Association of Kidney Function with Incident Hip Fracture in Older Adults

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Kidney dysfunction is associated with bone loss, and patients with ESRD have an increased risk for hip fracture. However, the association of mild to moderate kidney disease with hip fracture has not been studied previously. The association of kidney function with incident hip fracture was examined among participants in the Cardiovascular Health Study, a community-based cohort of older individuals. The primary measure of kidney function was serum cystatin C, a measure that does not depend on lean mass. Hip fractures were identified using *International Classification of Diseases, Ninth Revision* codes for hospitalizations. A total of 4699 individuals had cystatin C measured in 1992 to 1993 and did not have a hip fracture before cystatin C measurement. The association of kidney function with hip fracture was analyzed with Cox proportional hazards models. Analyses were conducted separately for men and women. After a mean follow-up of 7.1 yr, 195 incident hip fractures occurred in women and 79 occurred in men. Higher cystatin C levels were associated with a higher risk for fracture in women (hazard ratio [HR] 1.26; 95% confidence interval [CI] 1.14 to 1.38 per SD) and in men (HR 1.27; 95% CI 1.11 to 1.46). After multivariable adjustment, higher cystatin C levels were significantly associated with hip fracture in women (HR 1.16; 95% CI 1.01, 1.33) but not in men (HR 1.14; 95% CI 0.86 to 1.52), although the magnitude of the association was similar. Kidney dysfunction, as assessed by cystatin C, is associated with an increased risk for hip fracture. Further studies are needed to evaluate potential mediators of this relationship and to assess whether interventions can decrease this risk.

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Patients with ESRD are at increased risk for hip fracture (1). Chronic kidney disease (CKD) can affect bone metabolism in a number of ways, which could increase the risk for hip fracture. With decreasing GFR, 1,25 dihydroxyvitamin D [1,25 $(OH)_2$] levels decrease and parathyroid hormone (PTH) increases (2,3). Individuals with kidney disease also are more likely to have risk factors for bone loss, including diabetes, decreased physical activity, and increased homocysteine levels (2–7). Many of these risk factors develop early in kidney impairment.

Whether individuals with mild to moderate kidney disease are at increased risk for hip fracture is unclear. In a recent analysis of the Cardiovascular Health Study (CHS), we found that higher levels of cystatin C were associated with an increased rate of bone loss (8). In this study, we evaluated the association of kidney function with incident hip fracture in a community-based cohort of older individuals. We hypothesized that impaired kidney function would predict incident hip fracture.

Materials and Methods

Participants

The study participants were enrolled in the CHS, a prospective, longitudinal study of older community-dwelling adults. The study methods have been described previously in detail (9). In brief, CHS participants were recruited from Medicare eligibility lists at four locations: Forsyth County, NC; Sacramento County, CA; Washington County, MD; and Pittsburgh, PA. They were invited to participate when they were community-dwelling adults, were age 65 or older, expected to remain in the area for the next 3 yr, were not receiving active treatment for cancer, and were able to give informed consent without a proxy. The initial cohort was recruited in 1989 to 1990, and a second cohort of 687 black individuals was recruited in 1992 to 1993, resulting in 5888 individuals. All participants provided informed consent.

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Cystatin C and creatinine were measured on frozen samples that were collected at the 1992 to 1993 visit. Individuals who had an incident hip fracture between the baseline visit (1989 to 1990) and 1992 to 1993 were excluded from the analysis. The sample size for analysis was 4699 for cystatin C and 5215 for creatinine.

Hip Fracture

Data on incident hip fractures were gathered using *International Classification of Diseases, Ninth Revision* codes from hospitalization records. CHS prospectively gathers hospitalization data, including discharge summaries, from participants every 6 mo. To ensure completeness of hospitalization records, data were checked against Medicare claims data to identify any hospitalizations that were not reported by the participant. Hip fracture was defined as *International Classification of Diseases, Ninth Revision* code of 820.xx. The mean follow-up was 7.1 ± 2.3 yr (interquartile range 6.1 to 8.7 yr).

Kidney Function

Detailed methods regarding blood drawing, quality assurance, and assay performances have been described previously (10). Serum creatinine was measured using the Kodak Ektachem 700 Analyzer (Eastman Kodak, Rochester, NY), a colorimetric method. Cystatin C was measured using a BNII nephelometer (Dade Behring, Deerfield, IL) that used a particle-enhanced immunonepholometric assay (N Latex Cystatin-C) (11). Polystyrene particles were coated with mAb to cystatin C that agglutinate in the presence of antigen (cystatin C) to cause an increase in the intensity of scattered light. The increase in scattered light is proportional to the amount of cystatin C in the sample. The assay range is 0.195 to 7.330 mg/L, with the reference range for young, healthy individuals reported as 0.53 to 0.95 mg/L. The assay remained stable over five cycles of freeze/thaw without change in the measurement (11). Cystatin C was chosen as the primary measure of kidney function because its levels do not vary by lean body mass (12). Estimated GFR (eGFR) was calculated using the four-variable Modification of Diet in Renal Disease formula (13), and CKD was defined as an eGFR <60 ml/min per 1.73 m^2 (13).

Covariates

Variables that were related to kidney function and risk of hip fracture were selected *a priori* as potential covariates. Race was determined by participant self-report and for this analysis was categorized as white or nonwhite (black $n = 885$, American Indian/Alaskan native $n = 12$, Asian/Pacific Islander $n = 4$, other $n = 18$). Diabetes was defined as the use of insulin or oral hypoglycemic agents or fasting glucose level ≥126 mg/dl. History of broken arm or wrist or history of fall in past year was from participant self-report. Vision problem was defined as self-report of being unable to see to drive, to watch television, or to recognize someone across a room with or without glasses. Body weight was measured using a calibrated balance beam scale. Height was measured with a wall-mounted stadiometer. Body mass index (BMI) was calculated as weight/height^2. Smoking was defined as current smoking. Physical activity was calculated as kilocalories from activities, including housework and exercise, using the Minnesota Leisure Time Activities questionnaire (14). Use of prescription medications with the potential to affect bone metabolism or fracture risk—thiazide diuretics, loop diuretics, benzodiazepines, oral corticosteroids, and, for women, hormones—was ascertained from a review of prescription bottle labels by interviewers (15). In addition to prescription medications, participants were asked whether they took any calcium supplements one or more times per week. Physical function (gait speed) was evaluated using a timed 15-ft corridor walk (time to walk 15 ft). C-reactive protein was measured with high-sensitivity immunonephelometry on the BI nephelometer (Dade Behring).

Statistical Analyses

Differences among groups were tested with *t* test or Wilcoxon test for continuous variables and χ^2 for proportions. Correlations were assessed with Spearman rank correlation. Because the sample size is large, only correlations >0.15 were considered clinically relevant. Cox proportional hazards models were used to examine the relationship of kidney function with incident hip fracture. Cystatin C was analyzed as a continuous variable and as quartiles. Initial models examined kidney function as a univariate predictor and adjusted for age and race. Multivariable models controlled for age, race, height, BMI, log(C-reactive protein), physical activity, gait speed, history of broken arm in the past year, vision problems, current smoking, diabetes, fall in past year, use of benzodiazepines, use of loop diuretics, use of thiazide diuretics, use of calcium supplements, and, in women, use of estrogens. Proportionality was assessed statistically by testing for a time interaction. Analyses were done separately by gender, because the predictors for hip fracture in men and women may differ (16). In addition, gender did not satisfy the proportionality assumption because there was a time × gender interaction. Follow-up was to June 30, 2001. SAS 8.1 (SAS Institute, Cary, NC) was used for the analysis. $P < 0.05$ was considered statistically significant.

Results

During follow-up, there were 274 incident hip fractures, 195 in women (9.7 per 1000 person-years) and 79 in men (5.9 per 1000 person-years). The characteristics of individuals with and without hip fracture are shown in Table 1. Women with hip fractures were older; were more likely to be white; were more likely to have CKD; and had lower BMI, physical activity, and walk speed and higher cystatin C. Men with hip fracture were older, were more likely to be white, were more likely to have had a fall in the past year, and had lower BMI and walk speed. The level of cystatin C and prevalence of CKD were not significantly higher in men who had a hip fracture. In men, cystatin C was correlated with age ($\rho = 0.33$, $P < 0.001$), gait speed ($\rho = 0.23$, $P < 0.001$), the use of loop diuretics ($\rho = 0.21$, $P < 0.001$), and white race ($r = 0.20$, $P < 0.001$). In women, cystatin C was correlated with age ($\rho = 0.28$, $P < 0.001$), gait speed ($\rho = 0.24$, $P < 0.001$), lower kilocalories of exercise ($r = -0.16$, $P < 0.001$), and the use of loop diuretics ($\rho = 0.16$, $P < 0.001$). Figure 1 shows the rate of hip fracture by cystatin C quartile in men and women. The rate of hip fracture increased monotonically across quartiles in women ($P < 0.001$ for trend). In men, there was little difference in hip fracture for quartiles 1 to 3, whereas men in the highest cystatin C quartile had a higher incidence of hip fracture ($P = 0.001$ for linear trend).

In women, cystatin C was associated with a 26% higher risk for hip fracture (per SD; Table 2). Adjustment for age attenuated the association of cystatin C with incident hip fracture. However, further adjustment for other covariates strengthened the association. After multivariable analysis, the risk for hip fracture increased across cystatin C quartiles ($P = 0.03$ for linear trend), although only the hazard ratio (HR) fourth quartile was significantly different than the first: 1.0 (reference), 1.20 (95% confidence interval [CI] 0.75 to 1.92), 1.49 (95% CI 0.92 to 2.41), and 1.66 (95% CI 1.01 to 2.73) for quartiles 1 to 4, respectively.

Table 1. Characteristics of participants with and without hip fracture by gender[a]

Characteristic	Women			Men		
	No Hip Fracture (n = 2538)	Hip Fracture (n = 195)	P	No Hip Fracture (n = 1887)	Hip Fracture (n = 79)	P
Age (yr)	74.3 ± 5.0	77.7 ± 5.8	<0.001	75.1 ± 5.4	78.4 ± 5.7	<0.001
Race (% white)	79.9	91.8	<0.001	83.4	94.9	<0.001
Diabetes (%)	13.6	10.8	0.23	18.3	13.9	0.77
Broken arm/wrist in past year (%)	2.9	5.7	0.08	1.8	2.5	0.72
Fall in past year (%)	18.5	23.6	0.15	10.1	22.8	<0.001
Vision problem (%)	20.3	24.3	0.48	17.4	21.8	0.30
Current smoker (%)	10.0	12.7	0.11	9.5	10.3	0.98
Thiazide use (%)	19.7	20.1	0.78	13.1	6.3	0.11
Loop diuretic use (%)	8.8	6.7	0.40	8.4	5.1	0.18
Benzodiazepine use (%)	10.3	12.4	0.12	6.3	7.6	0.48
Oral steroid use (%)	2.4	4.1	0.02	2.2	3.8	0.49
Estrogen use (%)	13.8	9.3	0.08	—	—	—
Calcium supplement use (%)	24.4	29.9	0.06	9.3	10.1	0.80
Walk speed for 15 ft (s)	5.8 ± 2.7	6.7 ± 4.4	0.004	5.3 ± 2.0	6.0 ± 2.0	0.03
Physical activity from exercise/chores (kcal; median [IQR])	712 (236 to 1628)	525 (105 to 1410)	0.003	712 (236 to 1628)	525 (105 to 1410)	0.05
Height (cm)	158.5 ± 6.3	158.1 ± 7.0	0.34	172.7 ± 6.9	172.6 ± 7.1	0.86
BMI (kg/m^2)	27.3 ± 5.4	24.8 ± 4.4	<0.001	26.6 ± 3.8	25.5 ± 3.9	0.03
CRP (median [IQR])	2.91 (1.29 to 6.41)	2.48 (0.93 to 5.70)	0.02	2.45 (1.16 to 5.26)	2.03 (0.95 to 5.84)	0.51
Cystatin C (mg/L)	1.08 ± 0.33	1.16 ± 0.34	0.003	1.16 ± 0.36	1.21 ± 0.32	0.19
Creatinine (mg/dl)	0.90 ± 0.35	0.95 ± 0.29	0.05	1.18 ± 0.41	1.18 ± 0.30	0.997
CKD (eGFR <60 ml/min per 1.73 m^2; %)	23.1	33.9	<0.001	27.2	31.7	0.38

[a]Data are means ± SD unless otherwise indicated. BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated GFR; IQR, interquartile range.

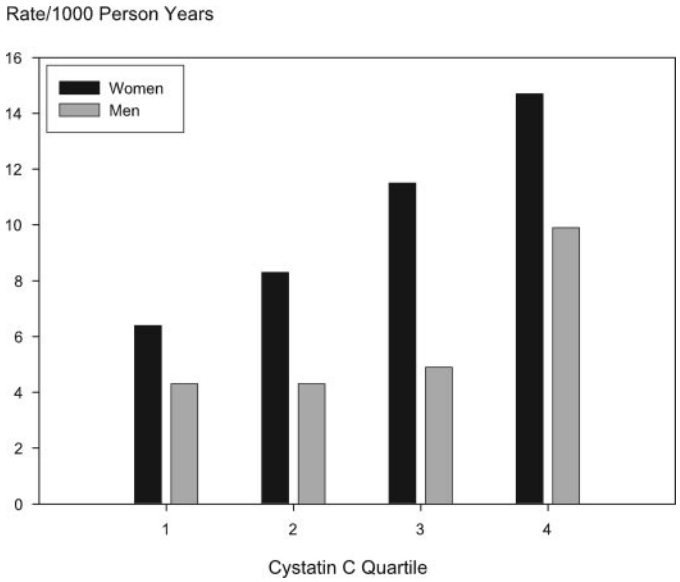

Figure 1. Rate of incident hip fracture by cystatin C quartile in women and men. The values for cystatin C quartiles are <0.92 (mean 0.83), 0.92 to 1.05 (mean 0.99), 1.05 to 1.22 (mean 1.13), and ≥1.22 mg/L (mean 1.52) for quartiles 1 to 4, respectively.

In men, cystatin C was associated with hip fracture in univariate analysis. After adjustment, cystatin C was not significantly associated with hip fracture in men; however, the magnitude of the association for cystatin C was similar to that observed in women, and a test for interaction was nonsignificant (P = 0.8). The power was low to analyze cystatin C as quartiles in men. The HR for the quartiles were 1.0 (reference), 0.91 (95% CI 0.41 to 2.11), 0.80 (95% CI 0.35 to 1.83), and 1.25 (95% CI 0.57 to 2.73) for quartiles 1 to 4, respectively (P = 0.43 for linear trend).

We also examined the association of CKD as defined by eGFR <60 ml/min per 1.73 m^2 with incident hip fracture. In univariate analysis, a low eGFR was associated with hip fracture in both women (HR 1.74; 95% CI 1.33 to 2.28; $P < 0.001$) with a trend for an association in men (HR 1.48; 95% CI 0.95 to 2.31; P = 0.09). After adjustment, there was a modest increased relationship in women (HR 1.38; 95% CI 0.99 to 1.94; P = 0.06) but no relationship in men (HR 0.97; 95% CI 0.58 to 1.62; P = 0.91).

Discussion

We found that kidney function was associated with incident hip fracture. To our knowledge, this is the first community-

Table 2. Association of kidney function (HR, 95% CI per SD) with incident hip fracture by gender[a]

Parameter	Women		Men	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Univariate	1.26 (1.14 to 1.38)	<0.001	1.27 (1.11 to 1.46)	<0.001
Adjusted for age, race	1.12 (0.97 to 1.30)	0.13	1.19 (0.94 to 1.52)	0.14
Multivariable adjusted[b]	1.16 (1.01 to 1.33)	0.03	1.14 (0.86 to 1.52)	0.22

[a]Mean cystatin and SD are 1.09 ± 0.34 in women and 1.16 ± 0.35 in men. HR, hazard ratio; CI, confidence interval.
[b]Adjusted for age, race, height, body mass index, physical activity, gait speed, history of broken arm in the past year, vision problems, current smoking, diabetes, fall in past year, use of benzodiazepines, use of loop diuretics, use of thiazide diuretics, use of calcium supplements, log(CRP), and, in women, use of estrogens.

based study to examine the role of mild to moderate impairment in kidney function as a predictor of hip fracture. Previously, an increased fracture risk was reported only in ESRD (1). In our unadjusted analysis, the relationship of kidney function with hip fracture was seen in both men and women. However after adjustment, cystatin C was significantly and linearly associated with hip fracture only in women. The null result in men most likely was due to inadequate power, because the HR were similar in men and women and there was not a significant gender interaction. However a gender difference in effect of kidney function on hip fracture risk cannot be excluded. Notably, there was a statistically nonsignificant 25% higher risk for hip fracture in the highest quartile of cystatin C in men. This may be a clinically important risk that would be statistically significant in a larger study.

As lean mass declines with age (17), it is harder to recognize decreased kidney function in older individuals using creatinine. Because cystatin C is not related to lean body mass, it might be a better marker of kidney function in the setting of loss of lean mass with aging and with disease. We previously found that cystatin C is linearly related to cardiovascular mortality and congestive heart failure, whereas the relationship with serum creatinine or eGFR is J-shaped, highlighting the usefulness of cystatin C as a predictor of outcomes in older individuals (18,19). Because normal values for creatinine vary by age, the National Kidney Foundation advocates the use of eGFR (13). However, others have questioned whether this formula is accurate in individuals without known kidney disease (20), and it has not been validated in a community-based population of older individuals. In our study, CKD as defined by a low eGFR also was associated with hip fracture, suggesting that the association of cystatin C with hip fracture is related to kidney function. However, the statistical significance of the association of CKD with hip fracture was marginal after adjustment.

The underlying mechanisms of the association of impaired kidney function with hip fracture cannot be determined from this study. Kidney disease could affect bone metabolism directly through its effects on vitamin D and PTH metabolism and acidosis (2). Although the changes are most marked in individuals with ESRD, changes in mineral metabolism and homocysteine levels are seen with milder degrees of kidney impairment. Martinez *et al.* (21), in a study of 157 patients with CKD, found that as creatinine clearance decreased below 80 ml/min, PTH levels rose and 1,25 $(OH)_2$ levels decreased. This rise in PTH levels with CKD is associated with increased bone turnover on bone biopsy (2). We previously reported that bone loss increased with higher cystatin C levels (8). These findings would be consistent with changes in bone metabolism as a potential mediator of the increased risk for hip fracture. Another potential mediator of the relationship of kidney function with hip fracture is homocysteine. Two recent studies found that homocysteine levels predict hip fracture in men and women (6,7). Homocysteine levels rise as renal function declines. In addition, cystatin C has a higher correlation with homocysteine levels than does serum creatinine in older individuals, which could account for some of the difference between cystatin C and creatinine (22).

Alternatively, kidney function could be simply a marker of comorbidity that leads to decreases in physical function and increases in frailty and falls, which thus increases the risk for hip fracture (23). In addition, GFR decreases with age, and part of the association of cystatin C with hip fracture could be age related. Although the relationship between markers of kidney function and risk for hip fracture persisted after adjustment for age and other important confounders, we cannot rule out the possibility that uncontrolled confounding accounts for some or all of the observed increase in risk.

This study has a number of limitations. We do not have a direct measure of GFR. Although cystatin C has been shown to be a reliable marker of GFR in the elderly (24), it may be that its predictive ability is due to its association with other confounders (25). We also are not able to assess potential mediators of the relationship because we do not have measures of vitamin D, PTH, or homocysteine levels. Because only a small subset of individuals had repeat bone mineral density evaluations, we also were not able to assess the relationship of bone loss as a possible mediator.

Our study has a number of important implications. Although the number of individuals on dialysis is relatively small, it is estimated that up to 25% of older individuals have CKD (26). Therefore, the attributable risk of kidney disease with hip fracture may be high. Many of the potential mediators of hip fracture in kidney disease are potentially treatable (*e.g.*, with 1,25 $(OH)_2$ vitamin D replacement). In addition, the recognition of kidney disease could be a used as a marker of increased risk for hip fracture in older individuals. These issues deserve further study in other populations.

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A full list of participating CHS investigators and institutions can be found at http://www.chs-nhlbi.org.

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