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, β₂-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...
against bone alkaline phosphatase has resulted in enzymatic assays utilizing a monoclonal antibody alterations in their respective half-lives.

enzymes to the total alkaline phosphatase because of contribution of the osseous, hepatic, and intestinal iso-

renal failure it is not possible to determine the relative information, but it lacks both sensitivity and specificity. In

phatase is the most commonly used marker of bone for-
mation or resorption (Table 2). Total alkaline phos-

ers, would be useful to direct therapy.

Biochemical markers of bone metabolism may be sub-

TABLE 2. Biochemical markers of bone metabolism

<table>
<thead>
<tr>
<th>Bone formation</th>
<th>Bone resorption</th>
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<tbody>
<tr>
<td>Total alkaline phosphatase</td>
<td>Tartrate-resistant acid phosphatase (TRAP)</td>
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<tr>
<td>Bone alkaline phosphatase (BAP)</td>
<td>Type I collagen cross-linked telopeptide (ICTP)</td>
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<tr>
<td>Osteocalcin</td>
<td>Pyridinoline*</td>
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<tr>
<td>Procollagen type I C-terminal extension peptide (PICP)</td>
<td>Deoxypyridinoline*</td>
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* Urinary measurements.
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>
<thead>
<tr>
<th>TABLE 3. Indications for bone biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitive classification of renal osteodystrophy</td>
</tr>
<tr>
<td>High-turnover bone disease</td>
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<td>Low-turnover bone disease</td>
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<tr>
<td>Osteomalacia</td>
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<td>Aluminum bone disease</td>
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<td>Prior to parathyroidectomy</td>
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<tr>
<td>Unexplained hyperparathyroidism</td>
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<td>Metastatic calcifications</td>
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<td>Transplant bone disease</td>
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</table>

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<thead>
<tr>
<th>Clinical presentation</th>
<th>Laboratory evaluation</th>
<th>Clinical expression</th>
<th>Biopsy results</th>
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<tbody>
<tr>
<td>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 Al(OH) 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.</td>
<td>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.</td>
<td>Severe osteitis fibrosa from refractory secondary hyperparathyroidism.</td>
<td>Mixed uremic osteodystrophy with marked Al staining (40% trabecular surface) and mild resorption with mild periosteal fibrosis.</td>
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<td>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 Al(OH) for the last 2 years and has been unable to take calcitriol.</td>
<td>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.</td>
<td>Mixed uremic osteodystrophy with significant Al accumulation.</td>
<td>Severe osteitis fibrosa with minimal Al (&lt;10% trabecular surface).</td>
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<td>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.</td>
<td>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.</td>
<td>Hyperparathyroidism with moderate osteitis fibrosa.</td>
<td>Low-turnover lesion with marked osteomalacia.</td>
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<td>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 Al(OH). Had a spontaneous rib fracture and complains of bone pain in her feet and has mild proximal myopathy.</td>
<td>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 &lt;10 ng/ml.</td>
<td>Moderate hyperparathyroid bone disease.</td>
<td>Adynamic bone disease, no evidence of Al accumulation.</td>
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Abbreviations: glomerulonephritis (GN), peritoneal dialysis (PD), hemodialysis (HD), aluminum hydroxide (Al(OH)), 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