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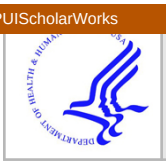

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Bone Quality in Chronic Kidney Disease: Definitions and Diagnostics

Erin M.B. McNerny and **Thomas L. Nickolas**
Indiana University School of Medicine, Indianapolis, IN

Department of Medicine, Division of Nephrology, Columbia University Medical Center, NY, NY

Abstract

Purpose of review—In this paper we review the epidemiology, diagnosis and pathogenesis of fractures and renal osteodystrophy.

Recent findings—The role of bone quality in the pathogenesis of fracture susceptibility in CKD is beginning to be elucidated. Bone quality refers to bone material properties, such as cortical and trabecular microarchitecture, mineralization, turnover, microdamage, and collagen content and structure. Recent data has added to our understanding of the effects of CKD on alterations to bone quality, emerging data on the role of abnormal collagen structure on bone strength, the potential of non-invasive methods to inform our knowledge of bone quality and how we can use these methods to inform strategies that protect against bone loss and fractures. However, more prospective data is required.

Summary—Chronic kidney disease (CKD) is associated with abnormal bone quality and strength which results in high fracture incidence.

Keywords

Bone quality; bone mineral density; renal osteodystrophy; kidney; fracture; dialysis

Introduction

Chronic Kidney Disease – Mineral and Bone Disorder

The term CKD-mineral and bone disorder (CKD-MBD) was coined 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, phosphorus, parathyroid hormone (PTH), or

Contact Author: Tom Nickolas MD MS, Associate Professor of Medicine, Columbia University Medical Center, Department of Medicine, Nephrology, 622 West 168th Street, PH4-124, NY, NY 10032, 212.305.5020 (phone), 212.305.4981 (fax), tln2001@cumc.columbia.edu.

Conflict of Interest
Thomas Nickolas and Erin McNerny declare no conflict of interest.

Human and Animal Rights and Informed Consent
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vitamin D metabolism; (2) abnormalities of bone turnover, mineralization, volume, linear growth or strength; and (3) vascular or other soft tissue calcification[1].

Renal osteodystrophy (ROD) is the bone component of CKD-MBD. It is a disorder of bone quality and strength secondary to effects of metabolic and hormonal disturbances that occur with kidney failure, including: hyperphosphatemia, hypocalcemia, secondary hyperparathyroidism (HPT), 25(OH)D deficiency and decreased renal synthesis of $1,25(OH)_2D$, chronic metabolic acidosis, chronic inflammation and premature hypogonadism. These abnormalities impair bone turnover and mineralization, collagen structure, and cortical and trabecular microarchitecture (Figure 1). Collectively, these effects increase fracture risk by reducing both bone mass and quality. Bone "quality" is a catchall term for the numerous properties influencing bone's mechanical function outside of bone mass, i.e. if two bones are of the same size but of dissimilar fracture resistance, this difference can be attributed to differences in quality.

Fracture epidemiology in chronic kidney disease

Fractures are 2- to 14-fold more common in CKD patients than in the general population[2–4], and have been reported to increase in prevalence[5] and incidence[6] as kidney function worsens (Figure 2). In patients on dialysis with end stage renal disease (ESRD), fracture incidence at the hip was reported to have peaked in 2004 at 21.9 events per 1,000 person-years, with subsequent decline to 16.6 per 1,000 person-years in 2010[7]. In contrast, rates of peripheral (arm and leg) fractures were reported to have increased continuously between 1992 and 2009, and the majority of increased fracture risk occurred in Caucasian patients[8]. Kidney transplant recipients are also susceptible to increased fractures[9–12]: early after transplantation hip fracture risk is 34% higher than in patients on dialysis[11]; risk of hip and spine fracture are more than 4- and 23- fold higher[12] than in the general population; and about 25% of recipients experience a fracture within the 5-years of their transplant[9]. Recent data suggests that improved management of CKD-MBD before and after transplantation have resulted in a 3-fold reduction of fracture incidence during the first post-transplant year[13].

Fractures in CKD patients are associated with excess morbidity, mortality and health economic costs[14–17]. In one study, one-third to almost one-half of patients with ESRD with a fracture admission to the hospital were discharged to a skilled-nursing facility. In the year following 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[18]. After hip fracture, mortality risk was reported to increase by 16%[18] to 60%[15], and healthcare associated costs have been estimated to exceed $100 and $500 billion for patients with ESRD and predialysis CKD respectively[17]. Therefore, improved identification and management of increased fracture risk in CKD patients could significantly reduce both the morbidity and economic burdens of CKD-MBD.

CKD impairs bone quality and strength

Bone strength (and fracture risk) is defined by both its mass and quality. Bone mineral density (BMD) is a determination of its mass or quantity and is measured in the clinic by

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dual energy X-ray absorptiometry (DXA). Bone quality is defined by bone material properties and includes bone turnover, microarchitecture, mineralization, accumulation of microdamage (microscale cracks), and collagen properties (such as glycation and crosslinking). The hormonal and metabolic disturbances associated with CKD cause defects in all aspects of bone quality (Table 1).

Alterations in bone turnover affect bone strength and quality by controlling bone mass, microstructure, and the balance and spatial distribution of newly formed, mature, and aged or damaged areas of tissue[19]. Microdamage, advanced glycation endproducts (AGEs), mineralization, mineral carbonate substitution, and mineral crystallinity can all increase or accumulate with time and influence bone mechanical properties[20, 21]. The presence of microcracks of sufficient size and/or number is thought to reduce bone's ability to withstand larger impacts[22]. AGEs form crosslinks in the collagen matrix, limit fibril stretching and slipping, and can embrittle the tissue[23]. Increased mineralization and carbonate substitution stiffen the bone matrix and may also contribute to brittleness in older bone[24]. In healthy bone, areas of aged or damaged bone are targeted for turnover, an ongoing repair process that removes problem areas and maintains the mean tissue age and properties of the bone. A disruption in the balance of turnover, and therefore this repair process, occurs in both high and low turnover ROD patients. As such, it is not surprising that bone quality is impaired in CKD-MBD. In addition to turnover-related effects on bone quality, CKD may directly affect the composition and quality of bone through factors including altered mineral metabolism and oxidative stress.

Measurement of Bone Mass

Dual energy X-ray absorptiometry

DXA is the clinical standard to measure bone mass and fracture risk in the general population. The use of DXA to predict fractures in patients with CKD has been controversial; however, the recent 2016 KDIGO Guideline updates now recommend DXA to predict fracture (out for public review). Longitudinal studies in patients with CKD stages 3 through 5D[25–27] and after kidney transplantation[28] demonstrated that low areal BMD measured by DXA at the forearm, hip (total and femoral neck) and spine predicts future fracture. These studies also indicate the World Health Organization T-score cut offs for osteopenia and osteoporosis can be used for CKD patients as for the general population. It is important to note that DXA does not assess either bone tissue quality or the type of renal osteodystrophy; thus, bone biopsy remains the gold standard to inform treatment decisions in patients with CKD.

High resolution imaging in CKD-MBD

In addition to DXA discussed above, QCT and HR-pQCT are imaging tools that measure 3-dimesional bone density and structural aspects of bone quality. They do not measure remodeling or mineralization. Therefore, they cannot be used to inform type of treatment since they are unable to determine ROD type.

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High-resolution imaging tools assess cortical and trabecular 3-dimensional (volumetric) density, geometry, microarchitecture, and strength. They allow us to explore the pathogenesis of bone fragility due to CKD or other metabolic bone diseases non-invasively. QCT has a resolution of 300 μm^3 and quantifies volumetric density and geometry of cortical and trabecular bone. Using QCT, studies have found that in CKD patients cortical deficits predominate[29, 30] and cortical abnormalities both discriminate[29] and predict fracture[31].

Similarly, HR-pQCT separately quantifies cortical and trabecular volumetric density and geometry, but its higher nominal resolution of 60 to 82 μm^3 permits measurement of trabecular number, thickness and separation. Finite element analysis, a computational method to measure bone mechanical competence (i.e., strength), is applied to 3-dimensional HR-pQCT datasets to assess biomechanical characteristics of either whole bone or individual cortical and trabecular compartments. Advanced HR-pQCT processing methods also permit characterization of cortical porosity[32, 33] and trabecular plate-rod structure[34].

Our group and others have shown that measures of bone density, geometry and microarchitecture at the ultradistal radius and tibia from HR-pQCT both discriminated and predicted fractures[35–39], identified abnormalities in bone quality that negatively impacted bone strength[40–42], and elucidated underlying microstructural defects that resulted in abnormalities of bone density measured by DXA[40, 41]. For example, in a longitudinal study of 54 patients with CKD stages 2 through 5D (ESRD) we found that mean annualized losses of bone density by DXA at the radius was 2.9%[40]. With HR-pQCT, we determined the bone loss by DXA was characterized by loss of cortical area (−2.9%), density (−1.3%) and thickness (−2.8%) and a significant increase in cortical porosity (+4.2%).

Measurement of Bone Quality

Tetracycline double-labeled transiliac crest bone biopsy with histomorphometry is the standard to determine bone quality. Histomorphometric analyses quantify volume and microarchitecture of cancellous and cortical compartments, microdamage, characteristics of mineralization, turnover, and collagen structure. 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); in turnover (low or high turnover); and in collagen structure (accumulation of advanced glycation end-products).

Unfortunately, bone biopsy is invasive, expensive, not widely available, and physicians performing this procedure require specialized training[1, 43, 44]. Also the biopsy only provides data about the type of ROD at one site (the anterior iliac crest) and at a single time-point. Due to these limitations of bone biopsy, non-invasive approaches that can be applied in the clinic to diagnose bone disease and monitor treatment responses would be helpful.

Assessing bone turnover and osteomalacia

Because treatment of ROD is based on turnover and the presence or absence of osteomalacia, their assessment is essential in determining bone quality in ROD. Pharmacologic agents that may prevent fractures in moderate CKD alter remodeling

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rates[45–47]. While anti-resorptive agents may be used in patients with high turnover, they should not be used in patients with low turnover or adynamic bone disease. Similarly, while osteoanabolic agents may be used in patients with low turnover, they are contraindicated in patients with high turnover.

Because bone biopsy may not be possible or practical, a non-invasive approach to turnover assessment would be helpful. Despite multiple limitations (discussed below), noninvasive assessment of remodeling can be achieved with reasonable accuracy by measuring circulating levels of parathyroid hormone (PTH) and bone turnover markers (BTMs)[48–54]. 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.

PTH and BSAP are the most commonly used markers of turnover in CKD-MBD. Generally, extremes of PTH predict extremes of bone turnover both in pre-dialysis[52] and dialysis-dependent[53, 54] patients. Unfortunately, prediction of underlying histology is poor when PTH levels are within the middle range. For BTMs, reference ranges in patients with CKD do not exist. Some markers are cleared by the kidney (osteocalcin, P1NP monomer and CTX); therefore, their application to ROD diagnostics is challenging. Prediction of ROD type can be improved if levels are at the extremes of their ranges. Combing PTH with BTMs may also provide diagnostic insight. Low vitamin D levels, and low levels of PTH in conjunction with high levels of BSAP have been reported to associate with osteomalacia.

Measurement of PTH and BTMs may have more applicability in the prediction of bone loss and fractures than in determining ROD-type[27, 36, 40, 41, 55]. For example, longitudinal studies in CKD patients have shown that high levels of PTH and BTMs predicted loss of cortical and trabecular bone and decreases in bone strength[40, 41].

In a cross-sectional study of CKD patients, higher levels of PTH and BTMs were associated with lower cortical and trabecular density, thinner cortices and trabeculae[36], and higher levels of BTMs discriminated fracture[36]. A longitudinal study of ESRD patients found that fracture risk was greater in patients with both low (<150 pg/mL) and high (>300 pg/mL) PTH levels, and with higher BSAP levels[27]. In a study of kidney transplant patients PTH levels ≥130 pg/mL 3-months after transplantation predicted fractures[55]. These data indicate that higher bone turnover, measured by PTH and BTMs, result in loss of bone density and microarchitecture and predict fracture. Longitudinal studies are needed to validate the findings of these small studies. Furthermore, longitudinal trends in BTMs have not been correlated against changes in bone histology, and correlations between changes in BTMs and changes in fracture risk have not been studied.

Can we non-invasively assess bone disease in CKD?

Non-invasive characterization of ROD needs to assess important aspects of bone quality (e.g., bone microarchitecture, mineralization and turnover), guide therapeutic choices, and

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predict clinical outcomes and responses to treatment. Studies have investigated how combining bone imaging with markers of bone turnover can assess bone disease severity and fracture status, important limitations need to be resolved. Non-invasive tools that identify osteomalacia and that accurately define bone turnover are lacking. Furthermore, although we know that low BMD and impaired cortical and trabecular microarchitecture predict fracture, it is not known whether increases in BMD and improvements in microarchitecture due to bone therapies predict decreases in fracture risk. In addition, the best intervals for bone disease monitoring has not been established. Thus, in the current era, the decision to treat and to monitor treatment response in a CKD patient managed with vitamin D analogs, or anti-resorptive or osteoanabolic agents may not be completely possible without a bone biopsy.

Biochemistries and DXA are non-invasive measures and provide insight into bone health, but neither approach directly tests bone material or mechanical properties. In recent years, efforts have been made to develop minimally invasive aproaches to directly probe bone material properties through the modification of traditional indentation material testing for in vivo use. Two devices, the BioDent (targeted for research) and OsteoProbe (targeted for clinical use), use small sharp probes inserted through the skin at the midshaft of the tibia to indent the bone surface[56, 57]. The OsteoProbe has shown promise in distinguishing patient populations of differing fracture risk or history[58–62], but questions remain regarding the interpretation and meaning of the device's outcome measure, "bone material strength index", or BMSi[63]. It remains to be seen whether one or both devices will successfully be translated to the clinic and if they might provide new insight into bone quality differences in CKD patients.

Conclusion

ROD is a complex bone disorder that occurs in patients with kdiney disease and results in high risk of fracture. The best method to determine ROD type and overall bone health in CKD is bone biopsy. However, bone biopsy is not a practial diagnostic method due to its expense and lack of availability. In the office, DXA can classify fracture risk in CKD patients, but it cannot be used as a sole method either to assess bone quality or to inform therapeutic decisions. Markers of bone remodeling can provide information on turnover status and help determine whether treatment with an anabolic or anti-resorptive agent might be appropriate. Prospective randomized clinical trials are needed to best assess diagnosis and management of CKD-MBD.

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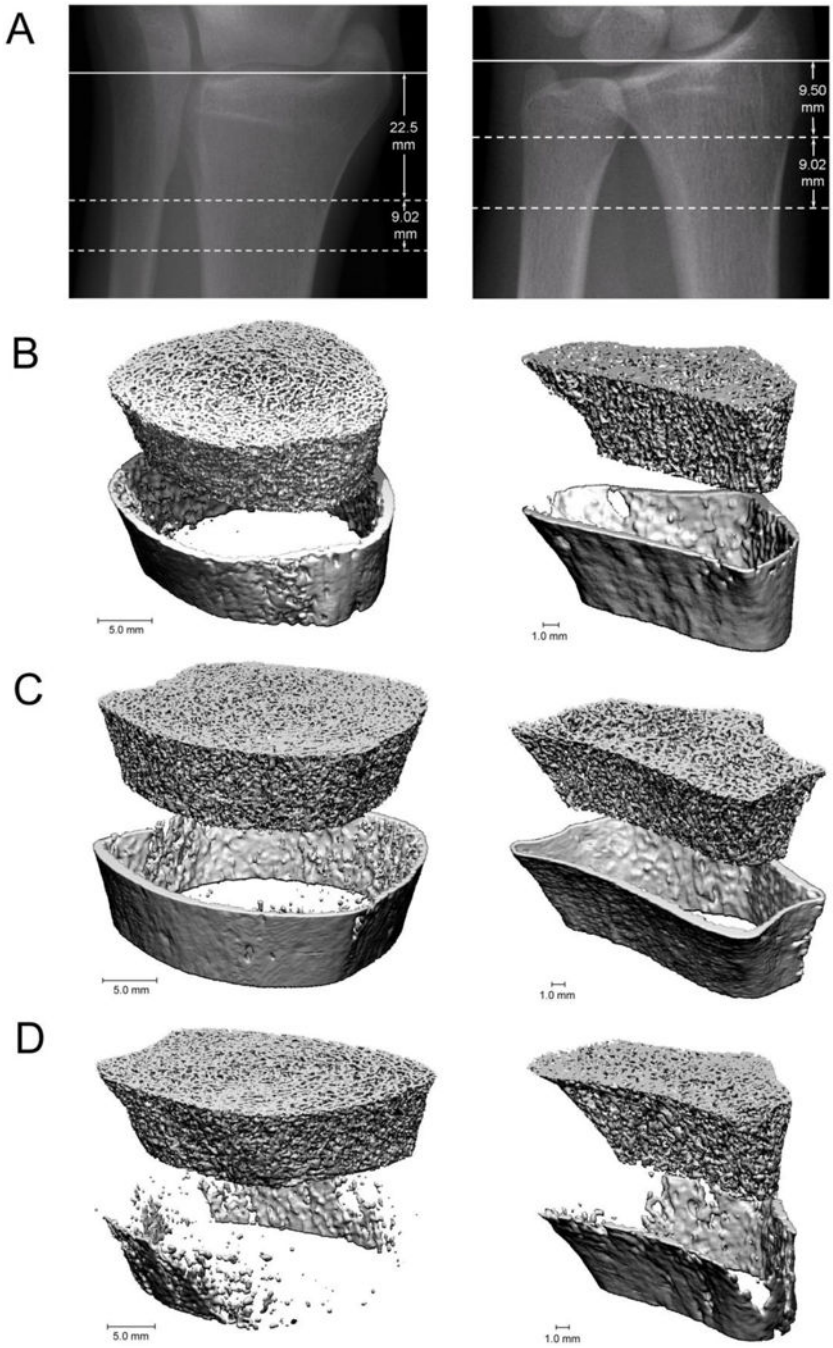

Figure 1.

[35]: HR-pQCT provides detailed images of bone geometry and microarchitecture at the radius (left) and tibia (right). (A) Scout view represents the reference line position (solid line) and the measurement site (dotted line). (B) Images from a healthy, post-menopausal white woman. (C) Images from a pre-dialysis female patient with CKD and without fracture. (D) Images from a pre-dialysis female patient with CKD and with prevalent fracture.

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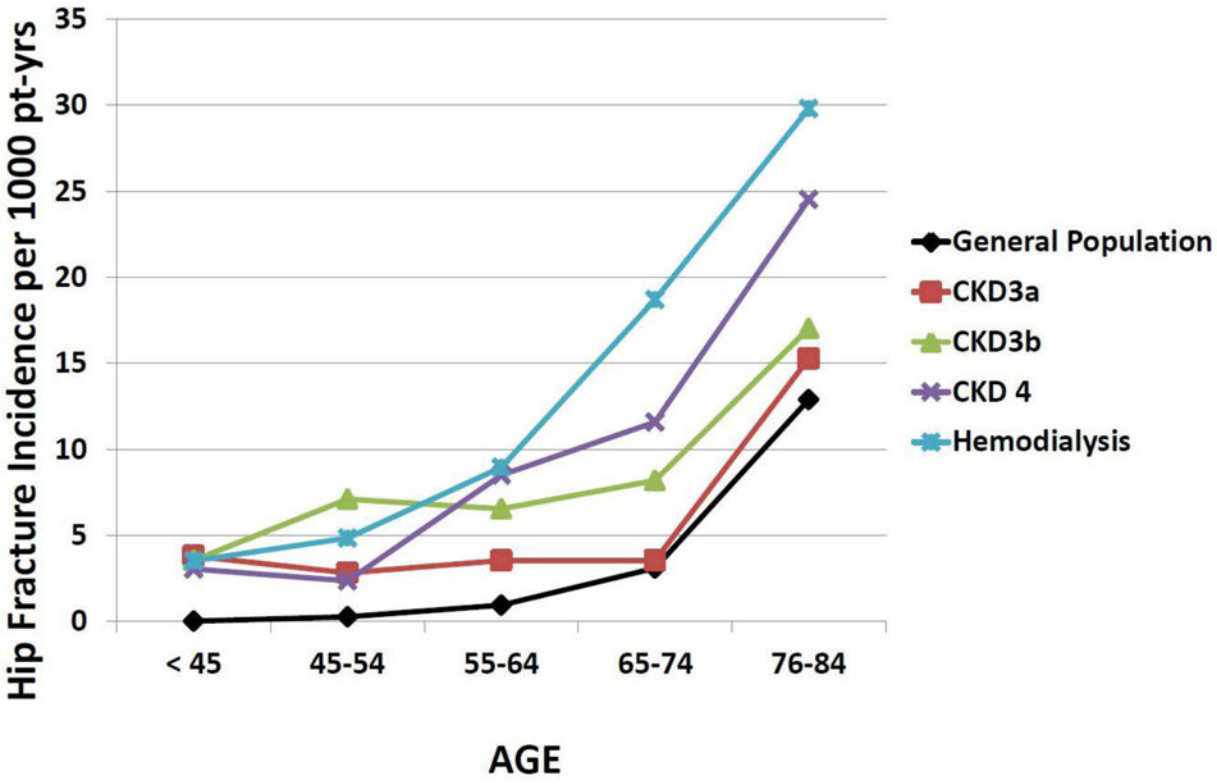

Figure 2.

Hip fracture incidence increases with progressive CKD. As patients age in the general population there is an increased incidence of hip fracture. This incidence increases with progression of CKD. Data from Alem et al for dialysis patients and the general population from Olmstead Minnesota[3], Naylor et al for CKD stages 3–4[5]. Pt-yrs = patient years.

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Table 1

Bone changes associated with hormonal and metabolic disturbances of renal osteodystrophy

Decreased bone density and microarchitecture • Cortical porosity • Cortical thinning and trabecularization • Trabecular thinning and dropout
Decreased bone quality • Mineralization (osteomalacia) • Abnormal remodeling adynamic bone disease low turnover high turnover • Microdamage accumulation • AGE crosslinking