Fracture Risk in CKD

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An increased risk of fracture, in particular hip fracture, has been consistently observed in studies of patients with ESRD (1–4). However, whether the mild to moderate reductions in renal function that are common in aged populations (5) increase the risk of fracture is less certain. Most studies examining this question have focused on the association between lower estimated GFR (eGFR) and risk of hip fracture. A review of this literature suggests that the observed association between eGFR and risk of hip fracture is, in part, a function of the method or equation used to estimate GFR.

Previous studies examining the association of serum creatinine-based estimates of GFR (eGFRCr) with hip fracture in adults not selected on the basis of kidney disease have reported inconsistent results, with some (6–8), but not all (9,10), studies reporting relationship between lower eGFRCr and higher fracture rate. Two prior cross-sectional studies (6,8) reported an association between lower eGFRCr and fracture history, and one prospective study in older women reported a relationship between lower eGFRCr (7) (estimated creatinine clearance by the Cockcroft-Gault method standardized for body surface area, but not GFR estimated by the Modification of Diet in Renal Disease [MDRD] equation) and higher hip fracture risk. However, more recent investigations have not corroborated these findings.

In this issue of CJASN, Elliot and colleagues (11) report findings from a retrospective cohort study that used a province-wide laboratory database and administrative outcome dataset in 1,815,943 community-dwelling adults aged 18 years and older from Alberta, Canada, to examine the association between eGFRCr (estimated using the CKD-Epidemiology Collaboration [CKD-EPI] equation) and rates of hip, wrist, and clinical vertebral fractures. Unadjusted and adjusted (taking into account sociodemographic characteristics and comorbidity burden) fracture rates were presented within strata defined by age group and sex. Among men and women aged 18–64 years, lower eGFRCr was associated in a graded manner with higher unadjusted and adjusted rates of hip fracture. However, among older age groups (65–74 years, 75–84 years, and ≥85 years), with the exception of women aged 85 years and older, there appeared to be evidence of a U-shaped pattern between eGFRCr and unadjusted hip fracture rates, with higher rates among older adults with higher and those with lower eGFRCr. After adjustment, the U-shaped trend reached the level of statistical significance for only three of the six groups examined, and the investigators concluded that adjusted hip fracture rates within older age groups were similar across categories of eGFRCr.

These results are in general agreement with those of recent prospective studies in older community-dwelling women (10) and men (12). Both of these investigations reported that lower eGFRCr (estimated using the CKD-EPI equation) was associated with a higher risk of hip fracture in unadjusted models but that this association was attenuated and no longer significant after adjustment for age alone. This finding suggests that the higher risk of hip fracture among older adults with lower eGFRCr was explained by their older age. In addition, a retrospective cohort study (9) of male veterans that used the creatinine-based MDRD estimating equation reported that the age-adjusted risk of hip fracture was increased among men with severe CKD (defined as an eGFRCr of 15–29 ml/min per 1.73 m²) but not among men with mild to moderate CKD (defined as an eGFRCr of 30–59 ml/min per 1.73 m²).

In contrast to accumulating evidence suggesting a lack of an association between eGFRCr and hip fracture risk among older adults without ESRD, several prospective studies in community-dwelling aged populations have consistently observed an association between a cystatin C–based measure of eGFR (eGFRcysC by the CKD-EPI equation) and hip fracture. Cystatin C is a low-molecular-weight protein whose concentration is primarily determined by glomerular filtration and is less dependent on muscle mass than is creatinine (13). Prospective studies of postmenopausal (14) and older (10,15) women without ESRD have reported independent associations between lower eGFRcysC and a higher risk of hip fracture that persisted despite consideration of multiple clinical risk factors (e.g., age, body mass index, health status, comorbid medical conditions, prior fracture, fall history, and frailty status) and bone mineral density of the hip. In addition, the associations between eGFRcysC and hip fracture remained despite further adjustment for levels of calcitropic hormones, inflammatory markers, hemoglobin, or homocysteine. In studies evaluating older men without ESRD (12,15), men with lower eGFRcysC had an increased risk of hip fracture that was explained in large part by a greater burden of traditional risk factors among men with lower eGFRcysC. The weaker relationship of lower eGFRcysC with higher hip fracture risk in...
older men versus women reported in these studies may be a consequence of the higher competing risk of mortality among men or limited statistical power. Investigations in community-dwelling older adults that have evaluated both eGFR<sub>cysC</sub> and eGFR<sub>cysC</sub> in the same population (10,12) have reported associations between lower eGFR<sub>cysC</sub> (but not lower eGFR<sub>cysC</sub>) and higher hip fracture risk; similarly, these studies have noted adjusted associations between CKD (eGFR < 60 ml/min per 1.73 m<sup>2</sup>) defined using a cystatin C–based equation (but not a creatinine-based equation) and increased hip fracture risk.

Discrepant findings regarding the association between eGFR and risk of hip fracture depending on whether a creatinine-based or cystatin C–based equation is used to estimate renal function might reflect the lower dependence of cystatin C on muscle mass and its greater accuracy in estimating GFR in older adults with modest to moderate renal dysfunction. Cystatin levels may be a misleading indicator of renal function in aged populations because of age-related declines in muscle mass resulting in lower creatinine production. Hence, even with a reduction in GFR to <60 ml/min per 1.73 m<sup>2</sup>, serum creatinine may not rise appreciably in elderly persons. Thus, low creatinine in many older adults may be the result of reduced muscle mass or frailty rather than normal renal function, and this misclassification might lead to a U- or J-shaped association between serum creatinine concentration and hip fracture. GFR-estimating equations based on serum creatinine, such as the CKD-EPI equation, include variables for age, race, and sex as surrogates for creatinine generation by muscle. However, these variables do not account for lower creatinine production due to malnutrition, inflammation, or loss of muscle mass in aged populations, in whom creatinine-based equations may overestimate GFR (16). On the other hand, any association of eGFR<sub>cysC</sub> as estimated by a creatinine-based equation that includes a term for age with risk of fracture might also be confounded by the strong relationship between advancing age and risk of hip fracture. Importantly, none of the studies evaluating the association between renal function and risk of hip fracture in community-dwelling older adults without ESRD has used a direct measure of GFR. Because factors other than GFR may affect cystatin C levels (17), the possibility remains that a mechanism links cystatin C with hip fracture risk, unrelated to renal function. For example, higher concentrations of cystatin C might indicate a pathophysiologic process or a response to injury, and not necessarily a fall in GFR.

Whatever the mechanism, the totality of evidence indicates that the observed association between renal dysfunction and risk of hip fracture in older adults depends on the method used to estimate GFR and suggests that eGFR<sub>cysC</sub> may be superior to eGFR<sub>c</sub> when the association between kidney function and hip fracture is evaluated, especially in community-dwelling older adults with at most moderate reductions in renal dysfunction. While cystatin C (and eGFR<sub>cysC</sub>) may be a promising biomarker for identification of older adults at increased hip fracture risk, future studies should evaluate whether its measurement provides additional prognostic information in the clinical setting for decision-making, such as improving prediction of subsequent 10-year fracture risk beyond that which is readily available by assessing traditional risk factors.

Disclosures
K.E.E. serves as a consultant on a Data Monitoring Committee for Merck Sharpe & Dohme.

References
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