The Role of the Bone Biopsy in the Diagnosis of Renal Osteodystrophy

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The bone and mineral complications associated with renal failure are numerous—hyperparathyroidism, adynamic bone disease, aluminum bone disease, acidosis, β_2-microglobulin amyloidosis, gonadal deficiency-associated osteopenia, and posttransplant osteoporosis. Renal osteodystrophy is the generic term generally used to describe the skeletal complications of renal failure. Renal osteodystrophy encompasses a wide spectrum of bone disorders and is often classified on the basis of the predominant histopathologic patterns. Several classification schemes have been used. Traditionally five major histopathologic patterns are described: osteitis fibrosa, mild lesion, osteomalacia, mixed uremic osteodystrophy, and adynamic bone disease. Others (1) proposed dividing the disorders into three major groups: predominant hyperparathyroid bone disease (including osteitis fibrosa and mild disease), low-turnover uremic osteodystrophy (including osteomalacia and adynamic bone disease), and mixed uremic osteodystrophy (mild to moderate hyperparathyroidism with defective mineralization).

Osteitis fibrosa (predominant hyperparathyroid bone disease) is characterized by a marked increase in bone turnover as assessed by an elevated bone formation rate, increased remodeling (both formation and resorption), and peritrabecular fibrosis. It appears to be decreasing in frequency and has been reported in 5–50% of patients (1–5). The primary metabolic abnormality with this lesion is long-standing hyperparathyroidism. Although hyperparathyroidism is common early in the development of renal failure, osteitis fibrosa is relatively rare prior to the development of end-stage renal disease (ESRD).

The mild lesion is characterized by a slight increase in the bone formation rate and remodeling, but is generally without significant peritrabecular fibrosis. It is the most common lesion seen prior to the development of ESRD (6) and has been increasing in frequency in dialysis patients, accounting for approximately 3–20% of patients (1–5). It is usually the result of mild or early secondary hyperparathyroidism or follows therapy for hyperparathyroidism.

Osteomalacia is defined by a defect in mineralization with increased osteoid formation; however, bone formation is decreased, thus it is a low-turnover lesion. Aluminum intoxication, iron intoxication, severe vitamin D deficiency, plus other unidentified factors probably play a role in its pathogenesis. It is decreasing in frequency and is seen in approximately 4–8% of patients (1–5, 7).

Features of osteomalacia with increased bone formation characterize the lesion of mixed uremic osteodystrophy. These features may coexist in varying degrees in different patients. Although there is no identifiable predominant cause, it appears to be secondary to hyperparathyroidism with a defect in mineralization. Aluminum or other unidentified factors may also be involved. This lesion may be found in 11–80% of patients (1–5).

Adynamic bone disease (low turnover) represents the opposite end of the spectrum from osteitis fibrosa. It is characterized by a marked decrease in both remodeling and mineralization. There is a profound decrease in both osteoblasts and osteoclasts, and sites of active bone formation are rarely observed. The clinical significance of adynamic bone disease is controversial; however, it is associated with a propensity for hypercalcemia, extraskeletal calcifications, and a decreased ability of bone to buffer calcium (8, 9). Although there are identifiable risk factors associated with adynamic bone disease, the pathogenesis is poorly understood. The frequency has been increasing and is observed in 25–60% of patients (1–5, 7, 10). It is associated with relatively low levels of parathyroid hormone (after parathyroidectomy, overly aggressive medical management), aluminum intoxication, diabetes, and peritoneal dialysis (1, 2, 5, 10, 11).

The current therapeutic approach to renal bone disease is to normalize the defect in bone remodeling. Thus it may be useful to classify renal osteodystrophy on the basis of being either a high- or low-turnover lesion (Table 1). The high-turnover lesions include predominant hyperparathyroid bone disease (osteitis fibrosa), the mild lesion, and the subset of those with mixed uremic osteodystrophy with increased bone formation. The low-turnover lesions include the adynamic (both aluminum- and non-aluminum-associated) and osteomalacia (both aluminum- and non-aluminum-associated). It needs to be appreciated that in any patient, transformation from one lesion to another may occur.

Therapy has predominantly focused on treating and or preventing the high-turnover lesion, which results from hyperparathyroidism. Thus parathyroid hormone (PTH) levels have become the surrogate measure of bone disease. In patients with markedly elevated PTH levels (>600–800 pg/ml), the diagnosis is rather obvious and therapy focuses on reducing PTH levels. In the rare patients who have had significant exposure to aluminum, aggressive therapy, especially parathyroidectomy, may

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TABLE 1. Classification of renal osteodystrophy

High turnover
Osteitis fibrosa
Mild lesion
Mixed uremic osteodystrophy
Low turnover
Adynamic bone disease
Osteomalacia
Aluminum

unmask aluminum bone disease. Thus the diagnosis of underlying aluminum bone disease should be entertained in these patients. Unfortunately serum aluminum levels may not be helpful and the deferoxamine infusion test is not a reliable diagnostic test, making bone biopsies a necessity (12). A specific histologic diagnosis may not be important in patients who have relatively low PTH levels (<100 pg/ml). These patients have either normal or low bone turnover, which would not require specific therapy to reduce PTH levels (13).

It is in patients with intermediate PTH levels that a specific diagnosis may be most important. Multiple studies have shown that the circulating PTH concentration does not necessarily reflect the rate of bone turnover (4, 13–16). Furthermore, it has become apparent that a single measurement of PTH does not provide sufficient information to make a definitive diagnosis. The insensitivity of PTH in predicting bone formation rate is greatest in patients who have PTH values between 100 and 400 pg/ml. This encompasses the range of serum PTH concentrations (100–250 pg/ml) most nephrologist target as a therapeutic goal. In most of these patients, both radiographs and bone mineral densitometry are generally too insensitive to provide additional useful diagnostic information. It is in this group of patients that additional noninvasive diagnostic tests, such as biochemical markers, would be useful to direct therapy.

Biochemical markers of bone metabolism may be subdivided into two major categories reflecting either bone formation or resorption (Table 2). Total alkaline phosphatase is the most commonly used marker of bone formation, but it lacks both sensitivity and specificity. In renal failure it is not possible to determine the relative contribution of the osseous, hepatic, and intestinal isoenzymes to the total alkaline phosphatase because of alterations in their respective half-lives.

The development of radioimmunologic and immunoenzymatic assays utilizing a monoclonal antibody against bone alkaline phosphatase has resulted in sensitive methods for measuring bone-specific alkaline phosphatase (BAP) in both normal and uremic patients (17–19). In dialysis patients, BAP correlates well with both serum PTH concentrations and bone histomorphometry (17, 19–21). When the BAP level is greater than 25 ng/ml, the specificity for high bone turnover is 92–100% (19, 21); however, the sensitivity is only about 70%. Thus, while few patients with low turnover have increased BAP, many patients with increased turnover do not have increased BAP. Unfortunately the addition of an elevated PTH level to the BAP does not increase the sensitivity or specificity for the diagnosis of high bone turnover (19, 21). Prediction of low bone turnover by plasma BAP is even less precise. Three biopsy-based studies have evaluated the predictive value of a low BAP for adynamic bone disease. Although the studies employed different methods for measuring BAP and were limited by the low number of patients with adynamic bone disease, it appears that the combination of PTH levels less than 150 pg/ml and BAP levels less than 8 ng/ml has a positive predictive value of 70–75% (17, 20, 22).

TABLE 2. Biochemical markers of bone metabolism

Bone formation	Bone resorption
Total alkaline phosphatase	Tartrate-resistant acid phosphatase (TRAP)
Bone alkaline phosphatase (BAP)	Type I collagen cross-linked telopeptide (ICTP)
Osteocalcin	Pyridinoline*
Procollagen type I C-terminal extension peptide (PICP)	Deoxypyridinoline*

* Urinary measurements.

Osteocalcin or bone Gla protein (protein containing γ-carboxyglutamic acid) is the most abundant noncollagenous protein in bone (23). Osteocalcin is produced by osteoblasts under the regulation of 1,25-vitamin D. It can be released from the bone matrix during resorption and from osteoblasts during formation. Osteocalcin circulates in several forms and is cleared by the kidneys, thus its use in uremia has been limited (21, 24, 25). In spite of these limitations, osteocalcin can help differentiate patients with high and low turnover (21), though it is not useful in differentiating patients with adynamic bone disease from those with normal bone turnover (25, 26). Although plasma osteocalcin levels correlate with bone histomorphometric parameters in dialysis patients, the correlation is much weaker than BAP (20, 27).

Another protein, procollagen type I C-terminal extension peptide (PICP), is produced by osteoblasts as the cleavage by-product of type I procollagen as it is incorporated into the bone matrix (28). PICP is degraded in the liver and levels do not appear to be affected by renal failure or dialysis (29). Patients with renal failure have increased levels that do not, however, correlate with other humoral markers of bone turnover or bone histomorphometry (29, 30).

The clinical utility of markers of bone resorption in renal failure has yet to be established. It has been suggested that serum levels of tartrate-resistant acid phosphatase (TRAP), a lysosomal enzyme produced by osteoclasts, may correlate with bone resorption (31). However, studies have yet to be performed in uremic patients. Type I collagen cross-linked telopeptide (ICTP) is a small fragment of type I collagen that is released during bone resorption. The few studies performed in dialysis patients have not supported its use as a humoral marker of bone remodeling (27, 32). Pyridinoline and deoxypyridinoline are two of the main collagen intermolecular cross-link molecules that are liberated into the plasma during bone resorption (33). The measurement of these components in urine is widely used in patients with normal renal function. Studies have shown that serum levels

TABLE 3. Indications for bone biopsy

Definitive classification of renal osteodystrophy
High-turnover bone disease
Low-turnover bone disease
Osteomalacia
Aluminum bone disease
Prior to parathyroidectomy
Unexplained hypercalcemia
Metastatic calcifications
Transplant bone disease

of these components correlate with PTH, osteocalcin, and BAP (27, 34). Routine serum assays are not yet available and additional studies are required to determine the usefulness of these assays.

For the clinician, the question remains as to when is it clinically appropriate to perform a bone biopsy for an accurate diagnosis (Table 3). This decision should be based on the presence of symptomatic manifestations and whether the possibility of aluminum accumulation exists. In the symptomatic patient—those with fractures, myopathy, hypercalcemia, and extraskeletal calcifications—the major differential is between severe hyperparathyroidism and aluminum bone disease. Clearly if PTH levels are not markedly elevated or there is no other clinical evidence of osteitis fibrosa (increased alkaline phosphatase, radiographic findings), a biopsy should be performed. If a parathyroidectomy is contemplated, then aluminum disease has to be ruled out, and a biopsy is indicated. In the asymptomatic patient, the decision is much more difficult. If PTH levels are relatively low (<200–300 pg/ml), specific anti-PTH therapy is probably not warranted, thus a specific diagnosis is not necessary. However, if the patient develops hypercalcemia or has extraskeletal calcifications, either high- or low-turnover disease may be present and a biopsy may be required. For those patients with PTH levels between 250 and 500 pg/ml, treatment is usually directed at preventing the

TABLE 4. Clinical examples of when a bone biopsy may be helpful

Clinical presentation	Laboratory evaluation	Clinical expression	Biopsy results
45-year-old man with an 11-year history of ESRD secondary to chronic GN. Treated with PD for 3 years, cadaveric transplant for 2 years and HD for the last 6 years. He had been on various phosphate binders including Ca carbonate, Ca acetate, and AlOH as well as intravenous calcitriol for 5 years. Major problem was refractory anemia in spite of adequate iron studies and 20,000 units of erythropoietin three times a week.	Over the last year serum Ca was between 9.0 and 10.5 mg/dl, serum P between 5.0 and 6.5 mg/dl, serum AP between 150 and 200 IU, serum PTH decreased from 1150 to 670 pg/ml, and Al between 20 and 40 ng/ml.	Severe osteitis fibrosa from refractory secondary hyperparathyroidism.	Mixed uremic osteodystrophy with marked Al staining (40% trabecular surface) and mild resorption with mild peritrabecular fibrosis.
34-year-old man with 9-year history of ESRD secondary to hypertension. Treated with HD for 4 years, cadaveric transplant for 1.5 years, and HD for the last 3.5 years. He complains of diffuse pain, pruritis, and proximal myopathy. He has been on various phosphate binders, but because of hypercalcemia has been predominantly on AlOH for the last 2 years and has been unable to take calcitriol.	Over the last year serum Ca was between 10.5 and 12.2 mg/dl, serum P between 5.9 and 9.0 mg/dl, serum AP between 150 and 200 IU, serum PTH between 600 and 900 pg/ml, and Al between 40 and 60 mg/ml.	Mixed uremic osteodystrophy with significant Al accumulation.	Severe osteitis fibrosa with minimal Al (<10% trabecular surface).
49-year-old woman with 15-year history of ESRD secondary to acute GN. Treated with HD for 6 months and a living related transplant for 15 years. Immunosuppressed with cyclosporine, azathioprine, and prednisone with a stable serum creatinine of approximately 1.5 mg/dl. Presents with 7 fractures over the last 5 years and diffuse bone pain.	Over the last 3 years serum Ca was between 10.5 and 12.0 mg/dl, serum P between 1.8 and 3.0 mg/dl, serum AP between 50 and 70 IU, and serum PTH between 120 and 180 pg/ml.	Hyperparathyroidism with moderate osteitis fibrosa.	Low-turnover lesion with marked osteomalacia.
37-year-old woman with 3-year history of ESRD secondary to insulin-dependent diabetes. Treated with PD for 6 months and HD for 2.5 years. She has taken both Ca carbonate and acetate, never taken AlOH. Had a spontaneous rib fracture and complains of bone pain in her feet and has mild proximal myopathy.	Over the last year serum Ca was between 10.0 and 11.2 mg/dl, serum P between 4.8 and 6.2 mg/dl, serum AP between 40 and 60 IU, serum PTH between 250 and 300 pg/ml, and Al <10 ng/ml.	Moderate hyperparathyroid bone disease.	Adynamic bone disease, no evidence of Al accumulation.

Abbreviations: glomerulonephritis (GN), peritoneal dialysis (PD), hemodialysis (HD), aluminum hydroxide (AlOH), aluminum (Al), calcium (Ca), phosphorus (P), alkaline phosphatase (AP), parathyroid hormone (PTH).

development of parathyroid hyperplasia and reducing PTH levels. However, these patients are at greatest risk of developing adynamic bone disease. Thus if hypercalcemia occurs, a biopsy should be considered. Table 4 illustrates several clinical examples of when a biopsy may be helpful.

Although noninvasive techniques may be useful for evaluating and monitoring many patients, they have not proved to be specific or sensitive enough to accurately diagnose all patients. Bone biopsy remains the gold standard for the classification of renal bone disease and for determining optimal therapy. As we further understand the pathogenesis of renal bone diseases and develop new therapies for these diseases, a precise diagnosis may become necessary. Currently bone biopsies are the most precise and accurate diagnostic tool available to access bone disease. Until better noninvasive monitoring techniques are developed, biopsies should be performed in appropriate patients.

References

1. Malluche HH, Monier-Faugere M-C: The role of bone biopsy in the management of patients with renal osteodystrophy. *J Am Soc Nephrol* 4:1631–1642, 1994
2. Hruska KA, Teitelbaum SI: Renal osteodystrophy. *N Engl J Med* 333:166–174, 1995
3. Hutchison AJ, Whitehouse RW, Boulton HF, Adams JE, Mawer EB, Freemont TJ, Gokal R: Correlation of bone histology with parathyroid hormone, vitamin D_3 and radiology in end-stage renal disease. *Kidney Int* 44: 1071–1077, 1993
4. Sherrard DJ, Hercz G, Pei Y, Maloney NA, Greenwood D, Manuel A, Saiphoo C, Fenton S, Serge GV: The spectrum of bone disease in end-stage renal failure. An evolving disorder. *Kidney Int* 43:436–442, 1993
5. Fournier A, Oprisiu R, Hottelart C, Yverneau PH, Ghazali A, Atik A, Hedri H, Said S, Sechet A, Rasolombololona M, Abighanem O, Sarraj A, El Esper N, Moriniere P, Boudailliez B, Westeel P-F, Achard J-M, Pruna A: Renal osteodystrophy in dialysis patients: diagnosis and treatment. *Artif Organs* 72:530–557, 1998
6. Coen G, Mazzaferro S, Ballanti P, Sardella D, Chicca S, Manni M, Bonucci E, Taggi F: Renal bone disease in 76 patients with varying degrees of predialysis chronic renal failure: a cross-sectional study. *Nephrol Dial Transplant* 11:813–819, 1996
7. Moriniere P, Cohen-Solal ME, Belbrik S, Boudailliez B, Marie A, Westeel P-F, Renaud H, Fievet P, Lalau JD, Schert JL, Fourinier A: Disappearance of aluminum bone disease in a long term asymptomatic dialysis population restricting aluminum hydroxide intake: emergence of an idiopathic adynamic bone disease not related to aluminum. *Nephron* 53:93–101, 1989
8. Musci I, Hercz G: Relative hypoparathyroidism and adynamic bone disease. *Am J Med Sci* 317:405–409, 1999
9. Kurz P, Monier-Faugere MC, Bognar B, Werner E, Roth P, Vlachojannis J, Malluche HH: Evidence for abnormal calcium homeostasis in patients with adynamic bone disease. *Kidney Int* 46:855–861, 1994
10. Musci I, Hercz G: Adynamic bone disease: pathogenesis, diagnosis and clinical relevance. *Curr Opin Nephrol Hypertens* 7:356–361, 1997
11. Hercz G, Pei Y, Greenwood C, Manuel A, Saiphoo C, Goodman WG, Serge GV, Fenton S, Sherrard DJ: Aplastic osteodystrophy without aluminum: the role of suppressed parathyroid function. *Kidney Int* 44:860–866, 1993
12. Faugere MC, Malluche HH: Stainable aluminum and not aluminum content reflect histologic changes in bone of dialyzed patients. *Kidney Int* 30:717–722, 1986
13. Torres, A, Lorenzo V, Hernandez D, Rodriguez JC, Concepcion MT, Rodriguez AP, Hernandez A, De Bonis, E, Darias E, Gonzalez-Posada JM, Losada M, Rufino, M, Felsenfeld AJ, Rodriguez M: Bone disease in predialysis, hemodialysis, and CAPD patients: evidence of a better bone response to PTH. *Kidney Int* 47:1434–1442, 1995
14. Cohen-Solal ME, Sebert JL, Boudailliez B, Marie A, Moriniere B, Gueris J, Bouillon R, Fourinier A: Comparison of intact, midregion, and carboxy terminal assays of parathyroid hormone for the diagnosis of bone disease in hemodialyzed patients. *J Clin Endocrinol Metab* 73:516–524, 1991
15. Qi Q, Monier-Faugere M-C, Geng Z, Malluche HH: Predictive value of serum parathyroid hormone levels for bone turnover in patients on chronic maintenance dialysis. *Am J Kidney Dis* 26:622–631, 1995
16. Quarles LD, Lobaugh B, Murphy G: Intact parathyroid hormone overestimates the presence and severity of parathyroid-mediated osseous abnormalities in uremia. *J Clin Endocrinol Metab* 75:145–150, 1992
17. Couttenye MM, D'Haese PC, Van Hoof VO, Lemoniatou E, Goodman W, Verpooten GA, De Broe ME: Low serum levels of alkaline phosphatase of bone origin: a good marker of adynamic bone disease in haemodialysis patients. *Nephrol Dial Transplant* 11:1065–1072, 1996
18. Gomez B, Ardakani S, Ju J, Jenkins D, Cerelli M, Daniloff G, Kung V: Monoclonal antibody assay for measuring bone-specific alkaline phosphatase activity in serum. *Clin Chem* 41:1560–1566, 1995
19. Fletcher S, Jones RG, Rayner HC, Harnden P, Hordon LD, Aaron JE, Oldroyd B, Brownjohn AM, Turney JH, Smith MA: Assessment of renal osteodystrophy in dialysis patients: use of bone alkaline phosphatase, bone mineral density and parathyroid ultrasound in comparison with bone histology. *Nephron* 75:412–419, 1997
20. Ureña P, Hruby M, Ferreira A, Ang KS, de Vernejoul M-C: Plasma total versus bone alkaline phosphatase as markers of bone turnover in hemodialysis patients. *J Am Soc Nephrol* 7:506–512, 1996
21. Ureña P, de Vernejoul M-C: Circulating biochemical markers of bone remodeling in uremic patients. *Kidney Int* 55:2141–2156, 1999
22. Coen G, Ballanti P, Bonucci E, Calabria S, Centorrino M, Fassino V, Manni M, Mantella D, Mazzaferro S, Napoletano I, Sardella D, Taggi F: Bone markers in the diagnosis of low turnover osteodystrophy in haemodialysis patients. *Nephrol Dial Transplant* 13:2294–2302, 1998
23. Delmas P: Biochemical markers of bone turnover: methodology and clinical use in osteoporosis. *Am J Med* 91:169–174, 1991
24. De Vernejoul M-C: Markers of bone remodeling in metabolic bone disease. *Drugs Aging* 12:S9–S14, 1998
25. Charhon SA, Delmas PD, Malaval L, Chavassieux PM, Arlot M, Chapuy MC, Meunier PJ: Serum bone Gla-protein in renal osteodystrophy: comparison with bone histomorphometry. *J Clin Endocrinol Metab* 63:892–897, 1986
26. Duda RJ, O'Brien JF, Katzmann JA, Petersen JM, Mann KG, Riggs BL: Concurrent assays of circulating bone Gla protein and bone alkaline phosphatase: effect of sex, age and metabolic bone disease. *J Clin Endocrinol Metab* 66:951–957, 1988
27. Urena P, Ferreira A, Kung V, Morieu C, Simon P, Ang K, Souberbielle J, Serge G, Drueke T, de Vernejoul M: Serum pyridoniline as a specific marker of collagen breakdown and bone metabolism in hemodialysis patients. *J Bone Miner Res* 10:932–939, 1995
28. Hamdy NAT, Risteli J, Risteli S, Harris S, Beneton M, Brown C, Kanis J: Serum type I procollagen peptide: a non-invasive index of bone formation in patients on hemodialysis? *Nephrol Dial Transplant* 9:511–516, 1994
29. Coen G, Mazzaferro S, Ballanti P, Bonucci E, Bondatti F, Manni M, Pasquali M, Perruzza I, Sardella D, Spurio A: Procollagen type I C-terminal extension peptide in predialysis chronic renal failure. *Am J Nephrol* 12:246–251, 1992
30. Coen G, Ballanti P, Mazzaferro S, Pasquali M, Bonucci E: Procollagen type I C-terminal extension peptide, PTH, and 1,25 vitamin D in chronic renal failure. *Bone* 14:415–420, 1993
31. Lau K, Orishi T, Wergedal J, Singer F, Baylink D: Characterization and assay of tartrate-resistant acid phosphatase activity in serum: potential use to assess bone resorption. *Clin Chem* 33:458–462, 1987
32. Mazzaferro S, Pasquali M, Ballanti P, Bonucci E, Costantini S, Chicca S, Demeo S, Perruzza I, Sardella D, Taggi F, Coen G: Diagnostic value of serum peptides of collagen synthesis and degradation in dialysis renal osteodystrophy. *Nephrol Dial Transplant* 10:52–58, 1995
33. Uebelhart D, Gineyts E, Chapuy MC, Delmas PD: Urinary excretion of pyridinium crosslinks: a new marker of bone resorption in metabolic bone disease. *Bone Miner* 8:87–96, 1990
34. Niwa T, Shiobara K, Hamada T, Miyazaki T, Tsukushi S, Uema K, Tsuzuki T: Serum pyridinolines as specific markers of bone resorption in hemodialyzed patients. *Clin Chim Acta* 235:33–40, 1995