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Estimated GFR and Risk of Hip Fracture in Older Men: Comparison of Associations Using Cystatin C and Creatinine

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Abstract

Background—Higher serum cystatin C is associated with an increased risk of hip fracture in postmenopausal white women, but there is a paucity of data in men. Whether an estimated GFR (eGFR) based on cystatin C (eGFR_{cys}) is superior in predicting hip fracture risk to an eGFR based on creatinine (eGFR_{cr}) or the combination (eGFR_{cr-cys}) is also uncertain.

Study Design—Nested case-cohort.

Setting & Participants—Participants enrolled in the Osteoporotic Fractures in Men (MrOS) Study (5,994 men aged ≥ 65 years from six U.S. centers) including a random subcohort of 1602 men and 168 men with incident hip fractures (51 of whom were in the subcohort).

Predictor—eGFR_{cys}, eGFR_{cr} and eGFR_{cr-cys} computed using the CKD-EPI equations and expressed in categories of <60, 60–74, and ≥ 75 mL/min/1.73 m² (referent group).

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Supplementary Material

Table S1: Association between eGFR quartiles and risk of hip fracture.

Table S2: Association between eGFR_{cys} and hip fracture for eGFR_{cr} ≥ 60 mL/min/1.73 m².

Note: The supplementary material accompanying this article (doi:_____) is available at www.ajkd.org

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Outcome—Incident hip fracture ascertained by participant contacts every 4 months and confirmed with radiographic reports.

Results—Median $eGFR_{cys}$ was 72.9 (IQR, 60.5–85.7) mL/min/1.73 m². In unadjusted models, all measures of $eGFR$ were associated with increased hip fracture risk. However, after adjustment for age, race, site and BMI, the association of lower $eGFR_{cys}$ (but not lower $eGFR_{cr}$ or lower $eGFR_{cr-cys}$) with higher hip fracture risk remained: for <60 vs. 75 mL/min/1.73 m², HRs were 1.96 [95% CI, 1.25–3.09], 0.84 [95% CI, 0.52–1.37], and 1.08 [95% CI, 0.66–1.77] for $eGFR_{cys}$, $eGFR_{cr}$, and $eGFR_{cr-cys}$, respectively. Similarly, after adjustment for age, race, site and BMI, $eGFR$ of <60 mL/min/1.73 m² defined by $eGFR_{cys}$ but not $eGFR_{cr}$ or $eGFR_{cr-cys}$, was associated with higher hip fracture risk. The association between $eGFR_{cys}$ and hip fracture was not explained by levels of calcitropic hormones or inflammatory markers, but the relationship was attenuated and no longer reached significance (for <60 vs. 75 mL/min/1.73 m²: HR, 1.43; 95% CI, 0.88–2.34) after consideration of additional clinical risk factors and bone mineral density.

Limitations—Findings not generalizable other populations; residual confounding may exist.

Conclusions—Older community-dwelling men with lower $eGFR_{cys}$ have an increased risk of hip fracture that is explained in large part by greater burden of risk factors among men with lower $eGFR_{cys}$. In contrast, lower $eGFR_{cr}$ or lower $eGFR_{cr-cys}$ were not associated with a higher age-adjusted hip fracture risk.

Keywords

kidney function; cystatin C; creatinine; hip fracture; elderly; men

Cystatin C is a low molecular weight protein produced by all nucleated cells. The concentration of cystatin C is mainly determined by glomerular filtration. Cystatin C has been proposed to be superior to serum creatinine-based measures of kidney function in detecting mild to moderate decreases in kidney function in older adults, in part because it is less dependent on muscle mass.¹ Previous prospective studies in postmenopausal white women have reported an association between higher concentrations of serum cystatin C (i.e., lower cystatin C–based estimated glomerular filtration rate [$eGFR_{cys}$]) and an increased risk of hip² and nonvertebral fractures.³ However, data about men are lacking. A prior study in older adults⁴ reported that while the magnitude of the relationship appeared similar among women and among men, higher cystatin C concentration was significantly associated with hip fracture only in women.

It is also uncertain whether a cystatin C-based measure of kidney function is superior to a traditional creatinine-based measure in predicting hip fracture risk. Previous studies examining the association of serum creatinine-based measure of $eGFR$ ($eGFR_{cr}$) with fracture in older adults not selected on the basis of kidney disease have reported inconsistent results, with some^{5–7}, but not all^{8–10}, studies reporting an association between clinical chronic kidney disease (CKD; as defined by an $eGFR_{cr}$ <60 mL/min/1.73m²) and higher fracture risk.

To test the primary hypothesis that older men with lower $eGFR_{cys}$ are at increased risk of hip fracture, we conducted a case-cohort analysis nested in the cohort of 5994 men aged 65 years and older attending the baseline examination of the Osteoporotic Fractures in Men (MrOS) Study that included a random sample of 1602 men from the cohort and 168 men with first incident hip fracture from the cohort. In addition, we compared $eGFR_{cys}$ with $eGFR_{cr}$ and $eGFR$ based on creatinine and cystatin C ($eGFR_{cr-cys}$) in predicting hip fracture risk.

METHODS

Study Population

From March 2000 through April 2002, 5994 men who were aged ≥ 65 years were recruited for participation in the baseline examination of MrOS.¹¹ Men were recruited from population based listings in six regions of the United States. Men with a history of bilateral hip replacement and men who were unable to walk without the assistance of another person were excluded. The institutional review board at each participating institution approved the study protocol and written informed consent was obtained from all participants.

Case-Cohort Study Design

This study is a case-cohort analysis¹² nested within the cohort of 5994 men attending the MrOS baseline examination. We randomly selected 1602 men out of the 5994 men to serve as the subcohort. From the overall cohort of 5994 men, we also selected 168 men with first incident hip fracture from baseline until August 3, 2010 (average follow-up, 7.9 years). Among these 168 participants, 51 men had also been sampled within the subcohort. Thus, the number of men without hip fracture was 1551 among the 1602 men in the subcohort.

Serum Cystatin C and Creatinine Assays

Fasting morning blood was collected at the baseline examination and processed for serum which was stored at -70°C until thawed. Serum cystatin C assays were performed at the University of Minnesota Medical Center in 2010. Serum cystatin C concentrations were determined using a BN100 nephelometer (Dade Behring Inc., Deerfield, IL) using a particle-enhanced immunonephelometric assay¹³ (assay range, 0.23–8.00 mg/L; inter-assay coefficients of variation [CV] of 4.0% and 3.1% at levels of 0.71 mg/L and 1.75 mg/L, respectively [mean, 3.7%]) and then converted to standardized values traceable to a certified reference material.¹⁴ eGFR_{cys} was computed using the CKD Epidemiology Collaboration (CKD-EPI) 2012 equation expressed for standardized cystatin C.¹⁵ Serum creatinine concentrations were measured using a Roche COBAS Integra 800 analyzer (Roche Diagnostic Corporation, Indianapolis, IN) at the Portland VA (Veterans Affairs) Medical Center using an enzymatic method calibrated with materials assayed by isotope-dilution mass spectrometry (IDMS). Inter-assay CV is 5.3%. eGFR_{cr} was calculated using the CKD-EPI 2009 equation¹⁶ which includes variables for standardized creatinine, age, gender and race. $\text{eGFR}_{\text{cr-cys}}$ was calculated using the CKD-EPI 2012 creatinine-cystatin C equation.¹⁵

Ascertainment of Hip Fracture

Participants were contacted every four months after the baseline examination to ask whether they had sustained a fracture; more than 99% of these follow-up contacts were completed through 8 years of follow-up. Hip fractures were verified by medical records and confirmed by blinded central adjudication.¹⁷

Other Measurements

Participants completed a questionnaire and were interviewed at the baseline examination and asked about date of birth, race/ethnicity, smoking status, a history of cardiovascular disease (CVD), previous fractures since age 50, and falls in the past year. Physical activity was assessed using the Physical Activity Scale for the Elderly (PASE).¹⁸ The Medical Outcomes Study 12-item Short Form Health Survey (SF-12)¹⁹ was completed by all participants.

Weight was recorded with a scale and height was measured with a Harpenden stadiometer; weight and height were used to calculate body mass index (BMI; given in kg/m^2). Tests of physical function included grip strength (using a handheld Jamar dynamometer) and walk

speed (time in seconds to walk 6 m at usual pace expressed as m/s). Total hip bone mineral density (BMD), total body fat mass, and total body lean mass including appendicular lean mass were measured with dual-energy x-ray absorptiometry (DXA; QDR-4500W, Hologic, Inc., Bedford, MA) using standardized protocols; details of these measurements and quality control procedures are published elsewhere.^{20;21}

Frailty status was defined using criteria similar to those proposed by Fried and colleagues using data collected in the Cardiovascular Health Study.^{22;23} Frailty was identified by the presence of 3 or more of the following 5 components: (1) shrinking/sarcopenia defined by appendicular lean mass (adjusted for height and total body fat) in lowest quintile; (2) weakness defined by grip strength in lowest quintile stratified by BMI quartile; (3) exhaustion defined by an answer of “a little or none” to the question “How much of the time during the past four weeks did you have a lot of energy?” from the SF-12; (4) slowness defined by a walk speed in lowest quintile stratified by standing height (median); and (5) low physical activity level defined by a PASE score in lowest quintile.

Measures of 25-hydroxyvitamin D₂ and 25-hydroxyvitamin D₃ were performed at the Mayo Clinic using mass spectrometry²⁴ and summed for total 25-hydroxyvitamin D. Total intact parathyroid hormone (PTH) was measured using an immunoradiometric assay (Scantibodies Laboratory, Inc., Santee, CA) at the Columbia University Laboratory. Markers of chronic inflammatory processes were assessed by serum levels of pro-inflammatory cytokines (tumor necrosis factor α [TNF- α], interleukin 6 [IL-6]) and their soluble receptors (TNF- α soluble receptor 1 [TNF α sR1], TNF α sR2, and IL-6 sR) using ELISA kits (R&D systems, Minneapolis, MN) for all markers with the exception of TNF- α which was measured using flow cytometry (Human Serum CVD Panel 3 multiplex kit, Millipore Corp., Billerica, MA). In addition, serum levels of high-sensitivity CRP were measured using ELISA based on purified protein and polyclonal anti-CRP antibodies (Calbiochem, San Diego, CA, USA). Assays for markers of inflammation were performed at the University of Vermont Laboratory for Cytokine Biochemistry.

Statistical Analysis

Characteristics of participants in the subcohort were compared across categories of eGFR_{cys} using chi-square tests for categorical variables and ANOVA for continuous variables. Characteristics of men with and without incident hip fracture were also compared. The association between eGFR_{cys} and incident hip fracture was analyzed using proportional hazards regression models modified for the case-cohort sampling design.¹² Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated across categories of eGFR_{cys} with eGFR_{cys} 75 mL/min/1.73 m² serving as the referent group. Analyses were also performed expressing eGFR_{cys} as a continuous variable and as quartiles.

Models were initially adjusted for age and then further adjusted for race, clinical site, and BMI (base multivariable (MV) model). Analyses were also performed substituting total body lean mass for BMI. To obtain final multivariable risk estimates for the association between eGFR_{cys} and hip fracture, we subsequently added covariates to models that included age, race, site and BMI as predictors. Factors associated with eGFR_{cys} or hip fracture at $p < 0.05$ were considered for inclusion in the final multivariable model.

To examine biological mechanisms that might underlie the association observed between eGFR_{cys} and hip fracture, levels of calcitropic hormones (25-hydroxyvitamin D, PTH) and markers of chronic inflammation (TNF- α , IL-6, TNF α sR1, TNF α sR2, IL-6 sR, and C-reactive protein [CRP]) were added one at a time to the base model. We also examined whether the association between eGFR_{cys} and hip fracture persisted when the analysis was

limited to men without evidence of clinical CKD (e.g., those with an $\text{eGFR}_{\text{cr}} \geq 60 \text{ mL/min/1.73 m}^2$).

To compare eGFR_{cys} with other measures of kidney function in predicting fracture, analyses were performed substituting a traditional measure of kidney function, eGFR_{cr} , for eGFR_{cys} . In addition, we performed analyses substituting $\text{eGFR}_{\text{cr-cys}}$ for eGFR_{cys} . Finally, we examined the association of risk of hip fracture with CKD as defined by an $\text{eGFR} < 60 \text{ mL/min/1.73 m}^2$ calculated using cystatin C-based, creatinine-based and creatinine and cystatin C-based equations.

Data collected from the study were compiled and analyzed using the SAS software (version 9.2, SAS Institute Inc, Cary, NC).

RESULTS

Study Participants

Among men in the subcohort ($n=1602$), mean cystatin C concentration was 1.06 ± 0.27 (standard deviation) mg/L and mean creatinine concentration was 1.02 ± 0.26 mg/dL. Mean eGFRs were 72.4 ± 18.1 , 74.6 ± 15.5 , and $74.2 \pm 16.4 \text{ mL/min/1.73 m}^2$ for eGFR_{cys} , eGFR_{cr} , and $\text{eGFR}_{\text{cr-cys}}$, respectively. Medians were 72.9 (interquartile range [IQR], 60.5–85.7), 77.0 (IQR, 64.4–86.8), and 75.6 (IQR, 63.9–86.2) mL/min/1.73 m^2 for eGFR_{cys} , eGFR_{cr} , and $\text{eGFR}_{\text{cr-cys}}$, respectively. The correlation of eGFR_{cys} with eGFR_{cr} was moderate in magnitude (Spearman correlation coefficient=0.68); eGFR_{cys} was highly correlated with $\text{eGFR}_{\text{cr-cys}}$ (Spearman correlation coefficient=0.94).

Lower eGFR_{cys} among men in the subcohort was associated ($p < 0.05$) with older age, Caucasian race, prevalent CVD, falling in the past year, higher BMI, lower lean mass, greater frailty status, lower eGFR_{cr} , and lower $\text{eGFR}_{\text{cr-cys}}$ (Table 1). There were no significant differences across categories of eGFR_{cys} in smoking status, fracture history, or hip BMD.

Compared to men without hip fracture, men who had incident hip fracture were older; more likely to report Caucasian race, CVD, prior fracture, and falling in the past year; and more likely to be classified as frail (Table 2). In addition, men with hip fractures were thinner, had lower lean mass, lower hip BMD, lower eGFR_{cys} and lower $\text{eGFR}_{\text{cr-cys}}$. There were no differences in smoking status or eGFR_{cr} between hip fracture cases and men without hip fracture.

Association of eGFR_{cys} With Risk of Hip Fracture

In the univariate model, age-adjusted model, and model adjusted for age, race, site, and BMI (base MV model), lower eGFR_{cys} was associated with an increased risk of hip fracture (for the base MV model, p for linear trend = 0.004) (Table 3). Compared with men with $\text{eGFR}_{\text{cys}} \geq 75 \text{ mL/min/1.73 m}^2$, men with $\text{eGFR}_{\text{cys}} < 60 \text{ mL/min/1.73 m}^2$ had a nearly 2-fold increase in risk (HR, 1.96; 95% CI, 1.25–3.09) and men with eGFR_{cys} of 60–74 mL/min/1.73 m^2 had a 1.4-fold increase in risk, albeit this was not at the level of significance (HR, 1.43; 95% CI, 0.93–2.20). Findings were similar when eGFR_{cys} was expressed in quartiles (see Table S1, available as online supplementary material) and when total body lean mass was substituted for BMI.

Addition of potential confounding clinical risk factors (prevalent CVD, prior fracture, fall history, frailty status) and hip BMD one at a time to the base MV model did not substantially alter the association between lower eGFR_{cys} and hip fracture, but after

simultaneous adjustment for multiple clinical risk factors and hip BMD, the association failed to reach significance (HR of <60 vs. 75 mL/min/ 1.73m^2 , 1.43; 95% CI, 0.88–2.34).

The association between lower eGFR_{cys} and increased hip fracture risk was not explained by levels of calcitropic hormones (PTH, 25-hydroxyvitamin D) or inflammatory markers (TNF- α , IL-6, CRP, TNF α sR1, TNF α sR2, IL-6 sR). Further adjustment of the base MV model for every potential biological mediator had little effect on the association (Figure 1A).

The association between lower eGFR_{cys} and increased risk of hip fracture continued when the analysis was limited to 1342 men without clinical CKD as defined by $\text{eGFR}_{\text{cr}} \geq 60$ mL/min/ 1.73m^2 (see Table S2).

Association of eGFR_{cr} With Risk of Hip Fracture

In the univariate model, lower eGFR_{cr} was associated with an increased risk of hip fracture (HR of <60 vs. 75 mL/min/ 1.73m^2 , 1.86; 95% CI, 1.23–2.81) (Table 3). However, after adjustment for age, the risks of hip fracture appeared to be lower among men with lower eGFR_{cr} compared with that among men with higher eGFR_{cr} , though none of the point estimates of associations were significantly different from 1.0. Results were similar when eGFR_{cr} was expressed in quartiles (see Table S1). There was no evidence of an interaction between eGFR_{cr} and age (median 73 years vs. 73 years) for the prediction of risk of hip fracture (p for interaction term=0.4). Results were essentially unchanged after additional adjustment for race, site, and BMI or adjustment for race, site and lean mass. After further adjustment for multiple clinical risk factors and hip BMD, the lack of an association between eGFR_{cr} and hip fracture remained. Findings also were not altered in base MV models further adjusted for each of the potential biological mediators (Figure 1B).

Association of $\text{eGFR}_{\text{cr-cys}}$ With Risk of Hip Fracture

In the univariate model, lower $\text{eGFR}_{\text{cr-cys}}$ was associated with an increased risk of hip fracture (HR of <60 vs. 75 mL/min/ 1.73m^2 , 2.49; 95% CI, 1.67–3.70) (Table 3). However, this increase in risk among men with lower $\text{eGFR}_{\text{cr-cys}}$ did not persist after adjustment for age (HR of <60 vs. 75 mL/min/ 1.73m^2 , 1.11; 95% CI, 0.69–1.80). Findings were similar when $\text{eGFR}_{\text{cr-cys}}$ was expressed in quartiles (see Table S1). There was no evidence of an interaction between $\text{eGFR}_{\text{cr-cys}}$ and age for the prediction of hip fracture risk (p for interaction term=0.7). The lack of an association between lower $\text{eGFR}_{\text{cr-cys}}$ and hip fracture remained after adjustment for traditional clinical risk factors and after adjustment for potential biological mediators (Figure 1C).

Association of CKD With Risk of Hip Fracture

After adjustment for age, men with CKD as defined by an $\text{eGFR}_{\text{cys}} < 60$ mL/min/ 1.73m^2 (HR, 1.62; 95% CI, 1.12–2.33), but not those with clinical CKD as defined by an $\text{eGFR}_{\text{cr}} < 60$ mL/min/ 1.73m^2 (HR, 0.98; 95% CI, 0.63–1.52) or those with CKD defined by an $\text{eGFR}_{\text{cr-cys}} < 60$ mL/min/ 1.73m^2 (HR, 1.14; 95% CI, 0.74–1.77) were at greater risk of hip fracture (Table 3). The association between CKD as defined by an $\text{eGFR}_{\text{cys}} < 60$ mL/min/ 1.73m^2 and increased risk of hip fracture was not changed after additional adjustment for race, site and BMI. However, after further adjustment for multiple clinical risk factors and hip BMD, the association was attenuated and no longer significant (HR, 1.28; 95% CI, 0.86–1.91).

DISCUSSION

In this prospective study of older community-dwelling men, men with lower eGFR_{cys} had an increased risk of hip fracture due in part to a greater burden of traditional risk factors among

men with lower eGFR_{cys}. In contrast, after minimal adjustment for age alone, neither eGFR_{cr} nor eGFR_{cr-cys} were associated with hip fracture risk. These findings indicate that the marker of kidney function examined has an impact on the reported association between decreases in kidney function and risk of hip fracture and suggest that eGFR_{cys} may be superior to eGFR_{cr}, especially in community dwelling populations with at most mild to moderate reductions in kidney function.

These results regarding the independence of the association between eGFR_{cys} and risk of hip fracture in older men are in agreement with those of the Cardiovascular Health Study⁴ that reported an increased risk of hip fracture in older adults with higher cystatin C concentrations (i.e., lower eGFR_{cys}), an effect that was attenuated and no longer significant in men after consideration of age and other clinical risk factors, though BMD was not measured in this study. Prospective studies of postmenopausal² and older^{22;25} women have reported associations between lower eGFR_{cys} and an increased risk of hip fracture that persisted despite consideration of multiple clinical risk factors and hip BMD.²⁵ Discrepancies between findings in men versus those in women may reflect a true gender difference in the effect of cystatin C on hip fracture events. On the other hand, the lack of an observed independent association in men in this and other studies might also be due to a higher competing risk of mortality or a consequence of limited statistical power. While results from this and other studies suggest that cystatin C might have potential as a biomarker for identification of older adults at increased hip fracture risk, it has not yet been demonstrated that its measurement gives further prognostic information in the clinical setting beyond that which is easily obtainable by assessing traditional risk factors.

The association between lower eGFR_{cys} and increased risk of hip fracture in this study remained when men with clinical CKD (defined as eGFR_{cr} <60 mL/min/1.73m²) were excluded from the analysis. These results suggest that older men with lower eGFR_{cys} and preserved eGFR_{cr} have an increased risk of hip fracture. A prior study²⁶ showed a greater risk of progression to adverse kidney events, cardiovascular events, and death in older adults with higher cystatin C concentrations (i.e., lower eGFR_{cys}) and preserved eGFR_{cr}. Together these investigations lend support to the contention that lower eGFR_{cys} in the presence of normal eGFR_{cr} may identify “preclinical” state of decreased kidney function in older adults, predating the development of clinical CKD, but associated with an elevated risk of adverse health consequences.

A number of biological mechanisms may mediate the association between lower eGFR_{cys} and increased hip fracture risk. While abnormalities in calcium, phosphorus, and vitamin D metabolism that occur in even mildly decreased kidney function among older adults may lead to secondary hyperparathyroidism, greater bone resorption, and higher hip fracture rates,^{27;28} the association between lower eGFR_{cys} and hip fracture in this study remained despite adjustment for 25-hydroxyvitamin D and PTH. Some, but not all, prospective studies, including a previous investigation from this cohort,²⁹ have reported an association between low vitamin D status and higher fracture risk^{30;31} and the association between PTH concentrations and hip fracture risk among older adults has been debated.^{32;33} Reduced kidney function has also been associated with higher concentrations of inflammatory factors and homocysteine, as well as anemia.^{34–36} Adjustment for pro-inflammatory cytokines TNF- α , IL-6 or their soluble receptors or levels of CRP had little effect on the association between eGFR_{cys} and hip fracture found in this study, which indicates that the increased risk of hip fracture may not have been explained by the effect of decreased kidney function on chronic inflammatory processes.

In unadjusted models, lower eGFR_{cr} in this study was associated with an increased risk of hip fracture, but this association was no longer evident after adjustment for age alone. Two

prior cross-sectional studies^{5,7} reported an association between lower $eGFR_{cr}$ and fracture history and one prospective study in women reported a relationship between lower $eGFR_{cr}$ ⁶ (calculated using the Cockcroft-Gault formula) and higher hip fracture risk; this relationship did not hold up when $eGFR$ was calculated using the MDRD (Modification of Diet in Renal Disease) Study equation. In contrast, a recent study in older women²⁵ reported that the increased risk of hip fracture among women with lower $eGFR_{cr}$ (calculated using the CKD-EPI equation) was due to the older age among those with lower $eGFR_{cr}$; after consideration of age, $eGFR_{cr}$ was no longer related to hip fracture risk. In addition, a retrospective cohort study⁸ of male veterans that estimated kidney function using the MDRD Study equation reported that the age-adjusted risk of hip fracture was increased among men with severe CKD (defined as $eGFR_{cr}$ of 15–29 mL/min/1.73m²), but not among men with mild to moderate CKD (defined as $eGFR_{cr}$ of 30–59 mL/min/1.73m²). Similarly, a recent investigation from Alberta, Canada utilizing a province-wide laboratory database and administrative outcome dataset reported that an $eGFR_{cr}$ <60 mL/min/1.73m² (calculated using the CKD-EPI equation) was not associated with an increased risk of hip, wrist or clinical vertebral fracture, including among adults 75 years and older.⁹ The paradoxical suggestion of a possible association between lower $eGFR_{cr}$ and decreased age-adjusted hip fracture risk in this cohort may in part reflect the dependence of serum creatinine on muscle mass as mild elevations in serum creatinine in healthy community-dwelling older men might reflect greater muscle mass with attendant lower risks of falls and fractures. However, further adjustment for lean mass or frailty status did not explain these results. In addition, any association of $eGFR_{cr}$ as calculated by creatinine-based equations that include terms for age with risk of fracture might also be confounded by the strong relationship between advancing age and risk of hip fracture. Whatever the mechanism, these findings indicate the observed association between decreased kidney function and risk of hip fracture in older adults is, in part, a function of the measure of kidney function evaluated. They suggest that $eGFR_{cys}$ may be superior to $eGFR_{cr}$ when evaluating the association between kidney function and hip fracture, especially in community-dwelling older adults with at most modest to mild decreases in kidney function.

This study has several strengths including use of $eGFR_{cys}$ and $eGFR_{cr}$, the large cohort with comprehensive assessment of fracture risk factors, and contemplation of multiple potential confounders and potential biologic mediators of the association. However, this study has a number of limitations. The cohort comprised older predominantly white community-dwelling men and the findings are not necessarily applicable to other populations. Importantly, GFR was not directly measured and factors other than GFR might affect concentrations of cystatin C.³⁷ Thus, that there might be a mechanism linking cystatin C with hip fracture risk, unrelated to kidney function, cannot be entirely excluded and there might be residual confounding. For example, higher concentrations of cystatin C might indicate a pathophysiologic process or a response to injury, and not necessarily a reduction in GFR. Conversely, the discrepancy between findings for $eGFR_{cys}$ versus those for a traditional $eGFR_{cr}$ observed in this study might reflect cystatin C being more accurate in detecting mild to moderate decreases in kidney function in older adults. Severe CKD (e.g., $eGFR$ <30 mL/min/1.73m²) was uncommon in this cohort. Thus, future studies including older adults with a wider range of kidney function are needed. Finally, bone disease that occurs with CKD is complex and multi-factorial and the outcome of this study was limited to hip fracture.

In conclusion, community-dwelling older men with lower $eGFR_{cys}$ are at increased risk of hip fracture due in large part to a greater burden of risk factors among men with lower $eGFR_{cys}$. Our findings indicate that $eGFR_{cr}$ (or $eGFR_{cr-cys}$) is not associated with a higher age-adjusted risk of hip fracture. These results suggest that $eGFR_{cys}$ may have advantages compared with $eGFR_{cr}$ when evaluating the association between kidney function and hip

fracture, especially in older populations with at most mild to moderate decreases in kidney function.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

a-c. eGFR as Calculated by Cystatin C and Creatinine-Based Equations and Risk of Hip Fracture: Effect of Adjustment for Potential Biologic Mediators

*adjusted for age, race, site, and body mass index

†analyses included 1590 men in subcohort and 128 hip fracture cases with baseline measures of cystatin C, creatinine and 25-hydroxyvitamin D (25(OH)D) and 1590 men in the subcohort and 128 hip fracture cases with baseline measures of cystatin C and PTH

‡analyses included 975 men in subcohort and 133 hip fracture cases with baseline measures of cystatin C, creatinine, and markers of inflammation

Table 1Baseline Characteristics of Participants in Subcohort by eGFR_{cys} Category

Characteristics	Category of eGFR _{cys} [*]			p-value
	<60.0 (n=388)	60.0–74.9 (n=452)	75.0 (n=762)	
Age (y)	77.1 (6.3)	74.7 (5.5)	71.6 (4.9)	<0.001
White race	354 (91.2)	418 (92.5)	667 (87.5)	0.01
Current smoker	14 (3.6)	22 (4.9)	21 (2.8)	0.2
Cardiovascular disease	133 (34.3)	100 (22.1)	128 (16.8)	<0.001
Previous fracture since age 50 y	92 (23.8)	99 (21.9)	172 (22.7)	0.5
Fall in past year	101 (26.0)	99 (21.9)	129 (16.9)	0.001
Lean mass (kg)	56.1 (7.3)	57.1 (7.2)	57.2 (6.9)	0.04
BMI (kg/m ²)	27.7 (4.0)	27.6 (3.9)	27.1 (3.4)	0.006
Frail status				<0.001
Robust	91 (23.5)	210 (46.5)	423 (55.5)	
Intermediate stage	224 (57.7)	210 (46.5)	309 (40.6)	
Frail	73 (18.8)	32 (7.1)	30 (3.9)	
Total hip BMD (g/cm ²)	0.95 (0.15)	0.95 (0.14)	0.96 (0.14)	0.5
eGFR _{cr}	58.7 (15.2)	73.5 (11.1)	83.5 (10.3)	<0.001
eGFR _{cys}	48.6 (9.9)	67.0 (4.0)	87.7 (9.4)	<0.001
eGFR _{cr-cys}	53.3 (11.5)	70.8 (6.4)	87.0 (8.8)	<0.001

Note: n=1602. All eGFR values are given in mL/min/1.73 m. Values for categorical variables are given as number (percentage); values for continuous variables are given as mean ± standard deviation.

* eGFR_{cys} calculated using the Chronic Kidney Disease Epidemiology Collaboration 2012 equation.

eGFR, estimated glomerular filtration rate; eGFR_{cys}, cystatin C-based eGFR; eGFR_{cr}, creatinine-based eGFR; eGFR_{cr-cys}, creatinine and cystatin C-based eGFR; BMI, body mass index; BMD, bone mineral density

Table 2

Comparison of Baseline Characteristics between Hip Fracture Cases and Participants without Hip Fracture

Characteristic	Cases (n=168)	No Hip Fracture (n=1551)	P value
Age (y)	78.1 (6.1)	73.7 (5.9)	<0.001
White race	159 (94.6)	1389 (89.6)	0.04
Current smoker	10 (6.0)	55 (3.6)	0.1
Cardiovascular disease *	60 (35.7)	338 (21.8)	<0.001
Previous fracture since age 50 y	69 (41.1)	340 (22.0)	<0.001
Fall in past year	51 (30.4)	316 (20.4)	0.003
BMI (kg/m ²)	26.5 (3.9)	27.4 (3.7)	0.003
Lean mass (kg)	54.7 (6.7)	57.0 (7.1)	<0.001
Frail status			<0.001
Robust	44 (26.2)	706 (45.5)	
Intermediate stage	88 (52.4)	720 (46.4)	
Frail	36 (21.4)	125 (8.1)	
Total hip BMD (g/cm ²)	0.82 (0.13)	0.96 (0.14)	<0.001
eGFR _{cr}	72.7 (15.1)	74.8 (15.6)	0.1
eGFR _{cys}	65.4 (17.5)	72.6 (18.0)	<0.001
eGFR _{cr-cys}	69.3 (15.4)	74.4 (16.4)	<0.001

* Cardiovascular disease defined by history of myocardial infarction, stroke, or congestive heart failure

Note: All eGFR values are given in mL/min/1.73 m². Values for categorical variables are given as number (percentage); values for continuous variables are given as mean ± standard deviation.

eGFR, estimated glomerular filtration rate; eGFR_{cys}, cystatin C-based eGFR; eGFR_{cr}, creatinine-based eGFR; eGFR_{cr-cys}, creatinine and cystatin C-based eGFR; BMI, body mass index; BMD, bone mineral density

Table 3
Association between eGFR as calculated by Cystatin C- and Creatinine-Based Equations and Risk of Hip Fracture

eGFR Marker *	Unadjusted model	Age-adjusted model	Base multivariable model†	Final multivariable model‡
eGFR_{cys}				
Per 1-SD decrease	1.69 (1.43–1.99)	1.23 (1.01–1.50)	1.22 (1.00–1.49)	1.04 (0.85–1.28)
Category				
75.0	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
60.0–74.9	2.07 (1.38–3.11)	1.47 (0.96–2.25)	1.43 (0.93–2.20)	1.22 (0.77–1.93)
<60.0	3.73 (2.53–5.51)	1.99 (1.28–3.10)	1.96 (1.25–3.09)	1.43 (0.88–2.34)
p-trend	<0.001	0.002	0.004	0.2
<60.0 vs. 60.0	2.70 (1.95–3.73)	1.62 (1.12–2.33)	1.60 (1.10–2.34)	1.28 (0.86–1.91)
eGFR_{cr}				
Per 1-SD decrease	1.23 (1.05–1.44)	0.84 (0.68–1.04)	0.83 (0.67–1.03)	0.84 (0.68–1.05)
Category				
75.0	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
60.0–74.9	1.08 (0.73–1.61)	0.71 (0.47–1.08)	0.69 (0.46–1.05)	0.76 (0.49–1.18)
<60.0	1.86 (1.23–2.81)	0.85 (0.52–1.37)	0.84 (0.52–1.37)	0.83 (0.50–1.37)
p-trend	0.01	0.4	0.3	0.4
<60.0 vs. 60.0	1.81 (1.22–2.68)	0.98 (0.63–1.52)	0.98 (0.63–1.54)	0.92 (0.58–1.47)
eGFR_{cr-cys}				
Per 1-SD decrease	1.51 (1.29–1.76)	1.06 (0.87–1.29)	1.03 (0.83–1.26)	0.92 (0.73–1.4)
Category				
75.0	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
60.0–74.9	1.36 (0.92–2.01)	0.95 (0.63–1.43)	0.88 (0.58–1.34)	0.93 (0.61–1.41)
<60.0	2.49 (1.67–3.70)	1.11 (0.69–1.80)	1.08 (0.66–1.77)	0.96 (0.58–1.59)
p-trend	<0.001	0.7	0.8	0.8
<60.0 vs. 60.0	2.23 (1.54–3.22)	1.14 (0.74–1.77)	1.15 (0.74–1.80)	0.99 (0.62–1.60)

Note: Values are given as relative hazard (95% confidence interval). All eGFR values are given in mL/min/1.73 m².

eGFR, estimated glomerular filtration rate; eGFR_{cys}, cystatin C-based eGFR; eGFR_{cr}, creatinine-based eGFR; eGFR_{cr-cys}, creatinine and cystatin C-based eGFR; CKD-EPI, Chronic Kidney Disease Epidemiology Equation; SD, standard deviation

* eGFR_{cys} calculated using the CKD-EPI 2012 equation; eGFR_{cr} calculated using the CKD-EPI 2009 equation; eGFR_{cr-cys} calculated using the CKD-EPI 2012 creatinine-cystatin C equation.

[†] adjusted for age, race, site and body mass index

[‡] adjusted for age, race, site, body mass index, cardiovascular disease, fracture history, fall history, frailty status, and bone mineral density