A Structural Approach to Skeletal Fragility in Chronic Kidney Disease

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Summary: Renal osteodystrophy is a multifactorial disorder of bone metabolism in chronic kidney disease (CKD). As CKD progresses, ensuing abnormalities in mineral metabolism result in distortions in trabecular microarchitecture, thinning of the cortical shell, and increased cortical porosity. Recent studies have shown significantly increased hip fracture rates in CKD stages 3 and 4, in dialysis patients, and in transplant recipients. The majority of studies of bone loss in CKD relied on dual-energy x-ray absorptiometry (DXA) measures of bone mineral density. However, DXA summarizes the total bone mass within the projected bone area, concealing distinct structural alterations in trabecular and cortical bone. Recent data have confirmed that peripheral quantitative computed tomography (pQCT) measures of cortical density and thickness provide substantially better fracture discrimination in dialysis patients, compared with hip or spine DXA. This review summarizes the growing evidence for bone fragility in CKD stages 3 through 5, considers the effects of CKD on trabecular and cortical bone structure as it relates to fracture risk, and details the potential advantages and disadvantages of DXA and alternative measures of bone density, geometry, and microarchitecture, including pQCT, high-resolution pQCT, and micro–magnetic resonance imaging for fracture risk assessment in CKD.

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Renal osteodystrophy is a multifactorial and universal disorder of bone metabolism in advanced chronic kidney disease (CKD). As renal failure progresses, ensuing abnormalities in vitamin D metabolism and parathyroid hormone (PTH) secretion result in distortions in trabecular microarchitecture, thinning of the cortical shell, and increased cortical porosity.[1] As detailed later, hip fracture rates are increased significantly in CKD stages 3 and 4, in dialysis patients, and in transplant recipients. The majority of studies of bone loss in CKD relied on dual-energy x-ray absorptiometry (DXA) measures of bone mineral density (BMD). However, DXA summarizes the total bone mass within the projected bone area (g/cm^2), concealing the distinct structural alterations in trabecular and cortical bone density and architecture that contribute to skeletal fragility in CKD. Newer imaging modalities, such as peripheral quantitative computed tomography (pQCT), high-resolution pQCT (HRpQCT), and micro–magnetic resonance imaging (micro-MRI) techniques may provide greater fracture discrimination in CKD and may prove useful as surrogate measures of bone strength for clinical trials of bone therapies.

FRACTURE EPIDEMIOLOGY IN CKD

In 2000, Alem et al[2] examined hip fracture rates in more than 300,000 maintenance dialysis patients, showing an overall 4-fold increase in fracture rates in male and female dialysis patients compared with population-based controls. Dialysis was associated with a greater than 80-fold increased risk of fracture in young adults (age <45 y), but the greatest population burden was observed in older adults, in whom

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the risk was increased more than 2-fold over the high rate observed in the general elderly population. For example, the magnitude of the added risk of hip fracture in women ranged from approximately 3 per 1,000 person-years in young adults to 18 per 1,000 person-years in those 75 years and older. The risk of hip fracture escalated with increasing duration since dialysis initiation across all age groups for men and women.

Risk Factors for Fracture

Subsequent studies identified multiple risk factors for fracture in dialysis patients. These included the following traditional risk factors for hip fracture that have been observed in the general population: older age, female sex, Caucasian race (compared with black race), lower body mass index, and cigarette smoking,[3] as well as impaired physical functioning (eg, 6-minute walk, functional reach, and timed up and go).[4] Among dialysis patients, additional risk factors for fracture included peripheral vascular disease,[3] and either low or high PTH levels.[5,6] In one study, the lowest risk of hip fracture was observed at a PTH level of 300 pg/mL,[5] and in another study parathyroidectomy in dialysis patients was associated with a significantly lower risk of fracture.[7] Population-based studies of the associations between either diabetes or cardiovascular disease with fracture risk have generated conflicting results, reporting either no associations with hip fracture risk[3] or significantly greater risk of long-bone fractures among diabetic patients and among patients with cardiovascular disease[6] in multivariate models.

Fractures in Transplant Recipients

Although one study reported that the risk of hip fracture was comparable among dialysis patients and renal transplant recipients,[2] this study likely was subject to selection bias because less-healthy dialysis patients who were not eligible for transplantation were included. Accordingly, these investigators subsequently conducted a study including only those patients on the waiting list for renal transplantation, resulting in a cohort of relatively more uniform health status.[8] Immediately after renal transplantation, the relative risk of hip fracture was 34% greater in transplant recipients compared with those patients who continued to undergo hemodialysis. However, over the ensuing months, the relative risk of fracture decreased until approximately 630 days after transplantation when rates were comparable between transplant recipients and dialysis patients (adjusted for interval since placement on the waiting list). The greater fracture risk observed soon after transplantation was attributed to high doses of glucocorticoids and postoperative immobility.

Fractures in CKD Stages 3 and 4

More recently, greater fracture rates also have been reported in adults with moderate CKD in population-based databases,[9,10] and in secondary analyses of existing observational studies.[11-13] In the first population-based study of the relationship between moderate to severe CKD and hip fracture, Nickolas et al[9] used the National Health and Nutrition Examination Survey to assess hip fracture rates in adults (>50 y) with an estimated glomerular filtration rate (eGFR) between 15 and 60 mL/min compared with those with an eGFR of greater than 60 mL/min.[9] An eGFR less than 60 mL/min was associated independently with an odds ratio of reported hip fracture of 2.12, and in multivariate logistic regression analysis, only the presence of CKD, a reported history of osteoporosis, and low physical activity levels were associated with a history of hip fracture. A subsequent study conducted in men older than 50 years of age at 8 Veterans Affairs Medical Centers showed that, compared with an eGFR greater than 60 mL/min/1.73 m^2, stage 3 CKD (eGFR, 30-59 mL/min/1.73 m^2) and stage 4 CKD (eGFR, 15-29 mL/min/1.73 m^2) were associated with relative risks of fracture of 1.28 and 3.98, respectively.[10]

Similar studies within the Women's Health Initiative Observational Health Study,[13] the Study of Osteoporotic Fractures (SOF),[11] and the Cardiovascular Health Study[12] confirmed a significant association between hip fracture and CKD. Importantly, in the 2 studies that included DXA scans,[9,11] the associations between CKD and hip fracture were independent of BMD, suggesting that CKD impairs bone quality in a way that is not fully captured by DXA BMD. Finally, unlike the other studies, the analysis