Renal Function and Risk of Hip and Vertebral Fractures in Older Women

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Background: An increased rate of hip fractures has been reported in patients with end-stage renal disease, but the effect of less severe renal dysfunction on fracture risk is uncertain.

Methods: We conducted a case-cohort study within a cohort of 9704 women 65 years or older to compare baseline renal function (estimated glomerular filtration rate [eGFR] using the Cockcroft-Gault equation) in 149 women who subsequently had hip fractures and 150 women who subsequently had vertebral fractures with eGFR in 396 randomly selected women.

Results: In models adjusted for age, weight, and calcaneal bone density, decreasing eGFR was associated with increased risk of hip fracture. Compared with women with an eGFR 60 mL/min per 1.73 m² or greater, the hazard ratio (95% confidence interval [CI]) for hip fracture was 1.57 (95% CI, 0.89-2.76) in those with an eGFR 45 to 59 mL/min per 1.73 m² and 2.32 (95% CI, 1.15-4.68) in those with an eGFR less than 45 mL/min per 1.73 m² (P for trend = .02). In particular, women with a reduced eGFR were at increased risk of trochanteric hip fracture (adjusted hazard ratio, 3.93 [95% CI, 1.37-11.30] in women with an eGFR 45-59 mL/min per 1.73 m² and 7.17 [95% CI, 1.93-26.67] in women with an eGFR < 45 mL/min per 1.73 m²; P for trend = .004). Renal function was not independently associated with risk of vertebral fracture (adjusted odds ratio, 1.08 [95% CI, 0.61-1.92] in women with an eGFR 45-59 mL/min per 1.73 m² and 1.33 [95% CI, 0.63-2.80] in women with an eGFR < 45 mL/min per 1.73 m²; P for trend = .47).

Conclusion: Older women with moderate renal dysfunction are at increased risk of hip fracture.

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RENAL FUNCTION DECLINES with age. At least 20% of adults in the United States 65 years or older have evidence of moderate to severe chronic kidney disease as defined by an estimated glomerular filtration rate (eGFR) of 60 mL/min per 1.73 m² or less. An increased rate of hip fractures has been reported in patients with end-stage renal disease. However, the relationship between mild to moderate impairment in renal function and risk of fracture in community-dwelling older persons is uncertain.

To test the hypothesis that reduced renal function is associated with an increased risk of hip and vertebral fractures in older women, we conducted a case-cohort study within the Study of Osteoporotic Fractures, a prospective cohort study of 9704 community-dwelling women 65 years or older. We compared eGFR, calculated using the Cockcroft-Gault method, in women who experienced a first hip fracture and in women with incident vertebral fracture with that in randomly selected women from the same cohort.

METHODS

PARTICIPANTS

From September 1986 to October 1988, 9704 women who were 65 years or older were recruited for participation in the baseline examination of the prospective Study of Osteoporotic Fractures. Women were recruited from population-based listings in 4 areas of the United States—Baltimore (Maryland) County; Minneapolis, Minn; Portland, Ore; and Monongahela Valley, Pa. We excluded from the original cohort black women because of their low incidence of hip fracture, women who had undergone bilateral hip replacement, and those who were unable to walk without assistance. The protocol and consent form were approved by the institutional review boards at all participating institutions. All participants provided written informed consent.
SELECTION OF CASE AND COHORT SAMPLES

Using the case-cohort approach,7 we randomly selected 149 of 332 women in the cohort of 9704 who had a first hip fracture during a mean follow-up of 5.9 years after the baseline examination. Among these 149 women, there were 61 trochanteric fractures and 85 femoral neck fractures. Three of the fractures could not be specifically classified as a femoral neck or trochanteric fracture. Renal function in the women with hip fractures was compared with that in 396 women randomly selected from the cohort regardless of fracture status using the case-cohort approach. In this sample, there were 14 women who subsequently had a hip fracture and 3 women who had a hip fracture before the baseline examination. Thus, the number of women without hip fracture was 377 of 396 women in the cohort sample.

Similarly, we randomly selected 150 of 389 women who had a new vertebral fracture, defined by morphometry as a decrease in vertebral height between a baseline lateral spine radiograph and a follow-up lateral spine radiograph obtained, on average, 3.7 years later at the third examination. Because time to event was unknown, we used logistic regression models to compare renal function in women with vertebral fractures with that in women in the control group without incident vertebral fractures drawn from the pool of 396 women randomly selected from the cohort. Women in this pool who were found to have incident vertebral fractures (n=15) were analyzed as cases. In addition, we excluded 88 women (22 of whom died before the third examination) from the pool because of an incomplete set of baseline and follow-up radiographs. Thus, the number of women in the control group was 293 in the vertebral fracture analysis.

ASSESSMENT OF RENAL FUNCTION

Blood was collected between 2 AM and 8 PM after fasting or a nonfat breakfast. Serum samples were stored for up to 1 week at −20°C and shipped on dry ice for subsequent storage in liquid nitrogen at −190°C. After selection of the cases and random sample of the cohort 7 to 8 years after collection, samples were sent directly without thawing to the San Francisco VA Medical Center, where serum creatinine concentration was measured using an automated technique (Technicon SMAC analyzer; Technicon Corp, Tarrytown, NY) that utilized the alkaline picrate (Jaffe) reaction.6 The intra-assay coefficient of variation was 3%, and the interassay coefficient of variation was 5%. Estimated glomerular filtration rate in milliliters per minute was calculated using the Cockcroft-Gault method7 and was standardized for body surface area using the Dubois formula.8 We also performed secondary analyses using eGFR calculated by the 4-variable version of the Modification of Diet in Renal Disease (MDRD) index.9

ASCERTAINMENT OF FRACTURES

We contacted the participants every 4 months to ask whether they had sustained a fracture; more than 99% of these follow-up contacts were completed during 6 years of follow-up. Hip fractures including the location were confirmed by radiologic review of copied preoperative radiographs.10 A vertebral fracture was classified as having a prevalent fracture at baseline if any of the vertebral height ratios was 3 SDs or more below the normal mean for that vertebral level.11 Incident vertebral fractures were defined by morphometry as a decrease of 20% and at least 4 mm in any one of the vertebral heights between the baseline lateral spine radiograph and the follow-up lateral spine radiograph obtained, on average, 3.7 years later.11

OTHER MEASUREMENTS

Participants completed a self-administered questionnaire and were interviewed and examined at the clinical centers. Women were asked about health status, smoking status, estrogen use, the presence of diabetes mellitus, previous fractures since age 50 years, walking for exercise, and falls within the past year. Weight was recorded with a balance beam scale. Tests of neuromuscular function included the ability to rise from a chair 5 times without using the arms. Bone mineral density (BMD) of the calcaneus was measured using single-photon absorptiometry at the baseline examination, and BMD at the lumbar spine and femoral neck was measured using dual-energy x-ray absorptiometry at the second examination, on average, 2.2 years after baseline. Details of the BMD measurement methods and precision are published elsewhere.12,13 Serum parathyroid hormone concentration was measured by immunoradiometric assay, and serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D concentrations by radioimmunoassay at the same laboratory that measured the serum creatinine concentration.14

STATISTICAL ANALYSIS

Categories of eGFR as calculated by the Cockcroft-Gault method were defined using a modified National Kidney Foundation classification of chronic kidney disease.13 Proportional hazards models that consider the case-cohort sampling design7 were used to analyze the association between eGFR and hip fracture. Logistic regression models were used to analyze the relationship between eGFR and vertebral fractures. The relative risk, approximated as hazard ratios or odds ratios, of fracture with 95% confidence intervals (CIs) was estimated for women with a mild decrease in eGFR (45-59 mL/min per 1.73 m2) and those with a moderate decrease in eGFR (<45 mL/min per 1.73 m2) using women with normal eGFR (≥60 mL/min per 1.73 m2) as the referent group.

Models were initially adjusted for age, and were further adjusted for body weight and calcaneal BMD. We tested for the possibility of an interaction between calcaneal BMD and eGFR for the prediction of risk of each fracture outcome. To obtain multivariable risk estimates for each fracture outcome, we subsequently added covariates to models that included age, body weight, and calcaneal BMD as predictors. Covariates included known risk factors for hip and vertebral fractures in our cohort.16 Tests for trend were performed by including eGFR (ordinal variable with 3 levels) as an independent variable in the models.

In additional analyses, renal function was expressed by eGFR calculated using the Cockcroft-Gault equation without adjustment for body surface area. Because the findings from these secondary analyses were similar, results from the primary analyses are presented. Renal function was also expressed by eGFR calculated using the 4-variable version of the MDRD index.9 In addition, analyses were performed replacing calcaneal BMD with femoral neck BMD (hip fracture models) and spine BMD (spine fracture models).

To determine whether the association between lower eGFR and risk of hip fracture varied by fracture location, we analyzed the association between eGFR and risk of trochanteric fracture and between eGFR and risk of femoral neck fracture. To assess whether any relationship between lower eGFR and risk of hip fracture might be explained by abnormalities in calcitropic hormones, we added levels of serum parathyroid hormone, serum 25-hydroxyvitamin D, and serum 1,25-dihydroxyvitamin D one at a time to hip fracture models.
In the random sample of the cohort (n=396), eGFR, as calculated by the Cockcroft-Gault method, was less than 45 mL/min per 1.73 m² in 77 women (19%), 45 to 59 mL/min per 1.73 m² in 109 women (28%), and 60 mL/min per 1.73 m² or greater in 210 women (53%). Among this sample, the 88 women who did not undergo repeat spine radiography 3.7 years later tended to be older (74 vs 72 years; P=.001), have slightly lower eGFR (60 vs 65 mL/min per 1.73 m²; P=.04), and were more likely to report poor to fair health status (32% vs 15%; P<.001) compared with the 308 women with a complete set of baseline and follow-up spine radiographs. Characteristics of women with first hip or vertebral fractures and women without fracture of the specified type are given in Table 1.

RENAI FUNCTION AND RISK OF HIP FRACTURE

After adjustment for age, decreasing eGFR, as calculated by the Cockcroft-Gault method, was associated with increasing risk of first hip fracture (P for trend <.001; Figure 1). While this association was partially mediated by lower body weight and BMD in those women with lower eGFR, the trend remained significant (P=.02). Compared with women with eGFR of 60 mL/min per 1.73 m² or greater, the hazard ratio (95% CI) adjusted for age, weight, and calcaneal BMD for hip fracture was 2.32 (95% CI, 1.15-4.68) in those with eGFR less than 45 mL/min per 1.73 m² and 1.91 (95% CI, 1.01-3.62) in those with eGFR of 45 to 59 mL/min per 1.73 m². There was no evidence of an interaction between eGFR and calcaneal BMD per 1.73 m² and 1.57 (95% CI, 0.89-2.76) in those with eGFR of 45 to 59 mL/min per 1.73 m². There was no evidence of an interaction between eGFR and calcaneal BMD.
for the prediction of risk of hip fracture ($P=.79$ for interaction term). After adjustment for multiple potential confounders, the association was similar but the trend did not reach significance ($P=.09$). Substituting femoral neck BMD for calcaneal BMD or further adjustment for serum parathyroid hormone, 25-hydroxyvitamin D, or 1,25-dihydroxyvitamin D level did not change the findings.

In particular, women with lower eGFR were at increased risk of trochanteric fracture (Table 2). Despite adjustment for several potential confounders, the risk of trochanteric fracture was increased 5-fold (95% CI, 1.4-18.45) in women with an eGFR less than 45 mL/min per 1.73 m$^2$ and 3.7-fold (95% CI, 1.2-11.2) in women with an eGFR 45 to 59 mL/min per 1.73 m$^2$ compared with that in women with an eGFR 60 mL/min per 1.73 m$^2$ or greater ($P$ for trend $= .02$). Women with lower eGFRs also appeared to be at increased risk of femoral neck fracture. However, the association was weaker compared with that for trochanteric fracture and did not reach significance after adjustment for factors other than age.

Although there appeared to be a relationship between impaired renal function and increased risk of hip fracture when renal function was expressed by eGFR calculated using the MDRD index, the hazard ratios were smaller and did not reach statistical significance. Hazard ratios adjusted for age, weight, and calcaneal BMD were 1.58 (95% CI, 0.59-4.23) in women with an eGFR less than 45 mL/min per 1.73 m$^2$ and 1.49 (95% CI, 0.93-2.38) in women with an eGFR 45 to 59 mL/min per 1.73 m$^2$ ($P$ for trend $= .09$).

### Table 2. Association Between Renal Function and Risk of Hip Fracture According to Fracture Location

<table>
<thead>
<tr>
<th>Hazard Ratio for Hip Fracture</th>
<th>$&lt;$45</th>
<th>45-59</th>
<th>$\geq$60</th>
<th>$P$ for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trochanteric fracture (n = 61)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted for age</td>
<td>5.73 (2.35-13.96)</td>
<td>3.31 (1.44-7.62)</td>
<td>1.00</td>
<td>$&lt;.001$</td>
</tr>
<tr>
<td>Adjusted for age, weight, and calcaneal BMD</td>
<td>7.17 (1.93-26.67)</td>
<td>3.93 (1.37-11.30)</td>
<td>1.00</td>
<td>.004</td>
</tr>
<tr>
<td>Final model*</td>
<td>5.04 (1.38-18.45)</td>
<td>3.69 (1.21-11.24)</td>
<td>1.00</td>
<td>.02</td>
</tr>
<tr>
<td>Femoral neck fracture (n = 85)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted for age</td>
<td>2.30 (1.23-4.28)</td>
<td>1.42 (0.78-2.60)</td>
<td>1.00</td>
<td>.01</td>
</tr>
<tr>
<td>Adjusted for age, weight, and calcaneal BMD</td>
<td>1.55 (0.70-3.40)</td>
<td>1.11 (0.58-2.15)</td>
<td>1.00</td>
<td>.28</td>
</tr>
<tr>
<td>Final model*</td>
<td>1.41 (0.59-3.36)</td>
<td>1.24 (0.60-2.56)</td>
<td>1.00</td>
<td>.43</td>
</tr>
</tbody>
</table>

Abbreviations: BMD, bone mineral density; CI, confidence interval; eGFR, estimated glomerular filtration rate.

*Adjusted for age, health status, smoking status, walking for exercise, history of falls, the presence of diabetes mellitus, previous fracture since age 50 years, weight, inability to rise from a chair, and calcaneal BMD.

Decreasing eGFR was associated with increasing age-adjusted risk of new vertebral fracture ($P=.01$; Figure 2). The association between lower eGFR and increased risk of incident vertebral fracture seemed to be primarily explained by lower body weight and lower BMD in women with impaired renal function. The odds ratio adjusted for age, weight, and calcaneal BMD was 1.33 (95% CI, 0.63-2.80) in women with an eGFR less than 45 mL/min per 1.73 m$^2$ and 1.08 (95% CI, 0.61-1.92) in women with an eGFR 45 to 59 mL/min per 1.73 m$^2$ compared with women with an eGFR 60 mL/min per 1.73 m$^2$ or greater ($P$ for trend $= .47$). Results were not substantially altered after further adjustment for other potential confounders or when spine BMD was substituted for calcaneal BMD. There was no evidence of an interaction between eGFR and calcaneal BMD ($P=.99$ for interaction term) or between eGFR and prevalent vertebral fracture status ($P=.41$) for the prediction of risk of incident vertebral fracture.

When renal function was expressed by eGFR calculated using the MDRD index, there was no evidence of an association between renal function and risk of vertebral fracture. Age-adjusted odds ratio was 0.73 (95% CI, 0.24-2.24) in women with an eGFR less than 45 mL/min per 1.73 m$^2$ and 0.75 (95% CI, 0.45-1.23) in women with an eGFR 45 to 59 mL/min per 1.73 m$^2$ ($P$ for trend $= .24$).
reduced renal function is not independent of traditional risk factors including age, body weight, and bone density.

To our knowledge, no previous longitudinal study has assessed the relationship between renal insufficiency and hip fracture risk in older women. Previous retrospective cohort studies have reported increased rates of hip fracture in patients undergoing dialysis\(^2,3\) and those who have received a renal transplant.\(^3,18\)

Reduced renal function in older women might be associated with higher rates of hip fracture for several reasons. Renal function may be a marker of other conditions that increase risk of hip fracture, although known risk factors, including advanced age, poorer health status, smoking, inactivity, history of falls, the presence of diabetes mellitus, previous fracture, low body weight, neuromuscular impairment, or lower bone density, did not entirely explain the higher rates of hip fracture in older women with reduced renal function. Abnormalities in phosphorus, calcium, and vitamin D metabolism that occur even in mild renal insufficiency may result in decreased formation of 1,25-dihydroxyvitamin D by the kidney, leading to decreased fractional calcium absorption, secondary hyperparathyroidism, greater bone resorption, and increased risk of hip fracture.\(^19-22\) In support of this hypothesis, a previous study in our cohort found an increased risk of hip fracture in older women with low serum 1,25-dihydroxyvitamin D levels.\(^23\) However, the association between reduced renal function and increased risk of hip fracture remained in our study despite controlling our analyses for levels of calcitropic hormones. Moderate impairment in renal function has also been associated with increased levels of inflammatory markers, homocysteine and procoagulant markers;\(^23-26\) as well as anemia\(^27,28\) and malnutrition.\(^29\) Any or a combination of these factors might mediate the increased risk of hip fracture observed with renal dysfunction.

Decreased renal function was most strongly associated with an increased risk of trochanteric hip fractures in our cohort. With advancing age, trochanteric fractures constitute an increasing proportion of hip fractures in white women.\(^30\) Previous studies comparing differences in risk factor patterns between femoral neck and trochanteric fractures\(^31,33\) have consistently reported that women with trochanteric fractures are more likely to be older, have poorer health status, and lower BMD. This constellation of risk factors suggests that an observed association between reduced renal function and trochanteric fractures in older women may reflect a higher likelihood of frailty in those with renal impairment.\(^34\) However, the association between renal function and trochanteric fractures persisted in our study despite adjustment for multiple correlates or components of frailty. While the association between reduced renal function and femoral neck fracture in our cohort failed to reach significance in adjusted models, lower renal production of 1,25-dihydroxyvitamin D in women with chronic ren-

nal insufficiency leading to secondary hyperparathyroidism may result in predominantly cortical bone loss that might preferentially increase the risk of femoral neck fractures.\(^35\)

Our results suggest that reduced renal function is not an independent risk factor for incident radiographic vertebral fractures in older women. Women with impaired renal function in our cohort seemed to be at increased risk of vertebral fracture primarily because of their older age and lower BMD. Previous studies of our cohort examining risk factors for hip and vertebral fractures\(^14,16,17\) have suggested that, while some factors such as advanced age and low BMD are strong predictors of both hip and vertebral fractures, other factors including physical frailty, poor health, neuromuscular impairment, and low 1,25-dihydroxyvitamin D levels are only related to risk of hip fracture. In addition 22% of the women in the random sample of the cohort did not undergo the repeat spine radiography necessary for the identification of new vertebral fractures, usually because of poor health status or death in the interim period. Inasmuch as mean GFR at baseline was lower among women without a complete set of spine radiographs compared with those with a complete set, survival bias may partially explain the absence of an independent association between renal function and risk of vertebral fracture.

Our study has several strengths. Measurements were blinded to fracture outcome, and incident hip and vertebral fractures were validated by radiographs. Because the random sample in our study was representative of the entire cohort, many of the biases inherent in a retrospective study were averted.

Our study has several limitations. A direct measure of GFR was not available, and we relied on eGFR using a serum creatinine concentration–based equation (Cockcroft-Gault). Serum creatinine concentration alone is an unreliable measure of renal function in older persons, especially elderly women, because of decline in muscle mass and alteration in creatinine metabolism with age.\(^36,37\) Formulas based on creatinine concentration and other factors including the Cockcroft-Gault equation and the simplified MDRD equation are commonly used estimates of renal function. While it is controversial whether the MDRD equation is more accurate than the Cockcroft-Gault equation in estimating GFR,\(^38\) it is concerning that we did not find a similar association between reduced renal function and hip fracture in our cohort when eGFR was calculated using the abbreviated MDRD equation. Because the MDRD equation was derived in middle-aged adults without diabetes but with chronic kidney disease, the accuracy and reproducibility of the MDRD equation in our study population of older white women not selected on the basis of chronic kidney disease are uncertain. Although some studies\(^39,40\) have suggested that the Cockcroft-Gault equation is less accurate than the MDRD equation in older persons, others\(^41,42\) have questioned the superiority of the MDRD equation over the Cockcroft-Gault equation, especially in women 65 years or older.

In addition, any association between renal function as estimated by formulas that include terms for age, weight, or both, and the outcome of hip fracture risk may
be confounded by the strong relationships between these factors and risk of hip fracture. Levels of cystatin C, a serum measurement of renal function not dependent on age, sex, or muscle mass, were not determined in our study. While it is recognized that the level of serum cystatin C is superior to serum creatinine as a marker of kidney function, it is controversial whether the level of cystatin C predicts GFR better than serum creatinine concentration–based formulas, including the Cockcroft-Gault equation.

Controlling for BMD in our analyses may have biased our estimates of the association between renal function and fracture toward the null hypothesis. Inasmuch as the participants were older white women, our results may not apply to other population groups.

We conclude that older white community-dwelling women with moderate impairment in renal function are at increased risk of hip fracture, particularly trochanteric fractures. These findings suggest that clinicians should consider including renal function as part of the risk assessment for hip fracture in elderly women. Further research should examine whether more direct and sensitive measures of renal function are associated with rates of bone loss and fracture risk in older persons.

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Author Contributions: Ms Lui performed the statistical analyses and is independent of any commercial funder. She had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses. Study concept and design: Ensrud, Stone, Jamal, and Cummings. Acquisition of data: Ensrud, Stone, and Cummings. Analysis and interpretation of data: Ensrud, Lui, Taylor, Ishani, Shlipak, Stone, Cauley, Jamal, and Antoniucci. Drafting of the manuscript: Ensrud and Jamal. Critical revision of the manuscript for important intellectual content: Lui, Taylor, Ishani, Shlipak, Stone, Cauley, Jamal, Antoniucci, and Cummings. Statistical analysis: Lui, Taylor, and Stone.

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