Bone Mineral Density and Fracture Risk in Older Individuals with CKD

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Summary

Background and objectives Kidney Disease Improving Global Outcomes guidelines recommend against bone mineral density (BMD) screening in CKD patients with mineral bone disease, due to a lack of association of BMD with fractures in cross-sectional studies in CKD. We assessed whether BMD is associated with fractures in participants with and without CKD in the Health, Aging, and Body Composition study, a prospective study of well functioning older individuals.

Design, setting, participants, & measurements Hip BMD was measured by dual-energy x-ray absorptiometry. Osteoporosis was defined as a femoral neck BMD (FNBMD) T score below −2.5 and CKD as an estimated GFR <60 ml/min per 1.73 m^2. The association of BMD with incident nonspine, fragility fractures to study year 11 was analyzed using Cox proportional hazards analyses, adjusting for age, race, sex, body mass index, hyperparathyroidism, low vitamin D level, and CKD. Interaction terms were used to assess whether the association of BMD with fracture differed in those with and without CKD.

Results There were 384 incident fractures in 2754 individuals (mean age 73.6 years). Lower FNBMD was associated with greater fracture, regardless of CKD status. After adjustment, the hazard ratios (95% confidence intervals) were 2.74 (1.99, 3.77) and 2.15 (1.80, 2.57) per lower SD FNBMD for those with and without CKD, respectively (interaction P=0.68), and 2.10 (1.23, 3.59) and 1.63 (1.18, 2.23) among those with osteoporosis in patients with and without CKD, respectively (interaction P=0.75).

Conclusions BMD provides information on risk for fracture in older individuals with or without moderate CKD.

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Introduction

Patients with ESRD and milder stages of CKD are at increased risk of hip fracture, perhaps due to a high prevalence of risk factors for fracture (1–10). However, the data on the relationship of CKD with bone mineral density (BMD) are mixed. Data from the National Health and Nutrition Examination Survey showed that individuals with decreased kidney function had lower BMD in unadjusted models (3). However, after adjustment for age, race, and sex, there was no significant relationship of CKD with BMD. In the Cardiovascular Health Study, kidney function was not associated with decreased BMD at baseline, but was associated with a faster rate of bone loss over time (4). In the Rancho Bernardo study, reduced kidney function as measured by Cockcroft-Gault, but not by Modified Diet in Renal Disease (MDRD) formula was associated with faster bone loss over time (5).

Recently, the Kidney Disease Improving Global Outcomes (KDIGO) foundation published a clinical practice guideline for mineral bone disease in CKD (11). One of the recommendations is as follows: "In patients with CKD stages 3–5D with evidence of mineral bone disease, we suggest that BMD testing not be performed routinely, because BMD does not predict fracture risk as it does in the general population, and BMD does not predict the type of renal osteodystrophy (2B)." However, to our knowledge, there are no prospective studies in stage 3 CKD to assess the relationship of BMD with fracture. Therefore, we set out to determine whether the association of BMD with fracture risk differs in individuals with and without CKD. It is our hypothesis that BMD will be predictive of fracture risk regardless of CKD status.

Materials and Methods

Participants

The Health, Aging, and Body Composition study is a longitudinal study of changes in body composition, clinical conditions affecting these changes, and their effect on functional status and development of disability in older individuals. Participants were recruited from Medicare eligibility lists in Pittsburgh, Pennsylvania, and Memphis, Tennessee, between March 1997 and July 1998. Whites were recruited from a random sample of

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the lists, and blacks were recruited from all age-eligible persons residing in the respective communities. Eligibility criteria were age 70–79 years, no reported difficulty in performing activities of daily living, ability to walk one-quarter of a mile or walking up 10 steps without resting, no reported need of assistive devices to ambulate, no history of active treatment for cancer in the prior 3 years, and no plan to move out of the area in the next 3 years. The study was approved by the institutional review board at the participating institutions, including the coordinating center and the National Institute on Aging. Of the original 3075 patients, we excluded 28 for missing serum creatinine, 267 for missing parathyroid hormone (PTH) levels, and 26 for missing femoral neck bone mineral density (FNBMD) measurements, resulting in an analytic sample of 2754 participants for this analysis.

Predictors

BMD testing (done at year 1) was estimated using dual-energy x-ray absorptiometry (DXA) using a Hologic QDR4500A Scanner (software version 9.03). The scans were read centrally at the University of California, San Francisco reading center. BMD measurements at the femoral neck (FNBMD) and total hip (THBMD) were evaluated. Osteoporosis was defined using the World Health Organization definition as a femoral neck DXA score of <2.5 SDs below the value for white women aged 20–29 years (M0.57 g/cm^2) (12). Race was defined by participant self-report. Weight was measured by a standard balance-beam scale to the nearest 0.1 kg. Body height was measured to the nearest millimeter using a wall-mounted stadiometer. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters.

All laboratory analyses were measured at year 1 except 25-hydroxyvitamin D levels and PTH, which were measured at year 2. Laboratory values were assessed after an overnight fast. Serum creatinine (sCr) was measured on the Kodak Ektachem 700 Analyzer (Eastman Kodak, Rochester, NY). The sCr values were not calibrated to the Cleveland Clinic assay or isotope dilution mass spectrometry traceable assay. We measured 25-hydroxyvitamin D in serum samples using a two-step RIA (25-hydroxyvitamin D ^{125}I RIA Kit; DiaSorin, Stillwater, MN). Intact PTH was measured in EDTA plasma with a two-site immunoradiometric assay kit (N-tact PTHSP; DiaSorin). CKD was defined as an estimated GFR (eGFR) <60 ml/min per 1.73 m^2 by the MDRD equation (13). Vitamin D level and PTH were dichotomized for the analysis. Elevated PTH was defined as greater than the upper limit of normal (>65 pg/ml) (14). Low vitamin D level was defined as a 25-OH vitamin D level <20 ng/ml (15,16).

Outcomes

The primary outcome was all nonspine fragility fractures. On secondary analyses, fracture events were limited to fragility, hip fracture alone. Individuals were contacted every 6 months and attended annual clinic visits. Fractures were identified by self-report and were then verified by radiology reports. All fracture reports were adjudicated, and were available through year 11 of the study. For this study, fracture was defined as the first nonspine fracture event of any cause. Fragility fractures were defined as "spontaneous or with modest trauma, such as a fall from a standing height." The time to fracture event was determined from the initial clinic visit date to the fracture event date. Individuals were censored if they did not have a nonspine, fragility fracture event on follow-up, died, or were lost to follow-up. The censored times were calculated from the initial visit date to the time of last contact.

Statistical Analyses

Characteristics between those with and without CKD were assessed with t tests or Wilcoxon rank sum tests for continuous variables and chi-squared tests for categorical variables. Cox proportional hazards models were used to analyze time to first fracture. The main predictor was BMD. BMD variables were adjusted to be scaled to 1 SD BMD. A separate model was fit to evaluate using either FNBMD or THBMD as the BMD variable. The initial model was adjusted for age, race, sex, and BMI. A second model was also adjusted for low vitamin D level and elevated PTH level. To test whether the association of BMD with fracture differed in those with and without CKD, we tested a BMD × CKD interaction. We also tested interactions including BMD × PTH status and BMD × vitamin D status. The models were also evaluated stratified by sex, CKD status, and PTH status. Survival curves were generated using the unadjusted model of osteoporosis on fracture risk, and were stratified by CKD status. Adjusted survival curves were generated using the form $S = S_0^{\exp(\sum \beta_i x_i)}$. The baseline survival function (S_0) was generated from the adjusted full model. The four curves were generated based on the inclusion of the coefficients from each of the representative CKD and osteoporosis groups. The coefficients from the covariates within the model were multiplied by their mean and coefficients. Four curves were generated detailing the represented strata, those with and without CKD, and those with and without osteoporosis. The proportionality assumption for the proportional hazards models was tested graphically, and we also tested for a linear association between scaled Schoenfeld residuals and time. No violations were observed. P values <0.05 were considered statistically significant for all analyses including interaction terms. We used STATA software (version 11.2; StataCorp, College Station, TX) for the analyses.

Results

Of the 3075 participants in the study sample, 2754 had BMD measurements and laboratory values. The mean age was 73.6±2.9 years, and the mean eGFR was 72.7±16.3 ml/min per 1.73 m^2. There were 587 patients (21%) with an eGFR <60 ml/min per 1.73 m^2, of which 487 (83%) had an eGFR between 45 and 59.9 ml/min per 1.73 m^2, 78 (13%) had an eGFR between 30 and 44.5 ml/min per 1.73 m^2, 17 (3%) had an eGFR between 15 and 29.9 ml/min per 1.73 m^2, and 5 (1%) had an eGFR <15 ml/min per 1.73 m^2. A comparison of demographic and clinical features between those with and without CKD is shown in Table 1. Individuals with CKD were slightly older, more likely to be women, and less likely to be black. There was no statistically significant difference in BMI by CKD status. The BMD measurements at the femoral neck and total hip areas were also similar between the two CKD groups. There were a higher proportion of participants with hyperparathyroidism in the CKD group, but no significant difference in vitamin D levels.

Table 1. Characteristics of individuals with and without CKD

Characteristic	No CKD (*n*=2167)	CKD (*n*=587)	*P* Value
Age (yr)	73.5±2.9	74.0±2.8	<0.001
Female	1087 (50)	322 (55)	0.04
Black race	918 (42.3)	176 (30)	<0.001
Body mass index (kg/m^2)	27.2±4.7	27.7±4.7	0.08
Femoral neck bone mineral density	0.75±0.14	0.74±0.14	0.22
Total hip bone mineral density	0.89±0.17	0.89±0.16	0.77
Parathyroid hormone (pg/ml)	32.7 (25.0, 43.4)	37.8 (26.0, 55.0)	<0.001
Hyperparathyroidism (>65 pg/ml)	137 (6)	98 (17)	<0.001
25 hydroxyvitamin D (ng/ml)	25.4±10.9	27.5±13.1	<0.001
25-OH vitamin D level <20 ng/ml	724 (33)	174 (30)	0.08
Any osteoporosis drug	87 (4)	23 (4)	0.93
Osteoporosis (femoral neck bone mineral density <0.57 g/cm^2)	210 (9.7)	58 (9.9)	0.89

Data are presented as mean ± SD, *n* (%), or median (interquartile range).

The median duration of observation time was 11.3 years per participant, during which there were 384 incident non-spine fragility fracture events (98 fractures in the CKD group and 286 fractures in the non-CKD group). The presence of osteoporosis defined by FNBMD was associated with a greater fracture risk in both the CKD and non-CKD groups (Table 2). The unadjusted survival curves (Figures 1 and 2) demonstrate the fracture-free survival among those with and without osteoporosis in the CKD and non-CKD groups, respectively. The unadjusted risk of fracture in those with osteoporosis was similar across CKD groups (Table 2). When adjusted for age, race, sex, and BMI, the risk of fracture in those with osteoporosis was attenuated but remained consistent across CKD groups. Further adjustment for hyperparathyroidism and low vitamin D level demonstrated little change in fracture risk. There were no significant interactions identified between osteoporosis and CKD, either in the unadjusted or adjusted models. The adjusted survivor curves for the osteoporosis and CKD groups are demonstrated in Figure 3. The presence of osteoporosis was clearly associated with increased risk of fracture with or without CKD ($P<0.001$). However, these associations were similar irrespective of CKD status (interaction $P=0.56$).

We also analyzed FNBMD in the model as a continuous variable, which was associated with risk of fracture, regardless of CKD group, in both unadjusted and adjusted models (Table 3), and we observed no interaction between FNBMD and CKD with risk of fracture (interaction $P=0.72$). A separate model was created using THBMD instead of FNBMD as a predictor. In the unadjusted model using THBMD, the hazard ratios (HRs), presented with 95% confidence intervals, were 2.06 (1.62, 2.63) among those with CKD and 2.33 (2.05, 2.65) among those without CKD. In the fully adjusted model, the HRs were 2.59 (1.86, 3.61) among those with CKD and 2.17 (1.82, 2.58) among those without CKD. These models were repeated using CKD status as defined by GFR <60 ml/min per 1.73 m^2 using the Chronic Kidney Disease Epidemiology Collaboration equation (17) and produced similar results (data not shown).

We also investigated whether there were interactions with elevated PTH or sex. The interaction term between hyperparathyroidism and FNBMD was statistically significant ($P=0.04$). When stratified by presence of hyperparathyroidism, the association of FNBMD and fracture risk was 1.56 (0.90, 2.70) per lower SD among those with hyperparathyroidism (28 fractures of 235 participants), and 2.41 (2.04, 2.85) among those without hyperparathyroidism (356 fractures of 2519 participants) when all participants were evaluated irrespective of CKD status. The interaction between BMD and sex was not statistically significant ($P=0.18$). Interactions were also tested between CKD and hyperparathyroidism. The interaction term was not significant ($P=0.86$). There were too few individuals with CKD and hyperparathyroidism (11 fractures of 98 participants) to evaluate in adjusted analyses; however,

Table 2. Association of osteoporosis with risk of fracture

	Hazard Ratio (95% Confidence Interval)			*P* Value for CKD Osteoporosis Interaction
	Overall	No CKD	CKD	
Unadjusted	2.85 (2.23, 3.64)	2.97 (2.24, 3.93)	2.53 (1.55, 4.13)	0.56
Adjusted for age, race, sex, and body mass index	1.77 (1.35, 2.32)	1.64 (1.20, 2.25)	2.10 (1.24, 3.59)	0.74
Positive parathyroid status and vitamin D status	1.76 (1.34, 2.32)	1.63 (1.18, 2.23)	2.10 (1.23, 3.59)	0.75

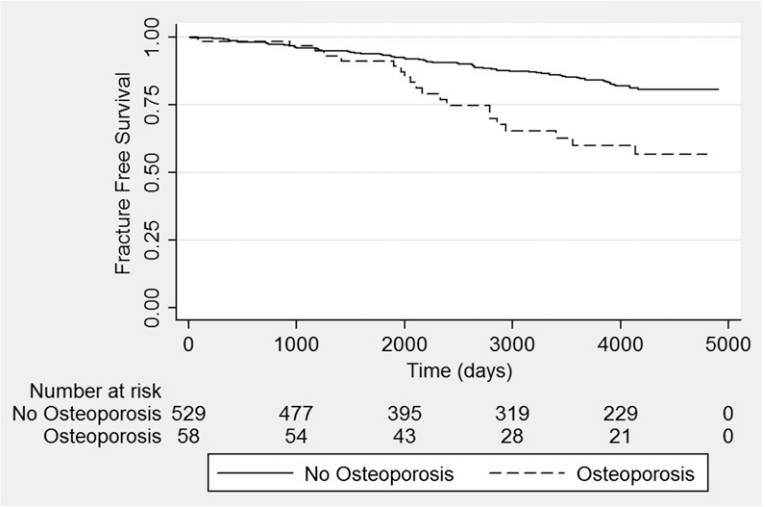

Figure 1. | **Unadjusted fracture-free survival curves for time to first nonspine fracture for those with and without osteoporosis among those with CKD**.

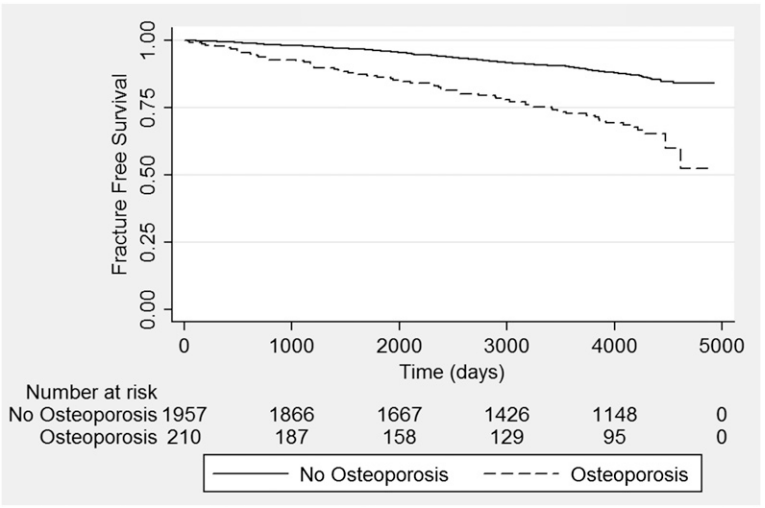

Figure 2. | **Unadjusted fracture-free survival curves to time to first nonspine fracture for those with and without osteoporosis among those without CKD**.

the unadjusted FNBMD HR was 2.10 (1.06, 4.14), which is similar to the overall group. When stratified by sex, the HRs for FNBMD were 2.83 (2.16, 3.72) for men and 2.05 (1.70, 2.49) for women.

The fully adjusted model using FNBMD was conducted using a companion analysis evaluating time to hip fracture as the event of interest. There were 149 fragility hip fracture events, which represented 39% of all fragility nonspine fracture events. The fully adjusted FNBMD HRs were 5.82 (3.27, 10.35) among those with CKD and 3.08 (2.29, 4.14) among those without CKD (interaction P=0.48).

Discussion

We found that among well functioning community-living older individuals, a low FNBMD measurement was similarly associated with nonspine fracture events among those with and without CKD. The diagnosis of osteoporosis carried a 110% increased risk of nonspine fracture among those with CKD and a 63% increased risk of fracture among those without CKD, findings that were statistically significant in both groups. The results did suggest that BMD was less strongly associated with fracture in individuals with hyperparathyroidism overall. The relationship of low FNBMD with fracture risk among individuals with concurrent CKD and hyperparathyroidism was slightly lower than that of the overall study population, although the numbers were too small to explore completely.

Currently, KDIGO guidelines recommend against BMD screening in patients with stage 3–5 CKD with mineral bone disease. This recommendation is based on several cross-sectional studies examining the relationship of BMD and fracture history in populations with CKD. The majority of these studies were done among patients with

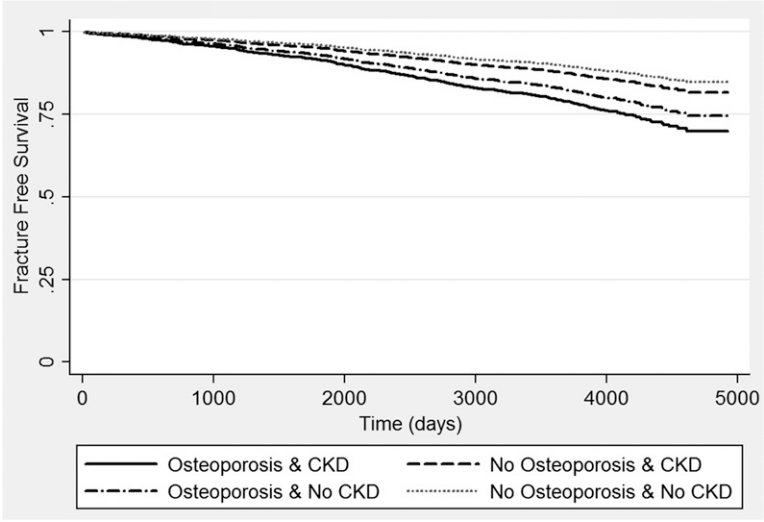

Figure 3. | **Fracture-free survival curves adjusted for age, race, sex, body mass index, hyperparathyroidism, and vitamin D deficiency**. The relationship with fracture risk is demonstrated between the CKD and osteoporosis groups.

Table 3. Association of femoral neck bone mineral density (per SD decrease) with risk of fracture

	Hazard Ratio (95% Confidence Interval)			*P* Value for CKD Bone Mineral Density Interaction
	Overall	No CKD	CKD	
Unadjusted	2.42 (2.14, 2.74)	2.45 (2.13, 2.82)	2.32 (1.79, 3.01)	0.72
Adjusted for age, race, sex, and body mass index	2.26 (1.94, 2.64)	2.14 (1.80, 2.55)	2.69 (1.96, 3.69)	0.70
Positive parathyroid status and Vitamin D status	2.30 (1.96, 2.68)	2.15 (1.80, 2.57)	2.74 (1.99, 3.77)	0.68

ESRD on dialysis, rather than with patients with stage 3–5 CKD. Several studies conducted in hemodialysis patients showed no relationship between BMD measurement and fracture history (18–22). Piraino *et al.* evaluated 31 dialysis patients using lumbar spine BMD measurements and found no association between low BMD and presence of fracture history (18). In another cross-sectional study by Ureña *et al.*, 70 dialysis patients were evaluated based on *Z* scores of the mid-radius, femoral neck, lumbar spine, and total body. Only the total body *Z* score was associated with a fracture history (19). However, despite these findings, there are several studies that have reported a relationship between BMD and history of fracture (23–28). A meta-analysis by Jamal *et al.* pooled six studies to evaluate 683 hemodialysis patients. Associations were found between fracture history and lower BMD measured at the lumbar spine, mid-radius, one-third radius, and ultradistal radius, but femoral neck BMD was not associated with fracture history (23). A cross-sectional study by Nickolas *et al.* examined the association of osteoporosis and self-reported hip fracture among 6270 participants aged >50 years (28). Fourteen percent of the participants had CKD as defined by a GFR between 15 and 60 ml/min per 1.73 m^2. Through an adjusted logistic regression model, Nickolas *et al.* identified CKD and history of osteoporosis as independently associated with history of hip fracture (28), which suggests that the presence of osteoporosis is associated with hip fracture regardless of CKD status. In another recent study by the same author, a cross-sectional analysis of 82 patients with predominantly stage 4 CKD revealed an association between history of fracture and low FNBMD measurements. This association was strengthened when FNBMD measurement was combined with bone turnover marker levels (29). Together, these cross-sectional studies show discordant results with DXA BMD measurements in predicting fractures among mostly ESRD populations. This is thought to be because DXA is a poor test to distinguish osteoporosis from the mineral bone disease that becomes prominent in ESRD patients. The mineral bone disease in these patients predominantly affects the cortical bone as opposed to the trabecular bone typically affected in osteoporosis. Attempts to measure cortical and trabecular bone density using peripheral quantitative computed tomography have shown an association between the cortical bone density and fracture, but not trabecular bone density in dialysis patients (24,30). Certain sites such as the forearm are composed of predominantly cortical bone as opposed to other sites such as the spine, which may have more trabecular bone (11). This may account for the differences seen in fracture risk at various BMD measurement sites.

To our knowledge, our study is the first to prospectively assess the association of BMD and nonspine fractures

among older adults with CKD and to compare it with the association in individuals without CKD. In a study by McCarthy *et al.*, the effect of eGFR on fracture risk was prospectively studied after adjustment for FNBMD in a sample of 427 postmenopausal females followed for 5948 person-years (31). Only 5% of the sample had a creatinine level >1.2 mg/dl. FNBMD, but not eGFR, was found to be predictive of fracture risk in the multivariate model; however, the relationship of FNBMD with fracture risk among individuals with CKD was not studied, nor was a test for interaction by CKD status provided.

It is possible that some of the relationship between BMD and fracture risk in our study may be attributed to the high proportion of patients with stage 3 CKD. This may represent a group of patients in whom low BMD reflects mainly osteoporosis and relatively little mineral bone disease. In this case, the predictive nature of BMD would be expected to be similar to the non-CKD group. There were too few patients with both high PTH and CKD to analyze the adjusted association of BMD with fracture in this population. However, in the unadjusted model, BMD was predictive of fracture risk. Furthermore, the few participants with an eGFR <30 ml/min per 1.73 m^2 (n=27) limit the validity of these results in this subgroup, which will be an important topic for future study. There is a lack of treatment trials for low BMD in CKD. Subgroup analyses of treatment trials evaluating individuals with CKD versus without CKD have shown similar benefits in both groups (32). However, the subgroups are also mainly stage 3A. Whether treatment of low BMD in advanced CKD is safe and effective requires further study. Another limitation of the study may be that the classification of fractures as fragility fractures were identified through patient self-report based on the definition included in the Materials and Methods. It is possible there may be a reporting bias inherent to this method. However, the results were similar if all nonspine fractures were analyzed.

In conclusion, we demonstrate that among well functioning community-living, older individuals with predominantly stage 3 CKD, BMD measurements in the femoral neck are useful for identifying patients at risk for nonspine fractures. This argues against the current KDIGO guideline recommendations and suggests that there may be a role for DXA screening in CKD.

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Disclosures

None.

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