function is associated with lower BMD (6, 7, 9-11, 15, 16), whereas, others failed to show the relationship between them (8, 12, 14). Besides the differences in the study population and the methods for calculating renal function and BMD measurements, the methods of adjustment for potential confounders such as age, sex and body

weight affected the study results and caused discrepancies (11, 12). Since age, sex and body weight are strongly associated with both BMD and renal function and usually included in the formulas for estimating renal function such as the Cockcroft-Gault (CG) and Modification of Diet in Renal Disease (MDRD) equations (17), correcting these potential confounders may be the most important in accurately assessing the relationship between renal function and BMD.

Considering that osteoporosis and subsequent fractures are major clinical burden to the public health care system in old age (18), and that the number of the subjects with early stage of renal dysfunction is increasing (19), assessing the association between renal function and BMD in elderly without significant renal impairment is of great importance.

This study was conducted to evaluate the association between renal function and BMD in Korean postmenopausal women with mild renal dysfunction by adjusting for potential confounders.

MATERIALS AND METHODS

Over a 5-yr period, between January 2005 and December 2009, 328 postmenopausal women who visited the Armed Forces

Seoul Hospital (Seoul, Korea) for their health check-ups and also underwent BMD measurements were selected on the basis of the following criteria. All subjects 1) were Korean; 2) were a minimum of 2 yr postmenopausal; 3) showed no evidence of any chronic diseases or alcoholism; 4) showed no abnormality in thyroid function test; and 5) had not taken calcium, vitamin D, estrogen, calcitonin, bisphosphonate, furosemide, thiazide diuretics, steroid, anticonvulsant, or any other medications known to influence bone metabolism or renal function.

A family medicine doctor performed the health check-ups which included the recording of medical and medication history as well as social habits including alcohol intake, cigarette smoking and regular exercise. Alcohol intake was considered when it consisted of at least 2 drinks per week and regular exercise was considered when it consisted of at least 3 times per week and at least 30 min each time. A gynecologist recorded history of menstruation and hormonal replacement therapy or that of medication for osteoporosis. Participants were studied in the morning following an overnight fast. A trained nurse measured systolic and diastolic blood pressure (SBP and DBP), body weight and height, and performed blood sampling. In addition to serum creatinine and blood urea nitrogen (BUN), serum levels of glucose and total cholesterol were measured on the same day (20). Renal function was estimated by estimated glomerular filtration rate (eGFR), which was calculated using the CG equation: $eGFR (mL/min/1.73 m^2) = (140 - \text{age}) \times \text{weight (kg)} / \text{serum creatinine (mg/dL)} / 72 \times (0.85 \text{ for females}) \times 1.73 m^2 / \text{body surface area (BSA)}$, BSA and body mass index (BMI) were

calculated as follows: $BSA = \text{weight (kg)}^{0.425} \times \text{height (cm)}^{0.725} \times 0.007184$, $BMI = \text{weight (kg)} / \text{height}^2 (m)$ (17).

BMD was measured at the lumbar spine (L1-L4), femoral neck, total proximal femur and femoral trochanteric area by Dual energy radiography absorptiometry (DXA) using a Prodigy Advance (GE Lunar Health Care, Madison, WI, USA), which was calibrated daily with a standard phantom which had been provided by the manufacturer (20). For the lumbar spine, the mean BMD for L1 to L4 was obtained unless individual values for one more of these vertebrae were spuriously elevated by osteophytes or sclerotic degenerative changes (7). All BMD was expressed as exact values in g/cm^2 . The measurements were within an accuracy of $\leq 1.0\%$. DXA was performed on all subjects with the same machine by the same examiner and analyzed with the same software.

Statistical analysis

Data are presented as mean values with standard deviation or percentage. The Pearson's correlation method was used to determine the correlation between eGFR and BMD. Simple and multiple linear regression analyses were used to estimate the association of variables of interest with BMD. A two-tailed *P* value of < 0.05 was considered statistically significant. All data were analyzed using SPSS for Windows 13.0 (Chicago, IL, USA).

Ethics statement

This cross-sectional study was approved by the institutional review board of the Armed Forces Medical Command (Seongnam, Korea, research number AFMC-10-IRB-018). Informed consent was exempted due to anonymous information collection.

RESULTS

The baseline characteristics of the study participants are shown in Table 1. The participants were aged 43-84 yr, 60% of whom

Table 1. Baseline characteristics of study participants (n = 328)

Characteristics	Values
Age (yr)	61.5 ± 7.1
Height (cm)	157.4 ± 4.7
Weight (kg)	56.8 ± 7.4
Body mass index (kg/m ²)	22.9 ± 2.8
Social habits	
Smoking, n (%)	15 (4.6)
Alcohol, n (%)	22 (10.1)
Exercise, n (%)	164 (50.0)
Blood pressure, mmHg	
Systolic	121.4 ± 16.2
Diastolic	76.0 ± 9.7
Laboratory parameters	
Serum albumin (g/dL)	4.11 ± 0.18
Fasting blood glucose (mg/dL)	94.1 ± 14.8
Cholesterol (mg/dL)	197.0 ± 34.6
Creatinine (mg/dL)	0.64 ± 0.12
BUN (mg/dL)	15.0 ± 3.5
eGFR (mL/min/1.73 m ²)	92.8 ± 20.3
Bone mineral density (g/cm ²)	
Lumbar spine	1.06 ± 0.16
Femoral neck	0.81 ± 0.10
Total proximal femur	0.87 ± 0.11
Femoral trochanter	0.69 ± 0.10

Values are expressed as mean ± standard deviation or number. BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate.

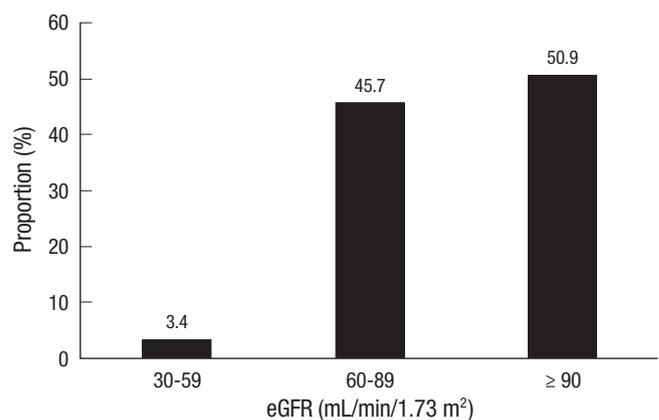


Fig. 1. Proportion of study participants according to their eGFR values. Participants who had eGFR ≥ 90 , 69-89, and 30-59 mL/min/1.73 m² were 50.9%, 45.7%, and 3.4% of all participants, respectively. eGFR, estimated glomerular filtration rate.

were aged > 60 yr. Most subjects were not overweight and did not smoke, and half of the subjects exercised regularly. The mean eGFR was 92.8 ± 20.3 mL/min/1.73 m² and mean serum creatinine level was 0.64 ± 0.12 mg/dL. The BMD for the lumbar spine (L1-L4), femoral neck, total proximal femur and trochanteric

areas were 1.06 ± 0.16 , 0.81 ± 0.10 , 0.87 ± 0.11 , 0.69 ± 0.10 g/cm², respectively.

Fig. 1 displays the distribution of the participants according to their eGFR values. About half (50.9%) had an eGFR of ≥ 90 mL/min/1.73 m², the other half (45.7%) had an eGFR between

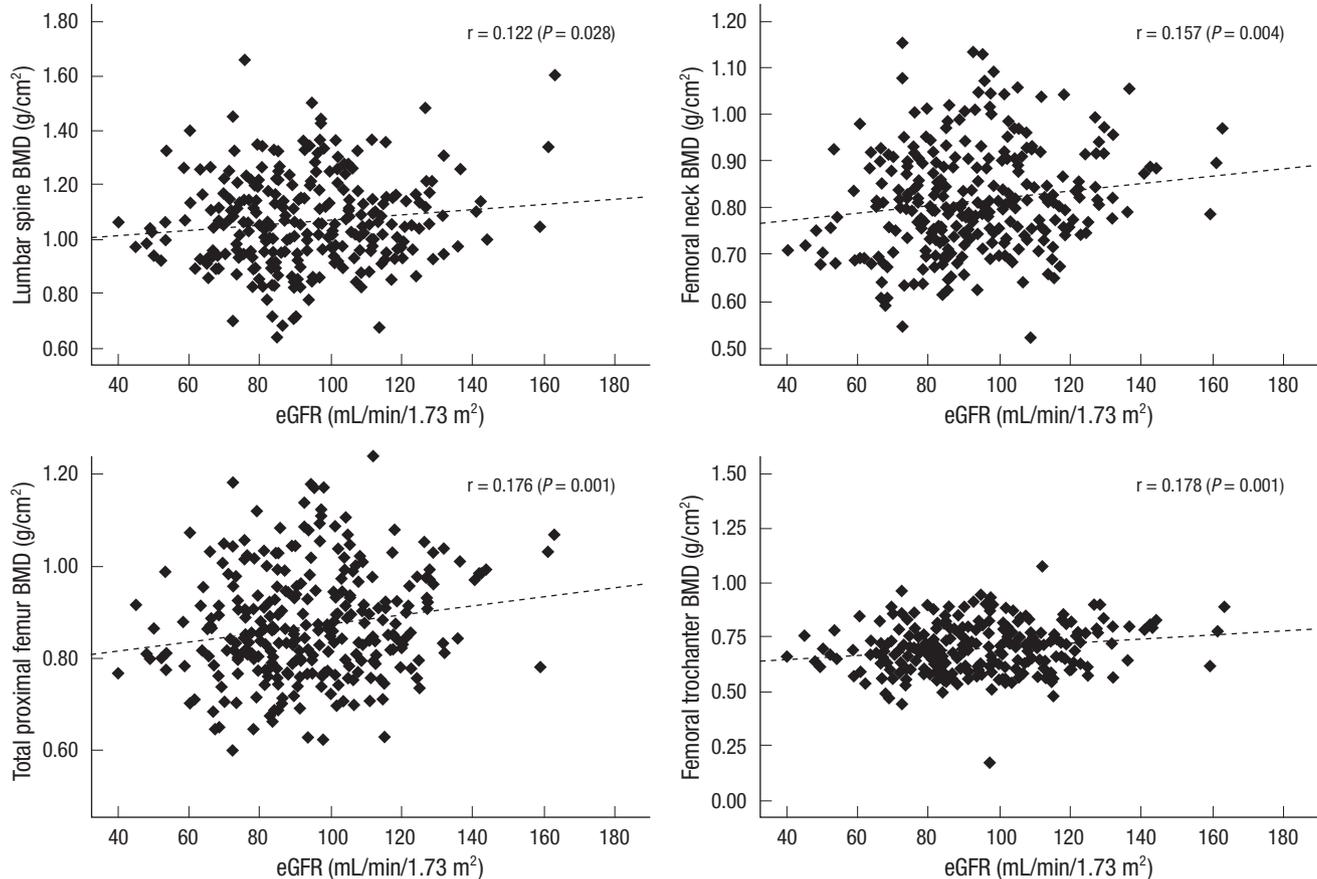


Fig. 2. Linear associations between eGFR and BMD. Significant positive linear associations between eGFR and BMD are shown in scatterplots. *r*, Pearson's correlation coefficient. eGFR, estimated glomerular filtration rate; BMD, bone mineral density.

Table 2. Simple linear regression analyses showing the associations between variables and BMD

Variables	Lumbar spine	Femoral neck	Total proximal femur	Trochanter
Age	-0.281 (0.001)/0.079*	-0.384 (0.001)/0.148*	-0.340 (0.001)/0.115*	-0.285 (0.001)/0.081*
Height	0.253 (0.002)/0.064*	0.306 (0.001)/0.093*	0.216 (0.001)/0.216*	0.217 (0.001)/0.047*
Weight	0.279 (0.001)/0.078*	0.267 (0.001)/0.071*	0.305 (0.001)/0.093*	0.298 (0.001)/0.089*
BMI	0.176 (0.003)/0.031*	0.141 (0.002)/0.020*	0.223 (0.002)/0.050*	0.217 (0.002)/0.047*
Smoking	0.032 (0.042)/0.001	0.060 (0.028)/0.004	0.040 (0.030)/0.002	-0.058 (0.028)/0.003
Alcohol	-0.008 (0.029)/0.000	-0.007 (0.020)/0.000	0.023 (0.021)/0.001	-0.003 (0.020)/0.000
Exercise	0.172 (0.017)/0.030	0.067 (0.012)/0.004	0.057 (0.013)/0.003	0.050 (0.012)/0.003
SBP	-0.106 (0.001)/0.011	-0.120 (0.000)/0.014 [†]	-0.079 (0.000)/0.006	-0.083 (0.000)/0.007
DBP	0.040 (0.001)/0.002	0.019 (0.001)/0.000	0.050 (0.001)/0.002	0.043 (0.001)/0.002
Albumin	0.055 (0.050)/0.003	0.095 (0.033)/0.009	0.159 (0.035)/0.025 [†]	0.122 (0.034)/0.015 [†]
FBG	0.034 (0.001)/0.001	-0.054 (0.000)/0.003	-0.016 (0.000)/0.000	-0.0074 (0.000)/0.000
Cholesterol	0.047 (0.000)/0.002	0.052 (0.000)/0.003	0.083 (0.000)/0.007	0.050 (0.000)/0.003
BUN	-0.102 (0.003)/0.010	-0.036 (0.002)/0.001	-0.047 (0.002)/0.002	-0.076 (0.002)/0.006
Creatinine	0.101 (0.070)/0.010	0.066 (0.047)/0.004	0.061 (0.050)/0.004	0.038 (0.047)/0.001
eGFR	0.122 (0.000)/0.015 [†]	0.157 (0.000)/0.025 [†]	0.176 (0.000)/0.031 [†]	0.178 (0.000)/0.032 [†]

Values are expressed as β (SE)/R². **P* < 0.001, [†]*P* < 0.01, [‡]*P* < 0.05. β , standardized regression coefficient; SE, standard error; R², percent variance explained by each variable. BMD, bone mineral density; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate.

Table 3. Multiple linear regression analyses showing the independent association between variables and BMD

	β (SE)	t	P	VIF
Lumbar spine BMD (Durbin-Watson = 1.853; adjusted R ² = 0.169)				
Age	-0.342 (0.001)	-5.889	< 0.001	1.317
Weight	0.317 (0.001)	5.901	< 0.001	1.122
eGFR	0.131 (0.000)	2.163	0.031	1.439
Femoral neck BMD (Durbin-Watson = 2.050; adjusted R ² = 0.231)				
Age	-0.435 (0.001)	-7.211	< 0.001	1.423
Weight	0.322 (0.001)	5.872	< 0.001	1.171
SBP	-0.086 (0.000)	-1.581	0.102	1.155
eGFR	0.122 (0.000)	1.997	0.047	1.465
Total hip BMD (Durbin-Watson = 2.609; adjusted R ² = 0.227)				
Age	-0.445 (0.001)	-7.775	< 0.001	1.333
Weight	0.315 (0.001)	5.988	< 0.001	1.128
Albumin	0.051 (0.030)	1.027	0.305	1.013
eGFR	0.145 (0.000)	2.429	0.016	1.446
Trochanter BMD (Durbin-Watson = 1.968; adjusted R ² = 0.202)				
Age	-0.308 (0.008)	-5.300	< 0.001	1.333
Weight	0.359 (0.007)	6.715	< 0.001	1.128
Albumin	0.098 (0.263)	1.942	0.053	1.013
eGFR	0.063 (0.003)	1.038	0.300	1.446

β , standardized regression coefficient; SE, standard error; t, corresponding t values; VIF, variance inflation factor. BMD, bone mineral density; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.

60 and 89 mL/min/1.73 m² and only 3.4% of the participants had an eGFR of < 60 mL/min/1.73 m².

Fig. 2 demonstrates a significant linear association between eGFR and BMD for the 4 different sites ($P < 0.05$ for each). The Pearson's correlation coefficients between eGFR and lumbar spine, femoral neck, total proximal femur and femoral trochanteric BMD were 0.122, 0.157, 0.176, and 0.178, respectively.

We performed simple linear regression analysis to assess association of each variable with BMD (Table 2). Age, height, body weight and BMI were all significantly associated with BMD at all 4 sites ($P < 0.001$ for each). SBP was associated with femoral neck BMD; and serum albumin was associated with total proximal femur and trochanteric BMDs ($P < 0.05$ for each). In addition, eGFR was associated with BMD for the 4 sites ($P < 0.01$ each versus femoral neck, total proximal femur and trochanteric BMDs; $P < 0.05$ each versus lumbar spine BMD). However, serum levels of creatinine and BUN were not associated with BMD ($P > 0.05$ for each). We performed multiple linear regression analyses to identify the independent variables affecting BMD (Table 3). We used variables that were significant ($P < 0.05$) in a simple linear regression model (Table 2) as confounding factors in this multiple regression analyses. Height and body mass index were not taken into account in the analyses because of the eventual problems with multicollinearity with body weight (21). Age and body weight still had a significant association with BMD from four different skeletal sites ($P < 0.001$ for each). A significant association of eGFR with BMD was remained in lumbar spine, femoral neck and proximal total femur ($P < 0.05$ for each) but not for trochanteric BMD ($P = 0.300$).

When the MDRD equation for estimating GFR was applied,

similar results were obtained demonstrating positive relationship between renal function and bone density. In multiple linear regression analyses, femoral neck BMD had a significant positive association with eGFR ($P = 0.012$), lumbar spine and proximal total femur BMD had a marginal significance ($P = 0.060$ and $P = 0.079$, respectively), whereas, trochanteric BMD was not associated with eGFR ($P = 0.422$) (data not shown).

DISCUSSION

The kidney plays a pivotal role in regulating calcium and phosphorous metabolism. The kidney is not only the target organ for various bone regulating hormones such as PTH, but also a principal site for the production of calcitriol (1,25-dihydroxyvitamin D). It has been known that decrease in calcitriol and abnormal retention of phosphorus occur from a relatively early stage of chronic kidney disease (CKD) followed by a subsequent increase in PTH (3-5). Although these changes contribute to the maintenance of serum levels of calcium and phosphorous within the normal range until advanced stage of CKD, the results adversely affect bone formation (22, 23).

In this study, we found independent association between eGFR and BMD for the lumbar spine, femoral neck and proximal total femur in 328 Korean menopausal women with mild renal dysfunction. No significant relationships of serum levels of creatinine and BUN with BMD were observed in our study, suggesting that eGFR is more important than serum creatinine or BUN in estimating the BMD in postmenopausal women.

CKD is a worldwide health problem. The prevalence of CKD is reported to be about 11% among the USA (19) and Australian adults (24). In a recent Korean population-based study with elderly aged > 65 yr living in a satellite city of Korea, 52% of the subjects showed an eGFR values of < 60 mL/min/1.73 m² as measured by the MDRD equation (25). In our study, only 3.4% had an eGFR of < 60 mL/min/1.73 m², which is much lower than those in previous reports (19, 24, 25). These differences may be due to a different study population. We selected postmenopausal women who had no medical problems such as hypertension and diabetes, whereas the previous study (25) included 71.1% of patients with hypertension and 20.9% of patients with diabetes, which may have negatively affected renal function. In addition, the subjects were relatively younger in our study and the methods for eGFR estimation were different: we used the CG while the previous study used the MDRD equation (25). It has been reported that the GFR calculated by the CG equation is likely to be overestimated compared to that by the MDRD equation (26).

Our study results are consistent with those of previous studies showing that the decline in renal function was associated with decreased BMD (6, 7, 11, 16). Yendt et al. (6, 7) reported a strong positive correlation between creatinine clearance (Ccr) and the

lumbar spine BMD, which was primarily independent on age and body surface area in healthy aging women with and without osteoporosis. They calculated Ccr using 24-hr urine samples, however, we did not include a 24-hr urine samples for the estimation of renal function in our study. Jassal et al. (11) also showed a significant positive linear association between calculated renal function (eGFR by using the CG and MDRD equations) and hip BMD in elderly. However, they did not adjust for age and body weight during the multiple regression analysis. Kaji et al. (16) showed significant positive correlations between eGFR and BMD values at the femoral neck and radius among Japanese postmenopausal women with stage 2 CKD. In the same study, they found that postmenopausal women with vertebral fractures have lower eGFR than those without vertebral fractures in stage 2 CKD ($60 \leq \text{eGFR} < 90 \text{ mL/min/1.73 m}^2$). Considering the study population of postmenopausal women at an early stage of CKD, the study results reported by Kaji et al. (16) are very similar to those of our study. When subgroup analysis was performed on 317 participants (96.6%) with stage 1 or 2 CKD ($\text{eGFR} \geq 60 \text{ mL/min/1.73 m}^2$), eGFR was significantly associated with femoral neck BMD in multiple regression analysis after adjustment for confounders ($P = 0.014$). However, the associations between eGFR and BMDs at lumbar spine, total proximal femur or trochanteric area were not observed in our study population ($P > 0.05$ for each).

Although simple linear regression analysis showed a positive association between eGFR and femoral trochanteric BMD in our study, this association disappeared after adjustment for confounding factors including age and body weight. This result is similar to those of previous studies showing the importance of confounding factors in assessing the association between renal function and BMD (8, 12-14). Ccr had a significant relationship with BMD in old men and women, however, this relationship was due to the inter-correlation of both variables with BMD and lost its significance after adjustment for age (8, 14). A recent epidemiological study with 13,848 adults (12) also showed that the association between renal impairment and lower BMD, which was shown to be significant in unadjusted analysis, disappeared after adjustment for age and body weight in the multivariate models. Cystatin-C, a new marker for kidney function, was associated with BMD in the linear regression model, however, this association disappeared after adjustment for age and body fat in 885 elderly women (13).

There is accumulating evidence that old age and lower body weight are strongly associated with low BMD (27), and these potential confounders are included when renal function is calculated using the CG or MDRD equations (17). Therefore, it is mandatory to properly adjust these confounders for accurate assessment of the relationship between BMD and renal function if renal function is estimated by the CG or MDRD equations as in this study. Some investigators have tried to avoid the effect

of these strong confounders by not adjusting for age and body weight because these confounders are included in the CG equation (11) or by using other markers that are independent of age and body weight (13). In our study, we attempted to overcome the multicollinearity problem by using the variance influence factor (VIF) (21). The maximal VIF value did not exceed 1.5 in each multiple regression model, which indicated that the degree of multicollinearity between the independent variables was not serious in our study.

Sometimes serum levels of creatinine and BUN can be useful markers for estimating renal function because they are less affected by age and body weight than using the eGFR by the CG or MDRD equation (12). However, serum creatinine levels do not predict renal function precisely, especially in old individuals because they usually have a normal serum creatinine levels in spite of impaired renal function (28). Our finding that serum levels of both creatinine and BUN were not associated with BMD suggest that renal function should be assessed by eGFR rather than either the serum creatinine or BUN level in elderly subjects because renal impairment can be masked by an apparently normal serum creatinine or BUN levels (14).

Proteinuria is an important marker for renal damage and progression to ESRD (29). In our study population, 10 subjects (3.0%) had proteinuria above the normal limit in the spot urine dipstick test. Among them, 9 (90.0%) had an $\text{eGFR} \geq 60 \text{ mL/min/1.73 m}^2$ (data not shown). These subjects with proteinuria had the potential of more advanced stage of renal dysfunction, however, we did not consider proteinuria as an additional factor for estimating renal function in this study.

This study has several limitations. First, because our data were obtained from a cross-sectional study, there is possibility of a temporal association between renal function and BMD which makes it difficult to ascertain our conclusion. Longitudinal studies are needed to better characterize this relationship. Second, since only Korean postmenopausal women were included in the study, our results may not apply to the general population. Third, other potential confounders, including the history of fractures, childbearing, income level, education background and calcium intake, which are known to affect BMD in Korean adults (30), were not considered in this study. Fourth, we did not analyze serum levels of vitamin D and PTH, which may be important in the association between renal function and BMD (3). Finally, we did not use gold standard measures of GFR such as inulin, radioisotope clearance or 24-hr urine samples, which would have helped accurately assess the association between renal function and BMD (13).

In conclusion, the results of this study demonstrate that a decline in renal function may be associated with low BMD in Korean menopausal women with mild renal dysfunction. Further studies with a larger sample size and various assessment methods are needed to confirm our results.

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AUTHOR SUMMARY**A Decline in Renal Function is Associated With Loss of Bone Mass in Korean Postmenopausal Women With Mild Renal Dysfunction**

Hack-Lyoung Kim, In Young Park, Jin Man Choi, Se-Min Hwang, Hyo Sang Kim, Jae-Sung Lim, Min Kim, and Min-Jeong Son

Kidney function is intimately associated with bone health. We assessed the relationship between estimated glomerular filtration rate (eGFR) and bone mineral density (BMD) in Korean postmenopausal women with mild renal dysfunction. BMD was measured in lumbar spine and femur regions by dual energy radiography absorptiometry, and eGFR was estimated by using Cockcroft-Gault equation. Of the 328 study subjects, 317 (96.6%) had an eGFR ≥ 60 mL/min/1.73 m². Significant positive association between eGFR and BMD was observed in Pearson's correlation. In multiple linear regression analyses, eGFR significantly associated with BMD in the lumbar spine, femoral neck and proximal total femur ($P < 0.05$) but not in the trochanteric area ($P = 0.300$) after controlling confounders including age and body weight. Our study demonstrated that, even with mild renal dysfunction, a decline of renal function is associated with lower BMD in Korean menopausal women.