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# Can One Evaluate Bone Disease in CKD Without a Biopsy?

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## Abstract

**Purpose—**Chronic kidney disease – mineral and bone disorder (CKD-MBD) is a complex disorder of bone and mineral metabolism that results in excess risk of fractures, cardiovascular events and mortality. Management of the bone disorder of CKD-MBD may require bone biopsy to determine appropriate treatment strategies. However, it is unclear when biopsy may be necessary and whether or not state-of-the art imaging and serologic testing can supplant the bone biopsy as a tool to assist with management decisions.

**Recent Findings—**Advances in imaging methods now permit the non-invasive assessment of structural aspects of bone quality. Furthermore, common bone imaging tools, such as dual energy X-ray absorptiometry can be used to stratify for fracture risk. Circulating markers of bone turnover can be used to assess risk of bone loss and fracture, but they are less useful to diagnose type of renal osteodystrophy.

**Summary—**Although advances in imaging now permit assessment of fracture risk more accurately in CKD patients, assessment of type of renal osteodystrophy remains poor without bone biopsy. The virtual bone biopsy will be possible only when we are able to non-invasively assess turnover with good accuracy. A bone biopsy is needed in settings of unclear bone turnover.

### Keywords

Renal osteodystrophy; CKD-MBD; bone biopsy; bone imaging; bone turnover markers

## Introduction

Renal osteodystrophy (ROD) is a bone disorder that occurs in chronic kidney disease (CKD) patients and is associated with increased fracture risk. Tetracycline double-labeled transiliac crest bone biopsy with histomorphometry is the gold standard for the diagnosis and classification of ROD. However, bone biopsy is not practical to obtain in all patients all of the time. Thus, there is great interest in developing non-invasive approaches that can be used in the clinic to assess ROD in CKD populations. Here we review non-invasive methods and their utility in assessing ROD.

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**Conflicts of Interest**
Dr. Babayev: none
Dr. Nickolas: Columbia University has licensed patents to Abbot Diagnostics for NGAL as a marker of AKI

## Chronic Kidney Disease – Mineral and Bone Disorder

ROD is a complex disorder of bone due to the individual and combined actions of metabolic and hormonal abnormalities that occur with CKD: hyperphosphatemia, hypocalcemia, hyperparathyroidism (HPT), deficiency of 25(OH)D and decreased renal synthesis of $1,25(OH)_2D$, chronic metabolic acidosis, and premature hypogonadism. These abnormalities impair bone remodeling and mineralization, and result in cortical and trabecular defects. The term CKD-mineral and bone disorders (CKD-MBD) has been implemented by the Kidney Disease Improving Global Outcomes (KDIGO) working group to refer more broadly to the systemic disorder of mineral and bone metabolism due to CKD; it is manifested by either one or a combination of (1) abnormalities of calcium, phosphorous, parathyroid hormone (PTH), or vitamin D metabolism; (2) abnormalities of bone turnover, mineralization, volume, linear growth or strength; and (3) vascular or other soft tissue calcification [1]. The most important clinical bone related outcome in CKD-MBD is fracture.

## Bone strength

Bone strength is dependent on both bone density and quality. Bone density is a measure of bone mass or quantity and is measured by dual energy X-ray absorptiometry (DXA). Bone quality describes bone material properties and includes bone turnover, microarchitecture and mineralization, accumulation of microdamage, and collagen properties. The gold standard to assess bone strength is tetracycline double-labeled transiliac crest bone biopsy with histomorphometry. Analyses performed on bone biopsy samples measure the volume and microarchitecture of cancellous and cortical compartments, the accumulation of microdamage, mineralization, and remodeling. In CKD, these abnormalities may include defects in bone volume and microarchitecture (cortical porosity, thinning and trabecularization, and trabecular thinning and dropout); in mineralization (osteomalacia); and in remodeling (adynamic bone disease, osteitis fibrosa cystica or mixed osteodystrophy). Unfortunately, the routine use of bone biopsy to evaluate ROD is not always practical. Bone biopsy is invasive, expensive, not widely available, and physicians performing this procedure require specialized training [1–3]. Furthermore, once obtained the biopsy only provides information about the type of bone disorder at one site (the anterior iliac crest) and at one point in time. Thus, non-invasive approaches that can be used in the clinic to diagnose bone disease and monitor treatment responses would be helpful.

## Contemporary fracture epidemiology in chronic kidney disease

Fracture is an important clinical outcome in ROD, and its prevention motivates our efforts to devise disease assessment strategies. In CKD fractures are common [4–9], increase in proportion to CKD severity [6,10,11] and are associated with excess morbidity, mortality and health economic costs [12–14]. Several investigations have provided 21$^{st}$ century updates on CKD-associated fracture epidemiology [10,15–18]. Naylor et al. [10] reported 3-year combined incidence rates of hip, forearm, pelvis, and proximal humerus fractures from a Canadian population of men and women age ≥40 years from across the CKD spectrum. In women older than 65 years fracture incidence per 1000 person-years was 15.0, 20.5, 24.2, 31.2, and 46.3 for patients with an eGFR ≥60 mL/min, 45–59 mL/min, 30–44 mL/min, 15–29 mL/min

and <15 mL/min respectively. Similarly, corresponding estimates for men older than 65 years were 5.7, 7.3, 10.1, 15.3, and 24.3 respectively. Nair et al. [15] used the United States Renal Data Systems (USRDS) to investigate trends in fracture epidemiology from 1996 to 2009 in patients with incident ESRD. Compared to incident ESRD patients in 1996, hip fracture rates were increased by 43% in 2004. It is noteworthy that in 2009 hip fracture rates had decreased from 2004 levels but remained increased by 27% compared to 1996. Arneson et al. [18] used Medicare data from 1993 to 2010 to investigate hip fracture incidence in ESRD patients compared to the general population and reported similar results. Potential explanations for decreasing hip fracture incidence rates in ESRD patients may include patient-specific characteristics and changes in CKD-MBD management. Kidney transplant recipients are also susceptible to fracture [5,8,19,20]. Over the first 3 years of transplantation hip fracture risk is 34% higher than patients on dialysis [5], and hip and spine fracture risk are more than 4- and 23- fold higher [20] than the general population, and about one-quarter of recipients will fracture within the first 5 years of transplantation [19].

These recent epidemiologic data confirm that fractures remain a serious and alarming CKD-MBD complication, in particular since they are associated with high morbidity, mortality and cost. In one study, a third to almost half of hemodialysis patients admitted with a fracture were discharged to a skilled-nursing facility after the incident hospitalization. During the year after discharge, patients had an adjusted mean of 3.8–5.2 additional hospitalizations, comprising on average an extra 33–52 inpatient days compared to patients without fracture [15]. Moreover, after hip fracture mortality risk was reported to increase by 16%[15] to 60%[13], and were associated with high economic costs [21].

## Mechanisms of decreased bone strength in CKD from bone histology

Recent bone biopsy studies have enlightened our understanding of how ROD effects bone strength, and suggest that a non-invasive assessment of bone disease must measure the underlying microstructural and dynamic defects in bone quality that drive decreases in skeletal fragility. [22,23]. Malluche et al. [22] reported findings from 630 biopsies obtained from patients in the United Stated and Europe. Their mean age was 55±1 years, 48% were women, 14% were blacks, 5% were on peritoneal dialysis, and mean dialysis vintage was 51±1.8 months. There were notable race differences in bone quality. Low turnover predominated in whites (62%) and normal turnover predominated in blacks (68%). Mineralization defects were rare (3% of patients). Trabecular bone volume was low in one-third of whites and high in two-thirds of blacks; for both races low trabecular volume was associated with thinned rather than lost trabeculae. The majority of blacks had normal cortical thickness but high porosity, whereas there was approximately the same number of whites with low or normal cortical thickness, and normal or high cortical porosity. Abnormal microarchitecture was associated with abnormal turnover. High turnover was associated with greater severity of cortical porosity, and low turnover was associated with lower trabecular volume and thinner cortices. Malluche et al. [23] also reported on relationships between bone quality and strength in 35 CKD-5D patients. Low turnover was associated with lower trabecular volume than either normal or high turnover. High turnover was associated with lower relative mineral content. Similar to their larger publication of 630 patients, low trabecular volume was associated with thinned trabeculae. Regarding bone

mechanical competence (i.e. strength), bone with high turnover had lower stiffness and failure load than bone with normal or low turnover.

## Imaging bone disease in CKD

DXA, QCT and HR-pQCT are imaging methods that quantify bone mass and structural aspects of bone quality. They do not measure turnover or mineralization. Therefore, they cannot be used alone to determine ROD type or assess completely disease severity. Furthermore, monitoring disease activity with imaging methods may be difficult because there is no data correlating changes in the parameters measured by these tools with changes in fracture risk.

DXA is widely available and is the clinical standard to measure fracture risk in patients with healthy kidney function. However, fracture risk screening by DXA in CKD has been controversial. DXA does not have sufficient resolution to discriminate between cortical and trabecular bone, it provides a composite measure of cortical and trabecular compartments, and is unable to determine turnover or mineralization. Furthermore, due to study limitations, results of cross-sectional and prospective studies on fracture discrimination and prediction were inconsistent [20,24–34]. However, recent prospective trials in patients with pre-dialysis CKD [35], ESRD on hemodialysis [33] and after kidney transplantation [36] strongly suggest that low areal BMD measured by DXA at the total hip and femoral neck predicts future fracture (Table 1). Indeed, these prospective trials have begun to clarify and validate the use of DXA in CKD and help clinicians use and interpret DXA imaging. They indicate that in CKD, fracture risk screening is possible by imaging the total hip and femoral neck and that the World Health Organization definition of osteoporosis (T-Score ≤ −2.5) is clinically relevant. Unfortunately, there are no prospective data determining whether measurement of areal BMD at the mainly cortical one-third radius (>90% cortical bone) is a better predictor of fracture than measurement of areal BMD at sites composed of mixed cortical and trabecular bone (i.e. total hip).

High-resolution imaging methods measure and quantify cortical and trabecular 3-dimensional (volumetric) BMD, geometry, microarchitecture, and strength. Currently, these tools are used for research. QCT has a resolution of 300 $\mu m^3$ and measures volumetric BMD and geometry of cortical and trabecular compartments. Peripheral QCT has been used to assess skeletal effects of CKD in patients pre-dialysis, on hemodialysis, and after kidney transplantation. Studies reported that in CKD patients cortical deficits predominated [28,37] and cortical abnormalities both discriminated [28] and predicted fracture [38]. Similarly, HR-pQCT separately measures cortical and trabecular volumetric BMD and geometry, but its higher nominal resolution of 82 $\mu m^3$ permits quantification of trabecular number, thickness and separation. Finite element analysis, a computational method to quantify bone strength, can be applied to 3-dimensional HR-pQCT datasets to measure strength either of whole bone or of individual cortical and trabecular compartments. Recently, advanced HR-pQCT processing methods have been developed to characterize cortical porosity [39,40] and trabecular plate and rod structure [41]. In patients from across the CKD spectrum, our group and others have demonstrated in cross-sectional and prospective studies that measurement of bone mass, geometry, and microarchitecture by HR-pQCT at the distal radius and tibia

discriminated fracture status [24,25,42–44], detected abnormalities in bone quality that negatively impact bone strength [45–47], and elucidated underlying microstructural defects that result in BMD abnormalities measured by DXA [45,46]. For example, in a prospective study of 54 patients with moderate to end stage renal disease we found that mean annualized losses of areal BMD at the forearm were 2.9% [45]. With HR-pQCT, we identified microstructural mechanisms of forearm bone loss detected by DXA; there was significant loss of cortical area (−2.9%), density (−1.3%) and thickness (−2.8%) and significant increases in cortical porosity (+4.2%). Prospective studies are needed to determine whether measurement of bone mass and microarchitecture by HR-pQCT predicts fracture, and whether therapies that mitigate microarchitectural abnormalities detected by HR-pQCT protect against fracture.

The utility of combining measures of areal BMD by DXA with measures of bone geometry and microarchitecture by HR-pQCT to enhance fracture prediction above that of either imaging test alone is not established. In a cross-sectional study of CKD patients with and without fracture, Jamal et al. [26] studied the utility of combing measures from DXA with measures from HR-pQCT. Areal BMD was measured by DXA at the mainly trabecular ultradistal radius and total volumetric BMD and cortical thickness were measured by HR-pQCT at the distal radius. When HR-pQCT measures were added to areal BMD by DXA, the AUC was 0.81 (95% CI 0.74 to 0.88). This was not significantly different than areal BMD by DXA at the radius alone (AUC 0.80; 95% CI 0.74 to 0.87; p 0.4). The reasons for this negative finding are likely due to redundancies in parameters measured by these imaging methods. Both DXA and HR-pQCT measure structural aspects of bone quality. Thus, enhancement of assessing bone disease severity in CKD-MBD will most likely be obtained by combining structural with dynamic measures of bone quality.

## Assessing bone turnover and osteomalacia

There are no recent bone biopsy studies that update the historical literature on assessing turnover and osteomalacia non-invasively. Nonetheless, their evaluation is an essential component of assessing bone disease. Turnover may range from extremely low (adynamic bone disease) to extremely high (osteitis fibrosa cystica), turnover may change over time, and turnover-type affects treatment. Pharmacologic agents that protect against fracture alter remodeling rates. While anti-resorptive agents may be used in patients with high turnover they are contraindicated in patients with adynamic bone disease. Similarly, while osteoanabolic agents (i.e. Teriparatide) may be used in patients with low turnover they are contraindicated in patients with high turnover. As discussed, bone biopsy is not always possible or practical. Thus, a non-invasive approach to turnover assessment is desirable. Despite assay limitations, non-invasive assessment can be achieved with reasonable accuracy by measuring circulating levels of parathyroid hormone (PTH) and bone turnover markers (BTMs) [48–53]. 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 telopeptides of type I collagen (CTX) are markers of osteoclast number and function, respectively. In clinical practice, PTH and BSAP are the most commonly used markers of turnover in CKD-MBD. In general, extremes of PTH predict extremes of bone turnover both in pre-dialysis [52] and dialysis-dependent [53] patients.

Unfortunately, prediction of underlying histology is less discriminatory when PTH levels are within the middle range. For BTMs, reference ranges in CKD populations do not exist and some BTMs are renally cleared (osteocalcin, P1NP monomer and CTX). Thus, their use and interpretation in CKD-MBD is challenging. In general, their predictive values are improved at the extremes of BTM levels, and with combining multiple BTMs with or without PTH [48–50]. Low vitamin D levels, and low levels of PTH in conjunction with high levels of BSAP have been correlated with osteomalacia, and osteomalacia has been associated with hip fractures.

Measurement of PTH and BTMs may be more helpful in predicting bone loss and fractures than in predicting type of turnover *per se* [24,33,45,46,54]. In a cross sectional study of pre-dialysis CKD patients with and without fracture, we reported that higher levels of PTH and BTMs were associated with lower cortical and trabecular density, and with thinner cortices and trabeculae [24]. Moreover, higher levels of P1NP, osteocalcin, CTX, and Trap-5b discriminated fracture [24]. In prospective studies of CKD patients both before [45] and after kidney transplantation [46], our group evaluated effects of remodeling measured by circulating levels of PTH and BTMs on changes in bone mass, geometry, microarchitecture, and strength measured by HR-pQCT. 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 BTMs to predict fracture, a prospective study of ESRD patients 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 [33]. In kidney transplant recipients PTH levels ≥130 pg/mL at 3-months post-transplantation predicted incident fractures [54]. These data indicate that higher remodeling rates, as assessed by PTH and clinically available BTMs, result in bone loss, deterioration of cortical and trabecular microarchitecture, and predict fracture. Prospective fracture studies of PTH and BTMs that include all CKD stages and demographic groups are needed to validate these findings, provide reference ranges that correlate with bone histology, and correlate changes in PTH and BTMs with changes in fracture risk.

## Can we non-invasively assess bone disease in CKD?

Non-invasive assessment of bone disease needs to detect abnormalities in bone structure, remodeling and mineralization, predict clinical outcomes, inform treatment decisions, and predict changes in clinical outcomes in response to treatment. In figure 1 we demonstrate a prototype approach to stratify patients into those who do and do not require bone biopsy. While this approach requires validation in prospective fracture trials and against bone histology, our group explored a modified version [24]. We investigated whether severity of disease and fracture status could be determined by combining imaging of bone structure by DXA and HR-pQCT with biochemical assessment of turnover by PTH and BTMs. This cross sectional study included 82 patients with stage 3–5 CKD, 23 with and 59 without fractures, we reported that higher levels of PTH and BTMs were associated with more severely deteriorated microarchitecture and that fracture discrimination was significantly improved by combing a markers of formation (P1NP, osteocalcin) and resorption (Trap-5b) with areal BMD at the femoral neck. The rationale for our approach is supported by new evidence indicating that DXA and high resolution imaging methods measure bone mass and

microarchitecture, uncover structural abnormalities that impact fragility, and risk-stratify patients for fracture. However, several important limitations to our approach remain to be resolved. We lack non-invasive tools to detect osteomalacia. PTH and BTMs are inconsistent markers of underlying histology, reference ranges for BTMs that correlate with histology across the CKD spectrum do not exist, changes in BTMs over time have not been correlated against changes in bone histology, and correlations between changes in BTMs and changes in fracture risk need to be determined. Furthermore, changes in bone mass and microarchitecture over time have not been correlated with changes in either disease severity or fracture risk, and the optimal time-interval for disease monitoring has not been established. Thus, the decision to treat and to monitor treatment response in a CKD patient managed with vitamin D analogs, or an anti-resorptive or osteoanabolic agent may not be completely possible without a bone biopsy.

## Conclusion

Bone disease is CKD is common and potentially life threatening. The current gold standard to assess ROD is invasive and suboptimal for disease screening and management. Advances in imaging methods enable non-invasive measurement of structural aspects of bone disease that drive increased skeletal fragility; however, before the “virtual bone biopsy” is ready for prime time more accurate methods of non-invasively assessing turnover and osteomalacia, validated against bone histology, are needed. Finally, prospective fracture trials are necessary to demonstrate that clinical bone outcomes are improved by a non-invasive approach to ROD management.

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**Key points**

- Renal osteodystrophy is a complex bone disorder that is associated with high risk of fractures, morbidity and mortality
- New data from prospective fracture studies in CKD populations indicate that low areal bone mineral density measured by dual energy X-ray absorptiometry predicts future fractures
- Advances in imaging methods now provide the ability to non-invasively assess microarchitectural aspects of bone quality that correlate with decreases in bone strength
- Non-invasive assessment of bone turnover and mineralization is still suboptimal
- Future research needs to focus on developing non-invasive methods to measure turnover and mineralization and to study whether combining measures of bone structure by imaging with measures of turnover by serum biochemistries quantifies disease severity, predicts fracture and informs treatment decisions

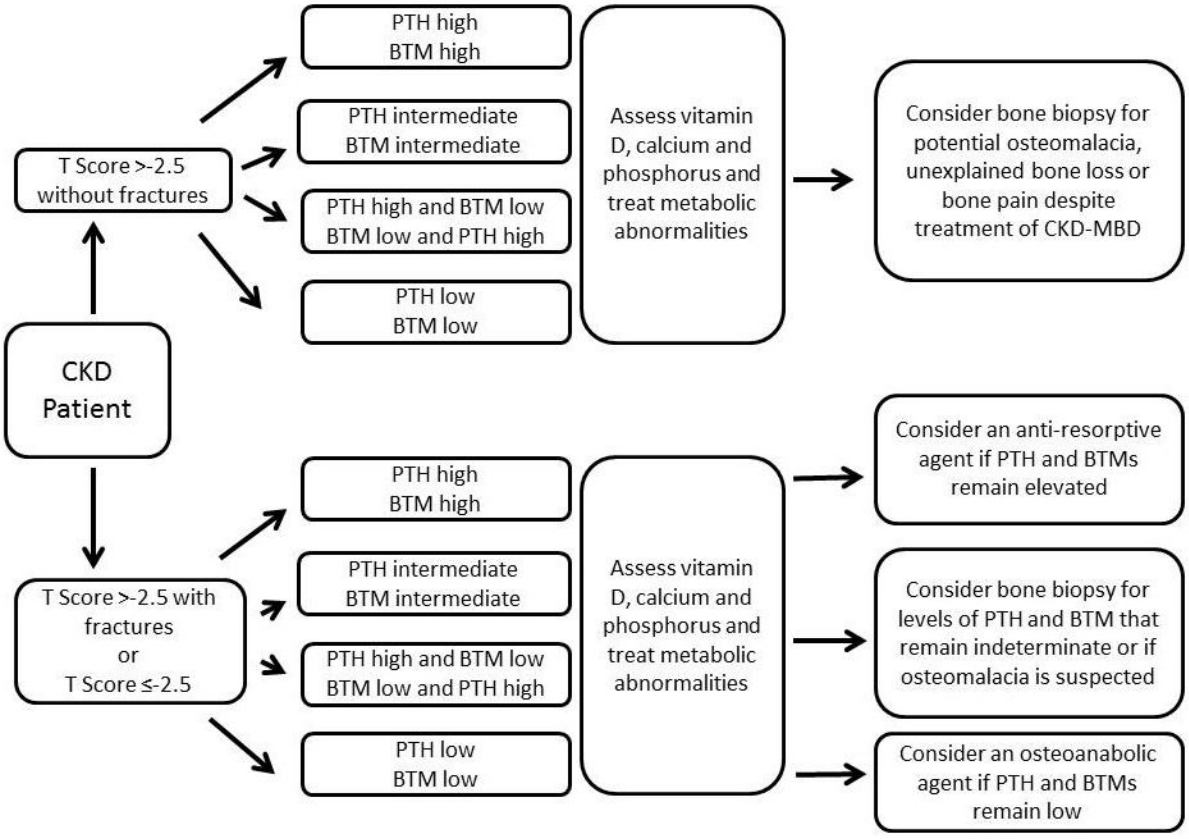


**Figure 1.**
Prototype algorithm of a non-invasive approach to assess bone disease in CKD

**Table 1**

Summary of prospective fracture trials evaluating the ability of areal BMD by dual energy X-ray absorptiometry to predict incident fracture

| Study | Study population | N | Follow up | Fracture incidence | Fracture risk and areal BMD |
|---|---|---|---|---|---|
| Yenchek et al 2012 (35) | Elderly patients (age 70–79) with and without CKD (GFR under 60ml/min/1.73m$^2$) | 2754 total<br>587 with CKD | 11 years | Non-CKD: 13.2%<br>CKD: 16.7% | Non-CKD:<br>FN BMD (T-Score <2.5)<br>HR 1.64 (95% CI 1.20, 2.25)<br>CKD:<br>FN BMD (T-Score <2.5)<br>HR 2.10 (95% 1.24, 3.59)* |
| Iimori et al 2012 (33) | HD dependent | 485 | 5 years | 1.9 fractures per 100 patient years | Total Hip BMD (per SD)<br>HR 0.65 (95% CI 0.49–0.87) |
| Akaberi et al 2008 (36) | Post renal transplant | 238 | 10 years | 19.3% | Total hip BMD (T-Score <2.5)<br>HR 3.5 (CI 1.8–6.4) |

* p value for CKD and osteoporosis interaction was not significant