Renal bone disease is a heterogeneous group of metabolic bone diseases that requires quantitative bone histomorphometry to make the correct differential diagnosis. Included in this group is osteoporosis. However, osteoporosis in stage 4 to 5 chronic kidney disease cannot be diagnosed on the basis of bone mineral density criteria established by the World Health Organization or the presence of fragility fractures because patients with all forms of renal bone disease can demonstrate low bone mineral density and fragility fractures. Clinical cases in patients with either low bone mineral density and/or low-trauma fractures will be used to demonstrate the value of bone biopsy and quantitative histomorphometry in making a diagnosis of the specific renal bone disease and assisting with subsequent management decisions.

Renal osteodystrophy (ROD) is a heterogeneous group of metabolic bone diseases that accompanies progressive chronic kidney disease (CKD (1–4) (Table 1). These metabolic bone diseases have both specifically defined quantitative histomorphometric diagnostic criteria as well as clinical features (5,6). More recently, the Kidney Disease Improving Global Outcomes working group offered a new and more encompassing definition of renal bone disease (7). The recent recognition that disorders of bone and mineral metabolism that accompany CKD involve multiple organ systems and are associated with cardiovascular events and death has led investigators to propose a new definition of renal bone disease. This more general definition recognizes that the pathophysiology of renal bone disease extends beyond the skeleton and that there are links between abnormal bone remodeling activity and the risk for soft tissue and vascular calcification (7–11). CKD-mineral and bone disorder (7) is the proposed new term for the changes in bone and mineral metabolism associated with declining kidney function (Table 1). In this new construct, the term “renal osteodystrophy” is limited to the specific changes in bone histology that accompany moderate and end-stage CKD and defined according to histomorphometric criteria.

In the specific arena of renal bone disease, it is the specific quantitative histomorphometric criteria that defines the renal bone disease and makes the specific diagnosis (5,12,13). For example, from a clinical standpoint, while osteomalacia may be associated with an elevated bone specific alkaline phosphatase (BSAP) and parathyroid hormone (PTH), proximal (shoulders/hips) bone pain, and muscle weakness, these identical clinical combinations may also be seen in hyperparathyroid bone disease. Hypercalcemia may be a feature of hyperparathyroid, aluminum, or adynamic renal bone disease; and, even although the intact 1 to 84 serum PTH level is often low to low-normal in adynamic renal bone disease, PTH levels (1 to 84) may also be elevated at times in adynamic renal bone disease (1–4,14–20). In addition, either by natural biologic means or induced by pharmacologic agents used to treat specific forms of renal bone disease (such as calcimimetics or vitamin D analogs), a patient can transition from one histologic form of renal bone disease to another. For example, an osteomalacic, histomorphometric form of renal bone disease may normalize to normal osteoid surfaces or transform from low bone turnover and impaired mineralization to high bone turnover and increased mineralization as vitamin D deficiency is corrected (21,22); or, as aluminum is removed by desferoxamine (DFO) chelation, the histology may change from an aluminum-induced low bone turnover to a high bone turnover as the bone becomes more responsive to PTH with aluminum withdrawal from osteoid surfaces (23). Treatment of secondary hyperparathyroidism with vitamin D analogs or cinacalcet may correct the underlying high bone turnover (24–32) or, if PTH suppression is excessive, lead to very low (or no) bone turnover, the so-called adynamic renal bone disease (33,34). In addition, low (or no) bone turnover may be reversible by modulating the PTH level (35,36). Thus, the evolving framework of redefining the quantitative morphology of renal bone disease as well as recognition of its systemic nature is both an advancement as well as a challenge in the management of patients with CKD (7,37).

The challenge is how to appropriately use bone biopsies to define the often changing landscape of renal bone disease to manage the systemic disorders that may accompany such change (12–14,38,39).

The heterogeneous group of renal metabolic bone diseases is associated with certain abnormalities in blood biochemical tests that can be helpful in the differential diagnosis in groups of patients (Tables 2, 3) (40,41). However, there is enough overlap in the biochemical profile among the renal bone diseases that makes the distinction between these histomorphometric forms of renal bone disease uncertain in individual patients (6, 7, 11,
particularly important to discriminate from osteoporosis, especially prevalent form of metabolic bone disease in all populations, including CKD patients, has no distinctly characteristic biochemical derangement, and can range from low to high bone turnover on histomorphometry, it is a unique diagnostic challenge to make in CKD patients and one that is important to differentiate from the other more traditional forms of renal bone disease (42–45). Two forms of renal bone disease that are particularly important to discriminate from osteoporosis, especially in the CKD patient that has a low bone mineral density (BMD) or low-trauma fragility fractures, are the very low bone turnover and impaired mineralization forms of renal osteodystrophy: adynamic and osteomalacia bone disease. One major reason for this important distinction is that osteoporosis therapies that reduce bone turnover and increase bone strength in specific forms of osteoporosis (postmenopausal, male, or glucocorticoid-induced osteoporosis) are bisphosphonates (46–55) may be contraindicated in specific low bone turnover renal bone diseases or in patients with glomerular filtration rates <30 ml/min (56,57). It is intuitive that the administration of a bone-active agent, such as a bisphosphonate that reduces bone turnover, may not be desirable in a patient with low-bone turnover to begin with. Nevertheless, bisphosphonates could be an effective therapy for specific forms of osteoporosis in patients with stage 4 CKD where post hoc analysis does suggest efficacy and safety through 3 yr of use (58,59). The major clinical issue is making the correct diagnosis of osteoporosis.

### How “Osteoporosis” Is Diagnosed in CKD

Postmenopausal osteoporosis can be diagnosed on the basis of BMD criteria or the presence of a fragility fracture once secondary causes of bone fragility are excluded (60–62). The BMD criteria were established in 1994 by a working group of the World Health Organization (WHO) (63). The WHO BMD criteria, a T-score at the lumbar spine by anteroposterior dual energy x-ray absorptiometry, or hip or forearm of −2.5 or lower, is the SD cut-off point chosen for the BMD criteria. This level was chosen because the prevalence of a BMD at or below this level at these 3 skeletal sites in white postmenopausal women (~40%) matched the lifetime fracture risk at the vertebrae, forearm, or hip as well (~40%). In addition, the development of a low-trauma fracture in postmenopausal women or elderly men can also be a criterion for the diagnosis of osteoporosis because fragility fractures of the hip, vertebrae (even morphometric), wrist, shoulder, humerus, pelvis, and ribs are associated with a high risk for other fragility fractures, and this risk is independent of the prevailing BMD or T-score (64–70). Hence, once other etiologies for fragility fractures are excluded (e.g., osteogenesis imperfecta, osteomalacia), then the diagnosis of osteoporosis can be established.

The major clinical problem in using either the WHO criteria or fragility fractures to make a clinical diagnosis of osteoporosis in the CKD (especially stage 4 to 5 CKD) is that all of the previously described histomorphometric forms of renal osteodystrophy may have low BMD and/or T-scores and can develop low-trauma fractures (71–74). Thus, the traditional criteria accepted as diagnostic criteria for osteoporosis in the postmenopausal or elderly male population cannot be used as diagnostic criteria for the diagnosis of osteoporosis in the more severe (stage 4 to 5) CKD population.

There are as of yet no established criteria for the diagnosis of osteoporosis in more advanced CKD (stage 4 to 5) (42–45). Early hyperparathyroidism may be seen in stage 3 CKD and may be associated with histologic changes of high bone turnover in these patients who have not been shown to have an increased fracture risk (24,75,76) There may be a role for sup-
pressing the elevated PTH levels as a therapeutic option in mild secondary hyperparathyroidism in stage 3 to 4 CKD as there clearly is for stage 5 CKD, and the vitamin D analogs have achieved Food and Drug Administration registration for this indication (77). Fracturing postmenopausal women and elderly men with mild primary or secondary hyperparathyroidism and stage 3 CKD are more likely to have osteoporosis as the etiology of their fractures (78,79), and it is far more probable that in these patients with low BMD and/or low trauma fractures the WHO criteria can be used for the diagnosis of osteoporosis.

However, this may not be a valid approach for patients with stage 4 to 5 CKD where fractures may be the result of some other form of renal bone disease just as likely as osteoporosis. In stage 4 to 5 CKD, diagnosis of osteoporosis is first established by excluding the other forms of renal bone disease and the finding of a low trabecular bone volume. It requires a bone biopsy to make this important clinical diagnosis in the individual patient with stage 4 to 5 CKD, and it is a decision upon which the diagnosis of osteoporosis is mandated.

Case Reports

The following cases highlight the value of quantitative bone histomorphometry in management of patients with CKD and fragility fractures.

Case 1

A 66-yr-old Hispanic woman with end-stage renal disease (ESRD) (type 1 diabetes mellitus and hypertension) was on hemodialysis for 2 yr when she developed 2 clinical (painful) vertebral compression fractures. She was 16 yr postmenopausal on no hormonal replacement therapy, received calcium carbonate and acetate as phosphate binders, and had never been exposed to aluminum phosphate binders. Her clinical/biochemical profile is as follows: BMD, T-score at femoral neck −3.2 (osteoporosis by WHO criteria); serum calcium, 9.6 mg/dl (normal, 8.5 to 10.5 mg/dl); serum phosphorus, 3.7 mg/dl (normal, 3.0 to 5.0 mg/dl); serum intact PTH, 64 pg/ml (normal, 10 to 65 pg/ml); serum BSAP, 14 IU/ml (normal, 10 to 65 IU/ml); and 25 hydroxyvitamin D, 32 ng/ml (normal, 30 to 100 ng/ml). Bone biopsy is shown in Figures 1 to 4. Diagnosis is low bone turnover/aluminum bone disease.

Comment: The histomorphometry and quantitative data show thin osteoid (matrix) and low bone formation rates consistent with low bone turnover. The osteoid surfaces were covered by aluminum, and this is aluminum bone disease. Aluminum bone disease still may develop without known aluminum exposure (e.g., aluminum phosphate binders) because of the ubiquitous presence of aluminum in the environment and the inability of the patient with CKD to excrete aluminum. After the biopsy was diagnostic, both a basal as well as post-DFO aluminum challenge test were negative (basal level <20 μg/L and post-DFO rise <50 μg/L). It is recognized that serum aluminum levels may not adequately reflect systemic (bone or brain) aluminum accumulation. In this case, the biopsy confirmed the diagnosis and guided therapy. It is possible that she could have been assumed to have osteoporosis (based on her T-score or vertebral fractures) and treated with a bisphosphonate. Although in the future management of this patient, Food and Drug Administration-approved osteoporosis pharmacologic therapies might be a consideration, identification of her aluminum bone disease was an important discovery that required proper management as the first step.

Figure 1. Bone biopsies. (Top left panel) von Kossa (left) and hematoxylin and eosin (right); original magnification ×40; shows thin trabeculae with incipient perforations and very small numbers of calcified trabeculae. (Top right panel) Eosin fluorescence stain for osteoid (original magnification ×40); shows very thin osteoid in yellow. (Bottom left panel) von Kossa hematoxylin and eosin stain; shows inactive bone lining cells and thin osteoid. (Bottom right panel) Unstained, fluorescent for mineralization, original magnification ×200); shows minimal tetracycline labels.

Figure 2. Bone biopsies. Both are stained with tartrate-resistant acid phosphatase (TRAP) for osteoclasts. (Left panel) Original magnification ×100; shows no osteoclasts. (Right panel) Original magnification ×400; shows very few osteoclasts in Howship’s lacunae.
Case 2

A 56-yr-old white woman on hemodialysis for chronic glomerulonephritis for 10 yr had a low trauma fracture of her pelvis and then her femur 3 yr apart. She was 10 yr postmenopausal on hormonal replacement therapy and calcitriol (0.25 μg twice daily) but had received no aluminum phosphate binders. Her clinical and laboratory data are as follows: BMD T-score, −4.0 (osteoporosis by WHO criteria); serum calcium, 9.7 mg/dl (normal); serum phosphorus, 5.2 mg/dl (slightly elevated); serum PTH, 98 pg/ml (mild elevation); serum 25 hydroxyvitamin D, 36 ng/ml (normal); and BSAP, 41 IU/ml (normal). Bone biopsy is shown in Figures 5 and 6. Diagnosis is low bone turnover/osteomalacia-aluminum.

Comment: The histomorphometry is diagnostic of osteomalacia with a very high osteoid surface percent, thick osteoid, and an infinite mineralization lag time. The etiology of osteomalacia in this case was aluminum accumulation. The patient had never been exposed to any aluminum. On the basis of her low BMD and fractures, she could have been assumed to have osteoporosis. Proper management involves first removal of aluminum and then addressing the low bone strength that might be related to osteoporosis.

Case 3

This 22-yr-old man with known nephrocalcinosis associated with long-term vitamin D-resistant rickets and long-term replacement with phosphorus (potassium phosphate, 250 mg 4 times a day) and calcitriol (0.25 μg twice daily), with little data on the levels of serum calcium/phosphorus over many years, has been on hemodialysis for 15 yr. He developed nontraumatic bilateral mid-shaft femur fractures at age 21 yr. His laboratory data are as follows: BMD T-score, −3.7 at femoral neck; serum calcium, 9.8 mg/dl; serum phosphorus, 2.5 mg/dl; serum PTH, 70 pg/ml (elevated); serum BSAP, 85 IU/ml (elevated); serum 25 hydroxyvitamin D, 45 ng/ml; and serum 1,25 dihydroxyvitamin D, 4 ng/ml (low). Bone biopsy is shown in Figures 7 and 8. Diagnosis is osteomalacia.

Comment: This was a known case of hereditary hypophosphatemic vitamin-D resistant rickets that had new fractures after having been off his phosphorus and vitamin D replacement for 3 yr. The bone biopsy is classic for severe osteomalacia; the fractures healed with calcitriol and phosphorus replacement, and his elevated bone-specific alkaline phosphatase also normalized with treatment. Although one could have assumed that his elevated BSAP was a return of his osteomalacia, it was important to make the exact diagnosis in an ESRD patient before giving phosphorus in this ESRD state. In addition, it could have been assumed, with femur fractures and very low T-scores, that he might have had osteoporosis, which would have been the incorrect diagnosis.

Case 4

This 47-yr-old white woman received a live-related renal transplant in Switzerland 15 yr before being evaluated for her metabolic bone disease. Her original renal disease was chronic poststreptococcal glomerulonephritis. She had had generalized and often incapacitating "bone pain" and low trauma fractures (pelvis in 1999 and tibia 2002), had never been on glucocorticoids, but had received long-term cyclosporine. Her data are as follows: serum calcium, 9.5 mg/dl; serum phosphorus, 3.8 mg/dl; serum BSAP, 150 to 300 IU/ml (elevated); serum PTH, 45 pg/ml; serum 25 hydroxyvitamin D, 16 ng/ml (low); serum 1,25 dihydroxyvitamin D, 12 ng/ml (low); serum creatinine, 1.6 mg/dl (elevated); BMD T-score, −4.8 (femoral neck); WHO diagnosis, osteoporosis; serum c-telopeptide, 454 (elevated); serum carbon dioxide, 15 mEq/ml (low); serum chloride, 121 mEq/ml (elevated); serum calculated anion gap, 13 mEq/ml (normal); and arterial blood gases: pH = 7.30, Pco2 = 32, HCO3 = 14, metabolic acidosis). Bone biopsy is shown in Figures 9 and 10.
and 10. Diagnosis is high bone turnover resulting from cyclosporine.

The clinical course is as follows: 1) treatment with bicarbonate to maintain serum bicarbonate 23 mEq/L; no effect on high turnover markers; 2) normalized 25 vitamin D; no effect on high bone turnover markers; and 3) high doses (90 mg pamidronate...
intravenously every 4 mo) in Switzerland with normalization of turnover markers, increase in BMD, and no subsequent fractures over 4 yr of follow-up and no change in serum creatinine concentration.

Comment: This was a patient with fractures and exceptionally high bone turnover by both biochemical marker levels as well as histomorphometry. The histomorphometry confirmed that exceptional bone resorption was occurring, and this process could have been related either to her metabolic acidosis and/or cyclosporine. Normalization of her acid-base balance did not reduce her high bone turnover. It required a large dose of intravenous bisphosphonate and bicarbonate replacement to normalize her very high bone turnover, eliminate her bone pain, and heal her fractures. Intravenous bisphosphonate would not have been considered in this patient with a post-transplant serum creatinine of 1.6 mg/dl and who had not received glucocorticoids without clear documentation of high bone turnover and fractures.

Case 5

This 49-yr-old Hispanic woman with stage 4 CKD (glomerular filtration rate, 20 ml/min by creatinine clearance) had several low trauma fractures of humerus and later mid-femoral shaft. She was postmenopausal and not on hormonal therapy. Her data are as follows: BMD (T-score, −4.4 at total hip and −4.4 at anteroposterior spine and −5.2 at forearm); serum calcium, 9.1 mg/dl; serum phosphorus, 4.4 mg/dl; serum 25 hydroxyvitamin D, 13 ng/ml (low); serum 1,25 dihydroxyvitamin D, 8 ng/ml (low); serum PTH, 271 pg/ml (elevated); and serum BSAP, 125 IU/ml (elevated).

The clinical course is as follows: The patient was replaced with 25 hydroxyvitamin D, and her biochemical testing changed to: repeat 25 vitamin D, 34 (normal); repeat PTH, 184 (elevated); repeat serum calcium, 10.7 and 11.2 mg/dl (elevated); serum BSAP, 122 (elevated); and Sestamibi scan (parathyroid scan), normal. Bone biopsy results are shown in Figures 11 to 13. Diagnosis is high bone turnover/increased mineralization/increased resorption. The clinical course is as follows: treatment, parathyroidectomy (histology, 4.2 g adenoma).

Comment: This stage 4 CKD patient had fractures, very low BMD, hypercalcemia after vitamin D replacement, and
moderately elevated PTH and bone alkaline phosphatase. The bone biopsy was striking for severe high bone turnover with tunneling bone resorption and abundant osteoid. (Bottom left and right panels) von Kossa hematoxylin and eosin stain, fluorescence for osteoid; shows Haversian systems and bone surfaces covered by tetracycline.

Case 6

This 45-yr-old white woman with stage 4 CKD (creatinine clearance, 28 ml/min) resulting from polycystic kidney disease was postmenopausal and on hormonal replacement therapy. She has had 3 fragility fractures in the past year of her tibia, forearm, and ankle. Her laboratory data are as follows: BMD (T-score), −1.4 at hip and −1.6 at spine (WHO classification, osteopenia); serum calcium, 9.6 mg/dl; serum phosphorus, 4.1 mg/dl; serum PTH, 86 pg/ml (elevated); serum 25 hydroxyvitamin D, 38 ng/ml; serum 1,25 dihydroxyvitamin D, 30 ng/ml; and serum BSAP, 16 IU/ml. Bone biopsy is shown in Figures 14

Figure 11. Bone biopsies. (Top left panel) von Kossa hematoxylin and eosin stain for calcium; shows enlarged cortical Haversian canals and prominent osteoid. (Top right panel) von Kossa hematoxylin and eosin for calcium; shows tunneling bone resorption and abundant osteoid. (Bottom left and right panels) von Kossa hematoxylin and eosin stain, fluorescence for osteoid; shows Haversian systems and bone surfaces covered by tetracycline.

Figure 12. Bone biopsies. (Left panel) von Kossa hematoxylin and eosin for calcium; shows active bone formation and resorption. (Right panel) TRAP stain for osteoclasts and osteoblasts; shows abundant osteoblasts and osteoclasts.

Figure 13. Bone biopsies. Both are unstained, fluorescence for tetracycline; show abundant tetracycline. This is all active bone remodeling.

Figure 14. Bone biopsies. (Top left and right panels) von Kossa hematoxylin and eosin for calcium; shows normal trabecular number (left) but very little osteoid (right). (Bottom panels on left) Flat bone lining cells. (Bottom panel on right) Flat lining cells (inactive) and little bone resorption.
and 15. Diagnosis is low bone turnover/low mineralization, unknown etiology.

The clinical course is as follows: treatment with teriparatide; 1-yr posttreatment spine BMD increased to 0.089 g/cm² (significant increase); currently in second year of treatment; and no incident fractures.

**Comment:** This patient has stage 4 CKD and fragility fractures despite being on hormonal replacement therapy. She had a mild secondary hyperparathyroidism, but bone biopsy showed a very low bone turnover with no single labels of tetracycline. This is the histomorphometric picture of adynamic bone disease of unknown etiology. Because she had fractures, she was treated with the anabolic agent teriparatide and her BMD increased; she has had no further fractures. She will be rebiopsied after her 2-yr therapeutic course of teriparatide. Without biopsy, she could have been treated with a bisphosphonate, which would have been a theoretical incorrect management choice because she had nearly no bone turnover to start with.

**Conclusion**

These cases demonstrate the value of quantitative bone histomorphometry in making management decisions in the CKD population. Although bone biopsy is invasive, it is a nearly painless procedure with very low morbidity when performed in trained operators. Physicians caring for these complex patients where clinical and biochemical evaluation make a distinct diagnosis need to consider bone histomorphometry before making management decisions in these high-risk for fracture patients.

**Disclosures**

None.

**References**


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**Figure 15.** Bone biopsies. (Top 2 panels) Very few osteoblasts or osteoclasts. (Panels 3 and 4) Very few bone lining cells and little osteoid (matrix). (Panels 5 and 6) Very thin osteoid (left) and no aluminum (right). (Bottom 2 panels) Few tetracycline labels. This is all characteristic of adynamic bone disease.


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