Patients with CKD are at increased risk of bone loss and fractures. Prospective observational studies have shown that the severity of kidney disease is directly associated with the amount of bone loss (1–4). In CKD, fractures are 2- to 14-fold more common than in the general population (5,6). The frequency of fractures increases as renal disease worsens (7,8), and the incidence of fractures has increased over the past 20 years (9,10). Compared with those without fractures, patients with CKD with fractures experience a 16% (9) to 270% (11) increased risk of mortality. The increasing numbers of fractures together with the high mortality rates have focused attention on methods to improve the diagnosis, risk stratification, and treatment of renal osteodystrophy in order to prevent fractures. The teracycline double-labeled transiliac crest bone biopsy with histomorphometry is the gold standard for diagnosing and classifying renal osteodystrophy and these biopsy results form the basis on which treatment decisions are made. However, bone biopsy is not practical in all patients all of the time. Bone biopsy is invasive, expensive, and not widely available, and physicians performing this procedure require specialized training (12–14). The pragmatic limitations of biopsy have fueled interest in the use of noninvasive imaging and biochemical methods to assess the type of renal osteodystrophy, classify risk of bone loss and fractures, and inform therapeutic decisions. Although the utility of noninvasive methods to improve patient-related outcomes remains to be proven in clinical trials, they have elucidated both mechanisms of bone fragility and potential targets for fracture prevention strategies in CKD populations.

Traditionally, the role of dual energy x-ray absorptiometry (DXA) to classify fracture risk in CKD was controversial. This is because the pathogenesis of renal osteodystrophy is not uniform, may be the result of either single or overlapping causes (e.g., hypogonadal, glucocorticoid-induced, hyperparathyroidism, low or high turnover bone disease, poorly mineralized osteoid, mixed), and is fluid (e.g., may change from low to high turnover and vice versa). In addition, the type of renal osteodystrophy does not correlate with low, high, or normal bone mineral density (BMD). Furthermore, elevated parathyroid hormone (PTH) levels, which are common in CKD, may be anabolic for trabecular bone and catabolic for cortical bone. Given the inability of DXA to separate these components, DXA may be limited in its use as a marker of bone strength. However, despite these limitations of DXA, recent prospective trials in patients with predialysis CKD (15), ESRD on hemodialysis (16), and after kidney transplantation (17) indicate that low areal BMD measured by DXA at the forearm and hip predicts future fracture. These new data will influence the updated recommendations on the screening and management of bone disease from the Kidney Disease Improving Global Outcomes Guidelines Committee.

Measurement of PTH and bone turnover markers also predicts bone loss and classifies fracture risk. Bone formation markers such as bone-specific alkaline phosphatase (BSAP), osteocalcin, and procollagen type 1 N-terminal propeptide (P1NP) are markers of osteoblast function. Bone resorption markers, such as tartrate-resistant acid phosphatase 5b (Trap-5b) and C-terminal telopeptide of type I collagen (CTX), are markers of osteoclast number and function, respectively. Other circulating markers that may have utility in classifying the risk of bone loss and fractures include fibroblast growth factor (FGF-23), which is involved in bone mineralization and remodeling, and sclerostin and dickkopf-1, which are inhibitors of WNT signaling and suppress bone formation. In CKD, the measurement of PTH and bone turnover markers has been historically reserved for predicting bone turnover. However, results from biopsy studies correlating levels of PTH and circulating markers with dynamic indices from bone histomorphometry have generally been disappointing; discrimination of turnover by serologic markers has been modest (18–23). Measurement of biochemical markers may be more helpful in predicting bone loss and fractures (4,16,24–26).

In prospective studies of patients with CKD both before (4) and after kidney transplantation (24), our group evaluated effects of hyperparathyroidism and elevated levels of turnover markers on changes in bone mass, geometry, microarchitecture, and strength measured by high-resolution peripheral quantitative computed tomography (QCT), a research tool used to assess bone microstructure that is available at only several institutions worldwide. Higher concentrations of PTH, BSAP, osteocalcin, P1NP, Trap-5b, and CTX predicted loss of cortical area, density and thickness, increases in cortical porosity, and decreases in bone
strength. Regarding the ability of PTH and bone turnover markers to predict fracture, a prospective study of patients with ESRD reported that fracture risk was higher in patients with either low (<150 pg/ml) or high (>300 pg/ml) PTH levels, and with higher BSAP levels (16). In kidney transplant recipients, PTH levels=130 pg/ml at 3 months after transplantation predicted incident fractures (26). These data indicate that hyperparathyroidism and higher remodeling rates, as assessed by PTH and clinically available turnover markers, predict loss of bone mass and strength before dialysis as well as fracture in ESRD. To date, it is unknown whether specific bone turnover markers or combinations of formation and resorption markers provide the best prediction of bone loss or fracture. Furthermore, few data were available regarding the ability of PTH and turnover markers to predict bone loss in dialysis patients.

In this issue of CJASN, an investigation by Malluche et al. fills this gap and lends further support to the use of PTH and markers of bone turnover to identify hemodialysis patients at risk for worsening bone disease, defined here as ≥2% bone loss over 12 months (27). In this prospective study, 81 patients were enrolled from dialysis centers across Kentucky between April 2009 and April 2012. At study entry, volumetric BMD and areal BMD of the spine and hip were measured by central QCT and DXA, respectively. Biochemical markers that reflect remodeling activity were also obtained, and included intact PTH, BSAP, PINP, Trap-5b, FGF-23, sclerostin, and dickkopf-1. Patients’ mean age was 52.6 ± 12.3 years, 56% were men, 53% were African American, and median dialysis vintage was 41 months. At baseline, QCT and DXA of the hip identified similar rates of osteoporosis (11.5% and 12.8%, respectively); however, at the spine, QCT identified more patients with osteoporosis than DXA (11.3% versus 4.9%, respectively). Baseline BMD correlated with intact PTH, BSAP, Trap-5b, sclerostin, and FGF-23. At 1 year, hip QCT identified a higher number of patients experiencing bone loss (51.3%) than DXA (38.5%). After multiple adjustments, baseline levels of Trap-5b and sclerostin predicted loss of total volumetric BMD at the hip by QCT, baseline levels of PINP predicted gain of cortical volumetric BMD at the spine by QCT, and baseline levels of FGF-23 predicted loss of areal BMD at the spine by DXA. Changes in PHT and sclerostin over 1 year predicted changes in trabecular volumetric BMD at the spine. Whereas increases in intact PTH predicted increases in trabecular density, increases in sclerostin predicted decreases in trabecular density.

This and other studies (16,24–30) published over the last decade are advancing our ability to noninvasively assess renal osteodystrophy. We can now classify the risk of bone loss and fractures by widely available noninvasive tools such as DXA and bone turnover markers. However, does the use of these tools to manage bone disease in our patients with CKD represent the next paradigm shift in CKD management, in which fractures are prevented, quality of life is preserved, and lives are saved? It is too early to make that assumption because the use and interpretation of noninvasive measures of bone mass and turnover remain challenging. First, the clinical significance of changes in bone mass in CKD needs to be clarified. Second, some biochemical markers are cleared by the kidney (osteocalcin, PINP monomer, and CTX) and their relationships to bone loss, fracture risk, and turnover are not fully defined. Third, levels of biochemical markers are influenced by sex, age, and race, and it is not known whether these characteristics are influenced by CKD or CKD type. Fourth, reference ranges for biochemical markers in CKD populations do not exist, and it is not clear whether CKD stage–specific ranges are necessary. Fifth, biochemical markers have high coefficients of variation, which decreases their utility in the individual patient. Sixth, relationships between changes in turnover markers and their prediction of changes in bone mass and fracture risk need to be determined. Seventh, paradoxical relationships between novel markers (e.g., sclerostin and bone mass) reported in cross-sectional studies of patients with CKD have not yet been explained and may be the result of confounding by bone mass, accumulation of degradation products as renal function declines, or osteocyte dysfunction in the setting of uremia. Finally, treatment of renal osteodystrophy cannot be decided without knowledge of underlying bone turnover and mineralization; in the majority of patients, the current battery of circulating markers do not provide sufficient discrimination to inform complex treatment decisions. Although studies to date suggest that biochemical markers might be useful in CKD to predict the risk of progressive bone disease and fracture and to identify patients in need of bone-active treatment strategies, prospective studies of PTH and biochemical markers as predictors of fractures that include all CKD stages and demographic groups are needed to demonstrate their utility in fracture prediction, provide reference ranges that correlate with bone histology, and correlate changes in PTH and biochemical markers with changes in bone mass and fracture risk. Thus, despite the vast potential of these tools to help us manage renal osteodystrophy and prevent fractures, further research is needed before we can safely use them in the clinic.

Disclosures
Columbia University has licensed patents to Abbott Diagnostics for the use of neutrophil gelatinase–associated lipocalin and a biomarker of AKI.

References

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See related article, “Bone Mineral Density and Serum Biochemical Predictors of Bone Loss in Patients with CKD on Dialysis,” on pages 1254–1262.