

BMD and Fracture Risk in CKD: Where Should We Go from Here?

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In patients without kidney disease, measurement of areal bone mineral density (aBMD) by dual energy x-ray absorptiometry (DXA) is a surrogate marker of bone strength and is the clinical standard for assessing fracture risk in postmenopausal women and older men. Multiple prospective studies have demonstrated its utility in the diagnosis, treatment, and monitoring of osteoporosis and the prediction of incident fragility fractures. However, the utility of aBMD measurement by DXA as a tool for fracture risk assessment in patients with CKD remains controversial for several reasons. Cross-sectional studies conducted in patients both before (1–3) and after (4–8) initiation of renal replacement therapy have been inconsistent regarding the ability of DXA to discriminate between CKD patients with and without fracture. The few prospective trials assessing the fracture prediction characteristics of DXA in CKD-mineral and bone disorder (CKD-MBD) patients are also inconsistent (9–11). Moreover, the spectrum of bone turnover and mineralization abnormalities that characterize renal osteodystrophy may be associated with low, normal, or high BMD (7,12,13). For these reasons, the 2009 Kidney Disease Improving Global Outcomes (KDIGO) Guidelines consensus statement on fracture risk assessment in CKD-MBD does not recommend using aBMD by DXA to screen patients for osteoporosis or to predict fracture risk (14). Given the current CKD epidemic, the absence of proven and effective fracture screening methods is a major clinical problem. Although we know that patients with CKD are at increased risk for fracture, we lack appropriate tools to assess fracture risk, and this in turn limits our ability to design appropriate studies focused on prevention of fractures and their associated high morbidity and mortality (15). To date, few studies have evaluated methods to optimize fracture risk assessment in this highly vulnerable population (1,16). In the current issue of *CJASN*, Yencheek *et al.* (17) provide us with important evidence that measurement of aBMD by DXA is predictive of incident fractures to a comparable extent in older adults with and without CKD.

Yencheek *et al.* analyzed the effect of CKD on fracture risk prediction by DXA in a cohort of healthy, community-living older adults enrolled in the Health, Aging and Body Composition Study. This longitudinal study enrolled 2754 participants without disabilities, 70–79 years of age, from March 1997 through July 1998 and

followed them for a median of 11.3 years. At enrollment, participants underwent measurement of total hip (TH) and femoral neck (FN) aBMD by DXA, and kidney function was assessed. One year after enrollment, intact parathyroid hormone (PTH) and 25-hydroxyvitamin D (25-OHD) levels were measured. Osteoporosis was defined as a T-score <−2.5, CKD was defined as an MDRD estimated GFR (eGFR) <60 ml/min per 1.73 m², hyperparathyroidism was defined as a PTH >65 pg/ml, and vitamin D deficiency was defined as a serum 25-OHD level <20 ng/ml. The primary fracture outcome included all non-spine fragility fractures, and the secondary outcome included fragility-type hip fractures. The incidence of clinical and morphometric spine fractures was not ascertained. At baseline, mean age was 73 years, eGFR was 73 ml/min per 1.73 m², and 21% had an eGFR <60 ml/min per 1.73 m². Of 587 CKD patients, 83%, 13%, 3%, and <1% had CKD stages 3A, 3B, 4, and 5, respectively. Participants with CKD had a higher prevalence of several clinical risk factors for fracture including slightly older age, female sex, and white race. Mean PTH levels, although normal in both groups, were slightly but significantly higher in patients with CKD, and 17% had prevalent hyperparathyroidism. TH and FN BMD did not differ between patients with and without CKD. Ninety-eight and 286 incident non-spine fragility fractures occurred in patients with and without CKD, respectively. In proportional hazard regression models adjusted for demographic factors and levels of PTH and 25-OHD, prevalent osteoporosis and each SD decrease in BMD at the FN were associated with greater than a 2-fold increased risk of fracture in patients with CKD (hazard ratio, 2.10; 95% confidence interval, 1.23–3.59 and hazard ratio, 2.74; 95% confidence interval, 1.99–3.77, respectively). Relationships between TH BMD and fracture risk were similar to those at the FN. It is noteworthy that a significant interaction was present between prevalent hyperparathyroidism and FN BMD for fracture. Although the number of participants was too small to perform adjusted subset analyses, fracture risk tended to be lower in patients with than without hyperparathyroidism. When these analyses were repeated for fragility-type hip fracture, low FN BMD was associated with greater than a 5-fold increased risk of fracture (hazard ratio, 5.85; 95% confidence interval, 3.27–10.35). Finally, the ability of TH or FN BMD to

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predict fracture was comparable in patients with and without CKD. These data suggest that BMD measurement at either the TH or FN can identify elderly CKD patients who are at increased risk for non-spine fragility fractures.

This is the first prospective study to show that aBMD measurement at the hip predicts fracture in elderly patients with moderate CKD compared with patients without CKD. The few other prospective studies are limited by smaller numbers of CKD patients (9), lack of biochemical assessments of CKD-MBD (9,10), a population not directly comparable to Yencheek *et al.* (9,11), or shorter duration of follow-up (10). Jassal *et al.* (10) investigated the association between several measures of kidney function and both bone loss and fracture risk in 1713 patients enrolled in the Rancho-Bernardo Study and found that kidney disease was associated with bone loss at the hip but not with fracture. However, mean follow-up was much shorter, only 4.1 ± 0.9 years, the study was smaller, and only 83 incident fractures occurred. McCarthy *et al.* (9) studied a cohort of 427 postmenopausal women residing in Rochester, MN, to determine whether measurement of kidney function in addition to FN BMD enhanced the prediction of spine and non-spine fractures. This study was even smaller and, because only 1 patient had an eGFR <30 ml/min per 1.73 m² and only 23 patients had an eGFR <60 ml/min per 1.73 m², it is not surprising that there was no effect of kidney function on fracture prediction. Imori *et al.* (11) showed that TH BMD predicted fractures in women on hemodialysis with low PTH levels.

Thus, the study by Yencheek *et al.* addresses several important knowledge gaps and the results should raise questions about the 2009 KDIGO DXA recommendations in patients with CKD-MBD. In a large prospective study with a fracture endpoint, they demonstrated that CKD patients with low bone density were at the same or even greater risk of fracture as patients without CKD. They showed that mild hyperparathyroidism has little material effect on the direction of fracture risk when combined with aBMD. Their findings expand on those of several cross-sectional studies in patients with CKD stages 3, 4, and 5 (1–3) and on dialysis (4) that found that low BMD at the spine, hip, or forearm discriminated between patients with and without fracture to a degree comparable to postmenopausal women (18–20). However, this study also has limitations. Only 4% of the patients had CKD stages 4 and 5, so their results really apply only to patients with CKD stage 3. Likely for this reason, few patients had severe hyperparathyroidism, so they were unable to assess the effects of hyperparathyroidism on fracture prediction by DXA. Patients younger than 70 years were excluded, and spine fractures were not included. Despite these limitations, this study provides further evidence that low BMD is a risk factor for fracture in CKD patients, even in the presence of mild metabolic abnormalities that define the mineral and bone disorder.

Do these data constitute sufficient evidence to support the use of DXA as a population screening tool for fracture risk in CKD patients? The study by Yencheek *et al.* is an important addition to a growing body of observational data and provides support for the clinical relevance of aBMD measurements in elderly patients with CKD, particularly CKD stage 3. Those with normal BMD are at low risk of fracture. Those with low aBMD are at high risk of fracture and constitute a group for which we urgently need to consider how best to

prevent fractures. However, renal osteodystrophy is also a disorder of bone turnover, which may be low, normal, or high. Treatment decisions should not be based solely on measurements of bone density by DXA since they provide no information on bone remodeling rates.

Regardless of BMD, fracture prevention benefits may be provided by nonpharmacologic interventions, such as counseling on methods to reduce the risk of falls (21,22). Optimizing the management of vitamin D deficiency, hyperparathyroidism, and metabolic acidosis improves bone health and is good nephrologic practice. However, patients with low aBMD, who are at high risk of fracture, may need more aggressive management. Unfortunately, there are few data on the use of pharmacologic interventions to prevent fracture in the setting of CKD, particularly CKD that is severe enough to be associated with biochemical evidence of CKD-MBD. The use of drugs such as bisphosphonates, teriparatide, and denosumab, which have been shown to reduce fracture incidence in patients with normal kidney function, is controversial in patients with CKD. *Post hoc* analyses of several phase III studies suggest these agents can be administered safely to patients with mild to moderate CKD without biochemical evidence of the mineral and bone disorder and that fracture risk is reduced significantly (23–27). However, those studies included relatively few subjects with more severe CKD.

Thus, although this study is an important addition to the literature, we still need prospective observational studies to determine whether measurement of BMD by DXA also predicts fractures in patients with CKD stages 4 and 5, with overt biochemical manifestations of CKD-MBD. These studies should include men and women of all ages and races and should assess incidence of both spine and non-spine fractures. We also need studies to investigate whether combining measurements of bone turnover markers with measurement of BMD by DXA will enhance our ability to predict incident fractures and assist with decisions to initiate bone active agents. Finally, we need strong evidence to act on fracture risk screening in this very vulnerable population. *Post hoc* analyses of studies of patients with osteoporosis that included a few patients with abnormal kidney function provide some reassurance. However, randomized clinical trials with fracture endpoints in patients across the spectrum of CKD-MBD would provide far stronger evidence for the safety and efficacy of pharmacologic agents that are currently approved for prevention of fractures in patients with normal kidney function.

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