Recent advances in the noninvasive diagnosis of renal osteodystrophy

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Chronic kidney disease–mineral and bone disorder (CKD-MBD) is the term used to describe a constellation of biochemical abnormalities, bone disturbances that may lead to fractures, and extraskeletal calcification in soft tissues and arteries seen in CKD. This review focuses on the noninvasive diagnosis of renal osteodystrophy, the term used exclusively to define the bone pathology associated with CKD. Transiliac bone biopsy and histomorphometry with double-labeled tetracycline or its derivatives remains the gold standard for diagnosis of renal osteodystrophy. However, histomorphometry provides a 'window' into bone only at a single point in time, and is not clinically practical for studying continuous changes in bone morphology. Furthermore, the etiology of fractures in CKD is multifactorial and not fully explained by histomorphometry findings alone. The propensity of a bone to fracture is determined by bone strength, which is affected by bone mass and bone quality; the latter is a term used to describe the structure and composition of bone. Bone quantity is traditionally assessed by dual X-ray absorptiometry (DXA) and CT-based methods. Bone quality is more difficult to assess noninvasively, but newer techniques are emerging and are described in this review. Ultimately, the optimal diagnostic strategy for renal osteodystrophy may be a combination of multiple imaging techniques and biomarkers that are specific to each gender and race in CKD, with a goal of predicting fracture risk and optimizing therapy.

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RENAL OSTEODYSTROPHY: THEN AND NOW

Kidney disease has been known to be associated with bone abnormalities for decades. As early as in 1883, Lucas[1] recommended the term 'renal rickets' for the bone deformities associated with albuminuria. In 1943, Liu and Chu[2] first used the term renal osteodystrophy as 'the generic name to include cases of osseous disorder associated with renal insufficiency, while the exact nature of the pathological process in the skeleton is still undetermined.' The term 'renal osteodystrophy' was then used to variably describe bone histology findings, skeletal abnormalities, and disordered biochemical and hormone levels (calcium, phosphorus, parathyroid hormone, vitamin D) associated with kidney disease through the rest of the twentieth century.

In 2005, expert nephrologists in the field of bone and mineral disease felt that the term renal osteodystrophy did not completely depict the full spectrum of systemic symptoms associated with mineral and bone disorders in chronic kidney disease (CKD). The term *chronic kidney disease–mineral and bone disorder* (*CKD-MBD*) was coined to encompass a constellation of abnormalities seen in progressive kidney disease that include: (1) altered levels of calcium, phosphorus, parathyroid hormone (PTH), and vitamin D; (2) disturbances in bone modeling and remodeling, with the associated development of fractures or impaired linear bone growth (in children); and (3) extraskeletal calcification in soft tissues and arteries.[3] It was recommended that the term *renal osteodystrophy* be used exclusively to define the bone pathology associated with CKD.[3] Renal osteodystrophy is one measure of the skeletal component of the systemic disorder of CKD-MBD. Transiliac bone biopsy and histomorphometry with double-labeled tetracycline or its derivatives remains the gold standard for diagnosis of renal osteodystrophy.

BONE IN CKD

Bone remodeling is an ongoing lifelong process. Bone resorption occurs by osteoclasts, and new bone or osteoid is formed by osteoblasts. The new bone is then mineralized to become the mature bone. This process relies on complex cell signaling pathways to achieve coupling between these various processes. Together, these processes control replacement of bone following microfractures that routinely occur with physical activity, thus maintaining bone architecture.

At any given time, ~10–20% of the skeleton undergoes remodeling, and a typical remodeling cycle can take up to 3–6 months.[4] The mineral and endocrine functions disrupted in CKD are critically important in the regulation of bone remodeling. As a result, bone abnormalities are found almost universally in patients with CKD requiring dialysis and in the majority of patients with CKD stages 3–5.[5–7] Dialysis patients in their 40s have a relative risk of hip fracture 80-fold that of age- and sex-matched controls.[8] In patients with stage 4 CKD, the risk of hip fracture was nearly fourfold that of the general population without CKD.[9] Therefore, identifying imaging techniques and biomarkers that can noninvasively identify those at risk for fractures is important, both from a research perspective and for patient care.

BONE STRENGTH AND FRACTURES IN CKD

Fracture risk is determined by bone strength, or the ability of a bone to resist breakage. Both cortical and trabecular bone are important for bone strength—cortical bones resist bending or buckling, and trabeculae distribute force in cancellous bone. Bone strength is composed of both bone quantity and quality.[10] Bone quantity is traditionally measured by bone mineral density (BMD) using dual-energy X-ray absorptiometry (DXA), although newer computerized tomography (CT)–based measures are now available. Bone quality is determined by bone turnover and mineralization (assessed by histomorphometry), as well as by microarchitecture such as geometry, connectivity, and collagen crosslinking (see Figure 1). Microarchitecture of bone has been predominantly evaluated in animal models, but recent magnetic resonance imaging (MRI) techniques hold promise in humans. In CKD, metabolic abnormalities, altered bone cell differentiation pathways, and disturbances in bone remodeling likely result in deterioration in bone quality. Thus, it is not surprising that there is increased fracture risk in CKD with abnormalities of both bone quantity and quality. Table 1 lists bone strength measurement techniques.

BONE HISTOMORPHOMETRY

The clinical assessment of bone remodeling is best done with a bone biopsy, usually of the trabecular bone at the iliac crest. The patient is given a tetracycline derivative ~3 to 4 weeks before the bone biopsy and a different tetracycline derivative 3 to 5 days before the biopsy. Tetracycline binds to hydroxyapatite and emits fluorescence, thereby serving as a label of the bone to allow assessment of bone change over time, termed dynamic assessment.

In 1983, Sherrard *et al.*[11] proposed a classification system for the histomorphometric analysis of renal bone disease using parameters of bone turnover, percentage of unmineralized bone (osteoid) area as a percent of total bone area and fibrosis to distinguish the various forms of renal osteodystrophy. Three groups were named: high-turnover disease (mild hyperparathyroidism or severe hyperparathyroidism with fibrosis called osteitis fibrosa cystica), low-turnover bone disease (adynamic bone disease or osteomalacia), and mixed uremic osteodystrophy. Aluminum bone disease, a cause of osteomalacia, was diagnosed by special staining for aluminum deposits at the mineralization

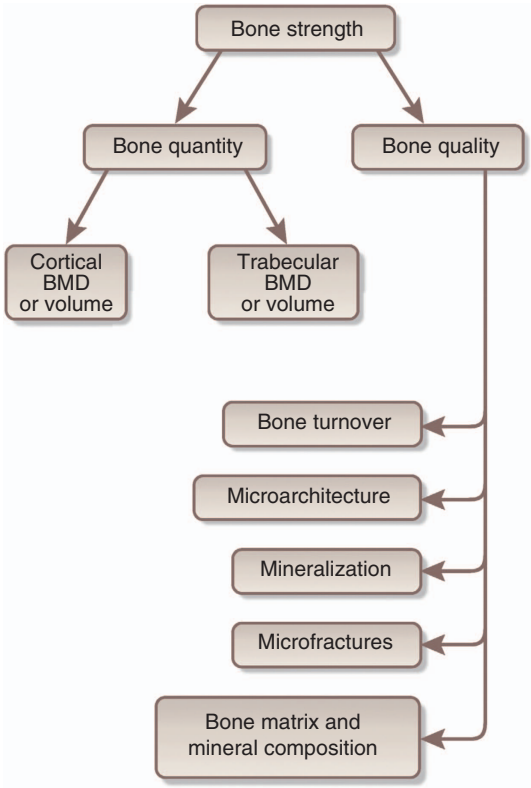

Figure 1 | Determinants of bone strength. Bone strength comprises both bone density and quality. Bone quality refers to bone turnover, microarchitecture, microfractures, mineralization, and the composition of mineral matrix. Trabecular microarchitecture includes trabecular thickness, the ratio of plates and rods, their connectivity, and spacing. Cortical microarchitecture includes cortical thickness, porosity, and bone size. Composition of mineral matrix includes changes in the crosslinking of type 1 collagen and alterations in the size and structure of bone mineral. Bones accumulate microfractures over time even with normal physical activity. The ability to repair these affects bone quality. BMD, bone mineral density.

Table 1 | Techniques to measure bone parameters

Bone measure	Technique
Total bone density	DXA
Cortical and trabecular bone density	QCT, pQCT
Bone turnover	Biomarkers (PTH, b-alp, sclerostin), histomorphometry
Microarchitecture	HR-pQCT, HR-MRI, histomorphometry, microCT, microMRI
Matrix composition	Infrared spectroscopy, Raman spectroscopy
Microfractures	Confocal microscopy, histology
Mineralization	Histomorphometry, spectroscopic techniques

Abbreviations: b-alp, bone-specific alkaline phosphatase; CT, computerized tomography; DXA, dual-energy X-ray absorptiometry; HR-MRI, high-resolution magnetic resonance imaging; HR-pQCT, high-resolution peripheral quantitative computerized tomography; MRI, magnetic resonance imaging; pQCT, peripheral quantitative computerized tomography; PTH, parathyroid hormone; QCT, quantitative computerized tomography.