Relationship between Moderate to Severe Kidney Disease and Hip Fracture in the United States

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People with ESRD are at a high risk for hip fracture. However, the effect of moderate to severe chronic kidney disease (CKD) on hip fracture risk has not been well studied. As part of the Third National Health and Nutrition Examination Survey, information on both kidney function and history of hip fracture was obtained. This survey is a complex, multistage, probability sample of the US noninstitutionalized civilian population and was conducted between 1988 and 1994. A history of hip fracture was identified from the response to a questionnaire that was administered to all participants. There were 159 cases of hip fracture. There was a significantly increased likelihood of reporting a hip fracture in participants with estimated GFR <60 ml/min (odds ratio [OR] 2.12; 95% confidence interval [CI] 1.18 to 3.80). In younger participants (aged 50 to 74 yr), the prevalence of CKD was approximately three-fold higher in those with a history of hip fracture *versus* in those without a history of hip fracture (19.0 *versus* 6.2%, respectively; $P = 0.04$). In multivariate logistic regression analysis, only the presence of CKD (OR 2.32; 95% CI 1.13 to 4.74), a reported history of osteoporosis (OR 2.52; 95% CI 1.08 to 5.91), and low physical activity levels (OR 2.10; 95% CI 1.03 to 4.27) were associated with a history of hip fracture. There is a significant association between hip fracture and moderate to severe degrees of CKD, particularly in younger individuals, that is independent of traditional risk factors for hip fracture.

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Hip fracture is very common in patients with ESRD. The risk has been estimated to be 4.4 to 14 times greater than that of the general population (1,2). Moreover, hip fracture is associated with a substantial increase in mortality in the ESRD population (1,2). Although the associations and risk factors for hip fracture in patients with ESRD are widely known (2–5), considerably less information is available on the risk for hip fracture in patients with less severe chronic kidney disease (CKD).

CKD and hip fracture are important public health problems that share multiple risk factors. Both are more common in older individuals and patients with diabetes. In addition, CKD and low bone mineral density (BMD), a major risk factor for hip fracture, are highly coincident. A recent study estimated that the prevalence of mild to moderate kidney dysfunction was 60% for women and 45% for men with osteoporosis (5). The reasons for this are not clear. Patients with moderate to severe CKD have a range of disturbances of bone and mineral metabolism, including secondary hyperparathyroidism, low serum levels of active vitamin D metabolites, and metabolic acidosis. These abnormalities may adversely affect the normal processes of bone remodeling, resulting in disruption of the skeletal microarchitecture and reduced bone quality and strength, and therefore might be expected to increase the risk for fracture. However, in patients with ESRD, in whom these metabolic derangements are more profound, risk factors for hip fracture are similar to those in the general population and include increasing age, female gender, white race, and low body mass index, rather than hyperparathyroidism or vitamin D deficiency (4). Similarly, in patients with CKD, Hsu *et al.* (6) reported that low hip BMD was related to traditional risk factors for osteoporosis, principally gender, weight, and age, rather than to kidney function.

Current epidemiologic evidence indicates that in the past decade, an epidemic of kidney disease has occurred, with a worldwide doubling in CKD incidence and prevalence (7,8). A previous analysis of the Third National Health and Nutrition Examination Survey (NHANES III) demonstrated that CKD, as defined by a GFR of <60 ml/min, affects approximately 8 million adults in the United States alone (9). From 2000 to 2015, the prevalence of ESRD is expected to increase by 70% (10). Gullberg *et al.* (11) reported similarly alarming projections for hip fracture, estimating that the number of hip fractures worldwide will double to 2.6 million by 2025. These disturbing demographic trends highlight the importance of exploring possible associations between hip fracture and CKD.

Given the recognized association between hip fracture and ESRD, we hypothesized that individuals with moderate to severe CKD also may be at increased risk for hip fracture. On the basis of the work of Hsu *et al.* (6), we suspected that an increase in the rate of hip fracture in patients with decreased kidney function would be attributable to risk factors that are common to both CKD and hip fracture, such as diabetes, age, and

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weight. To test these hypotheses, we used NHANES III, a probability sampled cohort based on the noninstitutionalized US population. After application of specific sampling weights that accommodate the sampling method, the information from NHANES III is generalizable to the noninstitutionalized population of the United States. NHANES III includes information that permits assessment of kidney function, as well as measurements of BMD and self-reported history of hip fracture.

Materials and Methods

NHANES III Population

The design and the operation of NHANES III have been described in detail (12). Briefly, NHANES III provides cross-sectional, nationally representative data on the health and nutritional status of the civilian, noninstitutionalized US population. To achieve this, a four-stage sampling design was used: (*1*) Primary sampling units that comprised mostly single counties, (*2*) area segments within the primary sampling units, (*3*) households within area segments, and (*4*) people within households. NHANES III oversampled older, Mexican American, and non-Hispanic black individuals to obtain reliable estimates in these groups. All survey participants were examined in a mobile examination center (MEC) or at home when they were unable to travel to the MEC.

Ascertainment of Hip Fracture and BMD

A history of hip fracture was assessed through the administration of a questionnaire by trained field staff. Participants were asked the question, "Has a doctor ever said you had a broken/fractured hip?"

BMD of the proximal femur was determined by dual-energy x-ray absorptiometry (DXA) scan at five regions: Femoral neck, trochanter, intertrochanter, total femur, and Ward's triangle. We chose femoral neck BMD as the main measurement of hip BMD in our analysis because this region is most predictive for hip fracture (13,14). Femoral neck BMD was classified according to the World Health Organization (WHO) criteria for the diagnosis of osteoporosis in postmenopausal white women (15) (≥2.5 SD below the gender-specific age 20 to 29 reference mean) and osteopenia (1 to 2.5 SD below the gender-specific age 20 to 29 reference mean). For women, osteoporosis was considered present at a BMD <0.64 g/cm^2 and osteopenia at a BMD between 0.64 and 0.82 g/cm^2; BMD >0.82 g/cm^2 was considered normal. For men, osteoporosis was considered present when the BMD was <0.68 g/cm^2 and osteopenia at a BMD between 0.68 and 0.90 g/cm^2; BMD >0.90 g/cm^2 was considered normal.

Ascertainment of Kidney Function

All NHANES III participants who were 12 yr and older were eligible for measurement of a biochemical panel that included serum creatinine measured by the Jaffe reaction. We chose to use the Modification of Diet in Renal Disease (MDRD) formula to calculate the estimated GFR (eGFR), the primary measure of kidney function in this analysis, because it is a more accurate measure of kidney function than other formulas (16):

$$\text{GFR (ml/min)} = 186.3 \times \text{serum creatinine}^{-1.154} \times \text{age}^{-0.203} \times 0.742 \text{ (if female)} \times 1.21 \text{ (if black)} \quad (1)$$

Before entry into the MDRD formula, serum creatinine values were adjusted to correct for calibration differences between the MDRD Study and NHANES III (17). For this study, we were interested in evaluating the association between moderate to severe CKD, as defined by an eGFR between 15 and 60 ml/min, and reported hip fracture prevalence rates. We therefore compared participants who had an eGFR between 15 and 60 ml/min with those with an eGFR >60 ml/min (Table 1). Patients with ESRD, defined as an eGFR <15 ml/min, were excluded from this analysis because they were not the primary focus of this study. Because our primary goal was to investigate the association between moderate to severe CKD and hip fracture in older adults in whom osteoporosis and CKD are highly co-prevalent, no exploratory analyses were performed for individuals who were younger than 20 yr. In addition, we restricted the population to participants who were 50 yr or older, because none of the 42 patients who were between ages 20 and 49 and had hip fracture met our criteria for CKD; 36 had eGFR >100 ml/min, and the remaining six had eGFR >60 ml/min.

Measurements of Vitamin D and Serum Vitamin A

Blood samples were collected at the MEC or at home when the participant was unable to travel to the MEC. Vitamin D samples were obtained from fresh or frozen serum. Frozen serum was stored at -20°C. Samples were analyzed for 25-hydroxyvitamin D (25-OHD) at the NHANES laboratory facilities by the INCSTAR 25-OHD assay. This is a two-step procedure in which 25-OHD and other hydroxylated metabolites first are extracted from the serum or plasma with acetonitrile. After extraction, the treated sample is assayed for 25-OHD by RIA.

Vitamin A levels were measured in fasting serum samples that were protected from exposure to light. Samples were frozen at -70°C and transported to NHANES laboratory facilities for measurement of vitamin A levels by isocratic HPLC.

Ascertainment of Covariates

Data on covariates were obtained from the NHANES III patient interview and the 24-h dietary recall. Confounders were selected on the basis of epidemiologic studies that demonstrated their ability to predict femoral neck BMD and hip fracture risk in both the general and ESRD populations (2,4,18–25). These included age (years), race/ethnicity (defined as non-Hispanic white, non-Hispanic black, Mexican American, and other), current estrogen use (oral or transdermal), diuretic use (thiazide and nonthiazide), dietary calcium intake (reported in mg), alcohol consumption (reported in g), dietary vitamin A intake (reported in IU), plasma concentrations of vitamin A (μg/ml), plasma concentrations of 25-OHD (ng/ml), plasma concentrations of calcium (mg/dl) and phosphorous (mg/dl), history of type 2 diabetes, history of osteoporosis, menopausal status (last period >1 yr ago), tobacco use (current tobacco use *versus* no current tobacco use), a history of maternal hip fracture, weight (kg), femoral neck BMD (reported in g/cm^2), and activity level (self-reported as below average, average, or above average).

Generation of Propensity Scores

This study was designed to measure the association of kidney function with hip fracture prevalence rates in older adults. Abnormal kidney function was defined as having an eGFR between 15 and 60 ml/min. The baseline covariates that are independent predictors of hip fracture were unevenly distributed between the groups with and without CKD (Table 1). We therefore developed a model to balance these differences in the covariate structure of the primary independent predictor of interest to derive an unbiased estimate of the effect of kidney dysfunction on hip fracture prevalence rates. A logistic regression model was created with abnormal kidney function as the outcome variable. Independent variables that were entered into the model included established risk factors for osteoporosis: Age, weight, race/ethnicity (as defined above), history of type 2 diabetes, menopausal status (last period >1 yr ago), personal history of osteoporosis, current

Table 1. Baseline population characteristics for the NHANES III[a]

Variable	Kidney Disease			No Kidney Disease			*P*
	n/N	Parameter Estimate	SE	*n/N*	Parameter Estimate	SE	
Demographics							
age (yr; mean)	875/6270	73.9	0.5	5395/6270	63.4	0.3	<0.0001
female gender (%)	493/875	61.8	2.6	2782/5395	54.17	0.7	0.01
race/ethnicity (%)							<0.0001
non-Hispanic white	637/875	86.8	2.1	2989/5395	83.0	1.3	
non-Hispanic black	145/875	7.6	0.9	1081/5395	7.9	0.6	
Hispanic	72/875	1.0	0.2	1123/5395	2.9	0.2	
other	21/875	4.6	2.0	202/5395	6.2	1.1	
Medications and nutrition							
estrogen use (%)	26/875	5.2	1.7	364/5395	9.4	0.6	0.01
diuretic use (thiazides and nonthiazides) (%)	356/768	48.2	2.5	836/3385	22.4	1.2	<0.0001
dietary calcium (mg; mean)	751/5753	664.9	21.0	5002/5753	770.0	12.6	0.0001
dietary alcohol (g; mean)	751/5753	2.4	1.0	5002/5753	7.2	0.7	0.0001
dietary vitamin A (IU; mean)	751/5753	7547.6	336.0	5002/5753	7775.9	216.8	0.59
serum vitamin A (μg/ml; mean)	874/6240	2.6	0.03	5366/6240	2.2	0.02	<0.0001
serum vitamin D (ng/ml; mean)	819/6065	27.8	0.5	5246/6065	28.1	0.3	0.59
serum calcium (mg/dl; mean)	875/6269	9.4	0.03	5394/6269	9.3	0.02	0.0001
serum phosphorus (mg/dl; mean)	875/6270	3.5	0.02	5395/6270	3.4	0.01	<0.0001
serum alkaline phosphatase (U/L; mean)	875/6269	95.8	1.5	5394/6269	90.1	1.2	0.002
Medical history							
diabetes (%)	178/875	16.5	1.3	712/5389	9.6	0.5	<0.0001
osteoporosis (%)	60/871	9.2	1.5	192/5372	4.3	0.4	0.003
postmenopausal status (%)	419/422	99.0	0.7	2430/2610	90.8	1.0	<0.0001
tobacco use (%)	119/181	65.9	5.4	1172/1506	75.4	1.7	0.10
history of hip fracture in mother (%)	50/846	6.0	1.3	390/5193	9.0	0.5	0.06
Body measurements and activity							
weight (kg; mean)	873/6255	73.5	0.8	5382/6255	76.0	0.3	0.001
femoral neck BMD (g/cm^2; mean)	767/5936	0.690	0.01	5169/5936	0.740	0.00	<0.0001
activity level (%)							0.03
high	300/841	37.2	2.8	2030/5276	42.0	1.1	
average	365/841	43.3	2.9	2307/5276	42.4	1.1	
low	176/841	19.5	1.4	930/5276	15.6	0.7	

[a]BMD, bone mineral density; NHANES III, Third National Health and Nutrition and Examination Survey.

estrogen usage (oral or transdermal), diuretic usage (thiazide and nonthiazide), dietary calcium intake, serum vitamin A level, tobacco use, alcohol consumption, a history of maternal hip fracture, activity level (self-reported as below average, average, and above average), and their first-order interaction terms. We also included six independent variables that have no relation to either CKD or hip fracture. Extraneous variables were added to the development of the propensity score as recommended by Robbins *et al.* (26) to improve both efficiency and bias. These included duration of residence at the present address, history of enlistment in the armed forces, type of drinking water used (tap *versus* bottled), the presence of pets at home, the type of furnace used in the home (hot air *versus* not hot air), and the type of cooking stove used at home (gas *versus* not gas). These terms and their first-order interactions with other predictors of interest were included in the propensity score model. All missing information was imputed into the propensity score model to create an information-matched approach. Propensity scores then were included, as a continuous variable, in the final logistic regression model of the association between hip fracture and CKD. In this study, propensity score defines the likelihood that an individual participant is a CKD case.

Statistical Analyses

NHANES III is a cross-sectional study of the US population that was conducted from 1988 to 1994. It was not a random sample, and individuals had different probabilities of being selected. Elderly, non-Hispanic black, and Mexican American individuals were oversampled. Sample weights therefore are used to obtain weighted estimates from the population. The sample weights are adjusted for noncoverage and nonresponse. The final results then are generalizable to the noninstitutionalized US population.

Initial statistical analyses were conducted using SAS v9.1 (SAS Institute, Cary, NC). Subsequent analyses used SUDAAN (version 8.0.2; Research Triangle Institute, Research Triangle Park, NC) to obtain accurate variance estimates secondary to the complex sampling design. All propensity scores were generated in SUDAAN.

The association of interest was the effect of CKD on the prevalence of hip fracture. As described above, propensity scores were generated to balance the covariate structure of participants with and without CKD, and these probability estimates were included in the final logistic regression model. Covariates that were included in the multivariate model were selected on the basis of significant predictors that were derived from the univariate logistic regression models. The referent category of kidney function in the categorical models was an eGFR >60 ml/min. We chose this level as the referent *a priori* because kidney disease complications typically begin after the GFR has decreased to <60% of normal, and kidney biopsy series have indicated that kidney-related bone disease is apparent at mild levels of kidney dysfunction (27,28).

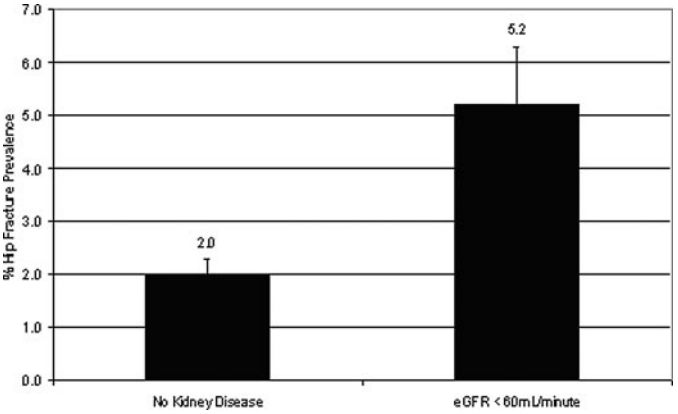

Figure 1. Prevalence of hip fracture among Third National Health and Nutrition Examination Survey (NHANES III) participants with and without kidney disease.

Results

A total of 6270 participants who were older than 50 yr both (*1*) had sufficient information to calculate an eGFR and (*2*) had responded to the hip fracture questionnaire. This group included 159 participants with a history of hip fracture. CKD, as defined by an eGFR 15 to 60 ml/min, was present in 875 (14.0%) of the participants. Serum creatinine ranged between 0.7 and 2.9 mg/dl in the participants who reported a hip fracture; 42 of these participants had an eGFR <60 ml/min. There were no hip fractures in the group of participants with an eGFR <20 ml/min.

In Table 1, we compare various characteristics between the two groups of participants: Those with CKD, as defined by an eGFR between 15 and 60 ml/min and those without CKD, as defined by an eGFR >60 ml/min. As a group, participants with CKD differed significantly in several respects from those without CKD. With regard to demographic characteristics, the CKD group was significantly older, included more women, and was more likely to be of non-Hispanic white race/ethnicity. Although more of the women were postmenopausal, fewer were taking estrogen replacement therapy. Other differences between the groups included a higher prevalence of diabetes and osteoporosis. Body weight, activity level, and femoral neck BMD also were lower in the CKD group.

The prevalence of hip fracture was 2.0% in participants without CKD and 5.2% in those with CKD ($P = 0.007$; Figure 1). To evaluate further the association between hip fracture and kidney dysfunction, we assessed the relationship between self-reported hip fracture prevalence and categories of eGFR (Figure 2). An eGFR <60 ml/min was associated with a significant two-fold increase in the likelihood of reporting a previous hip fracture (odds ratio [OR] 2.12; 95% confidence interval [CI] 1.18 to 3.80). In contrast, there were no significant associations between hip fracture prevalence rates and kidney function when eGFR was >60 ml/min.

We also noted a higher prevalence of CKD among participants with a reported history of hip fracture than among the NHANES III population as a whole. Although only 14.0% of the NHANES III participants had an eGFR <60 ml/min, they accounted for 24.3% (SE ± 4.9) of 159 participants with a history of hip fracture.

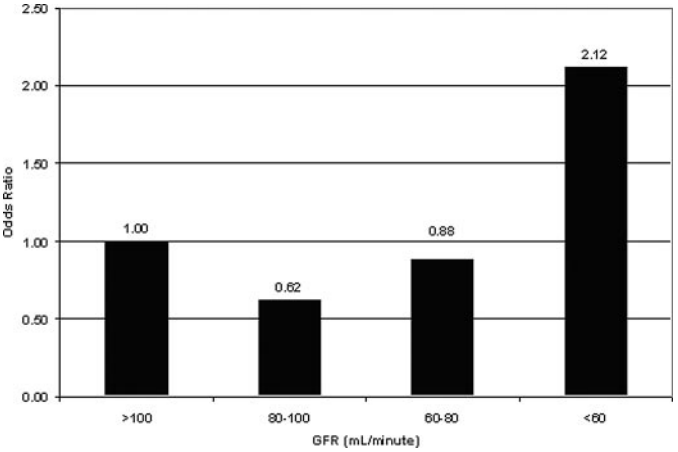

Figure 2. Association between a reported history of hip fracture and GFR in NHANES III participants.

It is interesting that when the demographic characteristics of the hip fracture populations were evaluated, there was an association among age, history of hip fracture, and prevalence of CKD (Figure 3). In younger participants (aged 50 to 74), the prevalence of CKD was approximately three-fold higher in the group with a history of hip fracture than in the group without a hip fracture (19.0 *versus* 6.2%; $P < 0.04$). However, in older participants (older than 75 yr), the prevalence of CKD was the same regardless of hip fracture history (32.1 *versus* 32.2%; $P = 1.0$).

The results of the univariate analysis are displayed in Table 2. Renal function, whether analyzed as a continuous variable (serum creatinine in mg/dl or eGFR in ml/min) or a categorical variable (eGFR <60 ml/min), was strongly associated with an increased prevalence of hip fracture. Other variables that were associated with increased prevalence of hip fracture included several traditional risk factors for osteoporotic fractures, such as increasing age, female gender, a history of maternal hip

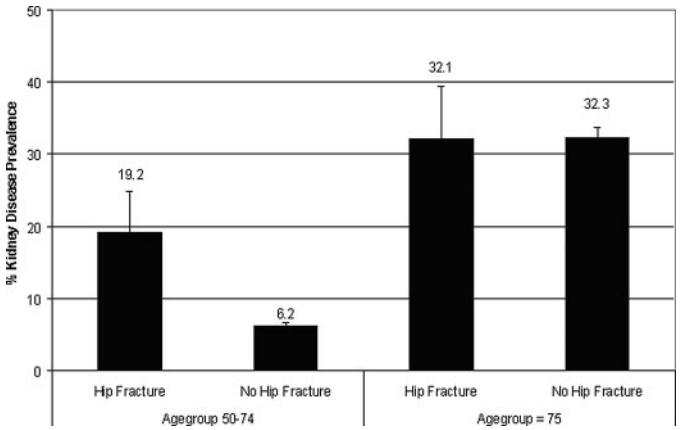

Figure 3. Prevalence of kidney disease in NHANES III participants stratified by age group and hip fracture status.

fracture, a history of osteoporosis, femoral neck BMD that met WHO criteria for osteoporosis, and low activity levels. Other race was protective against hip fracture. Increasing propensity score was associated with an increasing association with hip fracture, indicating that the likelihood of being a hip fracture case increased as the likelihood of being a CKD case increased. We also created bivariate models to evaluate potential modifying effects of risk factors for hip fracture on CKD (data not shown). All bivariate models confirmed the positive association between CKD and hip fracture prevalence. Only age, weight, a history of osteoporosis, and low BMD on the basis of WHO criteria reduced the association between CKD and hip fracture. However, even when these factors were considered, CKD remained strongly associated with hip fracture in these models.

The multivariate model, presented in Table 3, was constructed by including CKD, the independent predictor of interest, and propensity score, the covariate-balancing variable. CKD remained significantly associated with hip fracture (OR 2.32; 95% CI 1.13 to 4.74) after controlling for other predictors of hip fracture. In the multivariate model, only CKD, a history of osteoporosis, and low activity levels remained significantly associated with hip fracture prevalence. The propensity score variable was no longer significantly associated with hip fracture after adjustment for the main independent predictors.

Discussion

In this study of 6270 NHANES III participants, there was a 2.3-fold increase in the association of hip fracture with moderate to severe kidney dysfunction. In addition, we found that the prevalence of CKD was increased in those who reported a hip fracture. Furthermore, the co-prevalence of CKD and hip fracture was even more remarkable in participants who were aged 50 to 74 yr than it was in those who were older than 74 yr. In the younger group, the prevalence of CKD was approximately three-fold higher in those with than in those without a history of hip fracture. The association between hip fracture and CKD was strengthened further by the use of a balancing variable in the logistic model to control for differences in important risk factors for hip fracture between the CKD and non-CKD groups.

The high prevalence of kidney dysfunction in the NHANES III hip fracture population is consistent with recently published data indicating high prevalence rates of kidney dysfunction in patients who meet WHO criteria for both osteoporosis and osteopenia at the femoral neck. Using NHANES III, Klawansky *et al.* (5) reported that the prevalence of mild to moderate kidney failure (GFR of 35 to 60 ml/min) was 33.5% for women and 16.4% for men with osteopenia. Similarly, the prevalence of mild to moderate kidney failure was even higher in participants with osteoporosis, 61.3% for women and 46.5% for men. When more severe degrees of renal dysfunction (GFR <35 ml/min) were included in the prevalence estimates, approximately 85% of women and 57% of men with osteoporosis had some degree of renal dysfunction. In both men and women, the prevalence of renal dysfunction was low in younger age groups and rose precipitously with advancing age (5). Because low femoral neck BMD is an important risk factor for hip fracture and BMD decreases with increasing age, it is not surprising that we also observed a relationship between renal dysfunction and hip fracture. However, we also noted that in NHANES III participants with a history of hip fracture, there was a greater association between hip fracture and CKD in the younger age group. This observation may suggest that CKD plays a greater role in altering bone architecture and reducing bone strength in younger than in older age groups, when other traditional risk factors for hip fracture become more prevalent. Longitudinal studies on the role of CKD in the pathogenesis of hip fracture are needed to confirm this hypothesis.

Although there are no previously published reports of an independent association between hip fracture and moderate to severe degrees of CKD, our results are consistent with those that are available on the risk for hip fracture in the ESRD population. Alem *et al.* (3) demonstrated that patients with ESRD have a four-fold increase in hip fracture risk compared with the general population. Similarly, Coco *et al.* (2) reported that patients with ESRD had a standardized fracture rate that was 17.4 times that of the general population. The association that we observed between hip fracture and moderate to severe kidney failure was considerably lower than that between hip fracture and ESRD. This is not surprising, given that the metabolic disturbances in patients with moderate to severe kidney failure are not as severe as in patients with ESRD. Our results also are consistent with the literature on risk factors for hip fracture in the general population. We found that traditional risk factors for hip fracture, including increasing age, female gender, non-Hispanic white race/ethnicity, history of osteoporosis, history of maternal hip fracture, decreasing body weight, femoral neck osteoporosis, and low activity levels, also were associated with increasing risk for hip fracture in the univariate analysis. Notably, however, bivariate models indicated that CKD attenuated the association between these risk factors and hip fracture, and multivariate adjustment confirmed that CKD is potently associated with hip fracture. In this regard, only a previous history of osteoporosis and low self-reported activity levels remained significantly associated with hip fracture after multivariate adjustment.

BMD is a strong predictor of hip fracture in the general

Table 2. Univariate logistic regression models for risk factors of hip fracture[a]

Variable	OR	95% CI
Propensity score	5.30	2.81 to 9.98
Kidney disease		
serum creatinine (per 1-mg/dl increase)	1.26	1.01 to 1.59
GFR (per 10-ml/min increase)	0.87	0.78 to 0.96
GFR <60 ml/min	2.72	1.63 to 4.56
Demographics		
age (per 10-yr interval)	1.92	1.64 to 2.24
gender		
male	Reference	
female	1.59	1.05 to 2.42
race/ethnicity		
non-Hispanic white	Reference	
non-Hispanic black	0.50	0.24 to 1.03
Hispanic	0.89	0.50 to 1.61
other	0.33	0.14 to 0.76
Medical history		
diabetes (yes *versus* no)	0.70	0.33 to 1.46
history of osteoporosis (yes *versus* no)	3.44	1.74 to 6.83
postmenopausal status (yes *versus* no)	1.97	0.48 to 8.12
tobacco use (yes *versus* no)	1.76	0.56 to 5.58
history of hip fracture in mother (yes *versus* no)	1.88	1.04 to 3.42
Medications and nutrition		
estrogen use (yes *versus* no)	1.04	0.54 to 1.99
diuretic use (yes *versus* no)	1.25	0.76 to 2.05
dietary calcium (mg)	1.00	1.00 to 1.00
dietary alcohol (g)	1.00	0.99 to 1.01
dietary vitamin A (IU)	1.00	1.00 to 1.00
serum vitamin A (μg/ml)	1.08	0.72 to 1.64
serum vitamin D (ng/ml)	0.98	0.96 to 1.00
serum calcium (mg/dl)	1.14	0.87 to 1.49
serum phosphorus (mg/dl)	1.41	0.93 to 2.13
serum alkaline phosphatase (U/L)	1.00	1.00 to 1.01
Body measurements and activity		
weight (kg)	0.97	0.95 to 0.98
WHO BMD categories		
normal	Reference	
osteopenia	1.13	0.43 to 3.00
osteoporosis	3.49	1.28 to 9.51
activity level		
high	Reference	
medium	1.28	0.78 to 2.08
low	2.12	1.21 to 3.68

[a]CI, confidence interval; OR, odds ratio; WHO, World Health Organization.

population; therefore, the absence of an association between hip fracture and BMD in the multivariate model is noteworthy. However, although measurement of BMD by DXA provides an assessment of the amount of bone mass, it does not provide information on bone remodeling activity or bone quality or distinguish among the various possible metabolic processes that could affect the structural integrity of the skeleton in patients with CKD (29,30). Therefore DXA is not a robust predictor of risk for hip fracture in patients with CKD. Moreover, our data are in agreement with the observations of Hsu *et al.* (6). Using NHANES III, these investigators found that patients with renal dysfunction had significantly lower femoral BMD. However, after adjustment for age, weight, and gender, the negative association between renal function and BMD was extinguished. In contrast, Yendt *et al.* (31,32) observed that BMD at both the one-third radius and lumbar spine was asso-

Table 3. Multivariate logistic regression for the association between hip fracture and kidney disease[a]

Variable	OR	95% CI
Propensity score	0.49	0.09 to 2.77
Kidney disease (eGFR <60 ml/min)	2.32	1.13 to 4.74
Age (per 10-yr interval)	1.48	0.97 to 2.28
Gender		
male	Reference	
female	0.76	0.44 to 1.31
Race/ethnicity		
non-Hispanic white	Reference	
non-Hispanic black	0.86	0.36 to 2.04
Hispanic	1.51	0.59 to 3.88
other	0.49	0.15 to 1.58
History of osteoporosis	2.52	1.08 to 5.91
Activity level		
high	Reference	
medium	1.07	0.60 to 1.90
low	2.10	1.03 to 4.27
WHO BMD categories		
normal	Reference	
osteopenia	0.87	0.28 to 2.70
osteoporosis	1.93	0.53 to 7.01
History of hip fracture in mother	1.81	0.98 to 3.37
Weight (kg)	0.99	0.96 to 1.02

[a]eGFR, estimated GFR.

ciated with decreased creatinine clearance, assessed on a 24-h urine collection, and not with age. Because these investigators did not measure femoral BMD, it is not possible to compare their findings directly with those of Hsu *et al.* (6). However, their findings may be explained, in part, by the greater predominance of cortical bone at the one-third radius site than the femoral neck site and the particular susceptibility of cortical bone to the catabolic effects of excess parathyroid hormone secretion, even at minimally elevated levels (33).

In our study, the presence of CKD remained an important predictor of hip fracture prevalence despite controlling for strong hip fracture risk factors, including age, weight, low BMD, and a history of osteoporosis. These results are surprising in view of the power of these risk factors to predict hip fracture in both the general and ESRD populations (4,18,34,35). Because we could find no other reports of hip fracture risk in patients with CKD, we strongly encourage other investigators to evaluate this issue. One explanation for these results may be found in studies that suggest that low BMD is more closely related to renal function than age (31,32). Another explanation may be attributed to differences in study design. Whereas we directly compared participants with normal and abnormal kidney function, Stehman-Breen *et al.* (4), who evaluated risk factors for hip fracture among patients with ESRD, did not include a community-based control group for direct comparisons. Likewise, Atsumi *et al.* (22), who investigated risk factors for vertebral fractures in 187 male dialysis patients, did not include a control group with normal kidney function.

There are several limitations to this study. One potential pitfall was our measure of kidney function. The MDRD equation includes age, gender, and race in its calculation, which all are important risk factors for hip fracture. It is possible that entry of these variables into the MDRD formula could alter the association of CKD and the dependent variable or create interaction terms in our multivariate models. Also, the MDRD formula has not been well validated in geriatric populations and has been shown to overestimate the GFR of elderly individuals (36,37). Therefore, the association between CKD and hip fracture may have been biased depending on the direction of case misclassification. However, the substitution of serum creatinine for eGFR in the multivariate model did not significantly change the parameter estimates of any of the other independent variables. Serum creatinine trended toward an association with an elevated prevalence of hip fracture but lacked statistical significance (OR 1.26; 95% CI 0.96 to 1.64; data not shown). It is not surprising that the inclusion of serum creatinine in this multivariate model did not result in a significant association with hip fracture because it is less accurate than eGFR as a marker of kidney function. The inclusion of a continuous measure of eGFR in the multivariate model also was not significantly associated with a reported history of hip fracture (OR 0.93; 95% CI 0.83 to 1.05; data not shown). This also is not surprising because there were no reported fractures at an eGFR of <20 ml/min, and, therefore, hip fracture cases were not evenly distributed in the CKD group. Another limitation is that our predictor of interest, CKD, was based on an assessment that

was temporally related to the NHANES III study. Therefore, no information is available regarding the duration of kidney disease, making it impossible to assess the effect of age of onset or duration of CKD on hip fracture prevalence. This is in contrast to the assessment of hip fracture, which included all lifetime events. Ascertainment of hip fracture, our outcome variable, was determined by the participants' response to a questionnaire that asked whether they ever had a hip fracture. The question may be subject to recall and nonresponse bias and may result in misclassification of the data and bias of the results being either toward or away from the null hypothesis. However, it is unlikely that a hip fracture event would be forgotten or overlooked, because it is associated with substantial morbidity and mortality. In addition, although previous studies have demonstrated that low serum parathyroid hormone and vitamin K levels may be risk factors for fractures in patients with ESRD (2,4,22,38,39), we were unable to adjust for them in our analysis because they were not collected in NHANES III. Our estimate of the association between CKD and hip fracture may have been attenuated had we been able to include these parameters in our model. However, we used serum calcium, phosphorus, alkaline phosphatase, and 25-OHD levels as surrogates for secondary hyperparathyroidism, and they had no significant association with the outcome variable.

The presence of imbalances in the distribution of covariates between the abnormal and normal kidney function groups is another important limitation of this study. These imbalances favored the distribution of hip fracture risk factors into the abnormal kidney function group and might have had the effect of exaggerating the association between hip fracture and CKD. However, by including propensity scores, a method that may be used to balance covariates, we believe that we were able to correct for the inequalities in covariate structure. We created propensity scores that were information matched, meaning that imputation was performed to accommodate for missing information to allow these individuals to be included in the analysis. We believe that information matching has produced a more robust method of creating propensity scores because it takes into consideration all of the information provided for each individual. Finally, NHANES III is not a longitudinal study, and causality cannot be determined from this analysis. However, the prevalence estimates and the OR for the association between hip fracture and CKD suggest a strong association between the two processes.

Despite these limitations, there are several important strengths to this analysis. Application of the NHANES III sampling weights creates a database that is both large and generalizable to the noninstitutionalized US population. This makes it possible to derive reliable variance estimates for relatively rare events, such as hip fracture. We also were able to adjust our model for multiple imbalances in the distribution of covariates by using information-matched propensity scores. We believe that by using information matching, we were able to create a model that resembles more closely a randomized analysis method, because we were able to control for both known and unknown confounders.

These findings also highlight the need for further studies to determine optimal strategies for both hip fracture risk assessment and prevention in the CKD population. It is widely known that DXA does not assess fracture risk accurately in the CKD population, likely because this technology cannot distinguish among the differing bone microarchitectural and remodeling changes that occur secondary to various forms of renal osteodystrophy (ROD). BMD measurements, as measured by DXA, may be low, normal, or high in any form of ROD. Although CKD is highly co-prevalent with osteoporosis as measured by DXA (5), low DXA measurements may not signify osteoporosis in the setting of significant CKD (27,28). Standard therapies for osteoporosis often include calcium supplementation and bisphosphonates; both may be detrimental to patients with CKD. The decision to use bisphosphonates in these patients is particularly controversial because of the potential to induce low turnover bone disease. Although a recent study by Miller *et al.* (40) evaluated renal function–related adverse events and bone density and fracture data from nine clinical trials to demonstrate that risedronate can be used safely to treat osteoporosis in the presence of CKD, it still is unclear whether bisphosphonates precipitate adynamic bone disease in patients with CKD, particularly after long-term use in conjunction with accompanying slow declines in renal function. Until better noninvasive methods are developed, such as ultra-high-resolution peripheral quantitative computed tomography, to determine the bone microarchitectural changes in these patients, bone biopsy is the only definitive method to determine the cause of the bone abnormality and the best approach for prevention of hip fracture in this vulnerable population.

Our findings lead us to conclude that moderate to severe kidney failure is highly prevalent in the hip fracture population, particularly in individuals between the ages 50 and 74 yr, and that CKD is significantly associated with hip fracture risk. In addition, the contribution of kidney dysfunction to hip fracture risk is more potent than age, gender, race, family history, and weight. The degree to which this risk is attributable to metabolic derangements that may accompany moderate to severe CKD is unknown. Longitudinal studies that include more complete biochemical data and more robust measures of bone microarchitecture and quality are required to delineate the pathogenesis of the association between moderate to severe CKD and hip fracture.

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