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Diagnosis of Renal Osteodystrophy

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Abstract

Chronic Kidney Disease (CKD) is commonly associated with alterations in bone and mineral metabolism (renal osteodystrophy). To date, bone biopsy remains the gold standard for the diagnosis and classification of the various types of renal osteodystrophy, namely: osteitis fibrosa, mixed uremic osteodystrophy, osteomalacia, aplastic and adynamic bone disease. However, due to its invasive nature and the fact that it is quite expensive, there has been a clamor for a search for other tests. Traditionally, the level of parathyroid hormone (PTH) has been considered a surrogate of bone turnover. At this time, the search continues for a specific and sensitive biochemical marker for monitoring bone turnover in CKD., e.g., alkaline phosphatase, osteocalcin, collagen degradation products, etc.

In this chapter, we also present the common radiographic findings that are commonly seen in patients with renal osteodystrophy. Other radiographic techniques such as, dual energy x-ray absorptiometry (DEXA) and deferoxamine challenge test (DFO) are also briefly discussed.

Key Words: renal, osteodystrophy, osteoblast, osteoclast, osteitis fibrosa, osteomalacia, histomorphometry, histochemical, hypercalcemia, hyperphosphatemia, deferoxamine, alkaline phosphatase, acid phosphatase, subperiosteal, calcifications, absorptiometry, pseudofractures, bisphosphonates

It has been reported in recent studies that over 50% of patients with only moderate renal failure have abnormal bone histological findings consistent with renal osteodystrophy (1). To date, the gold standard for the diagnosis of renal osteodystrophy remains histomorphometric and histochemical examination of a bone biopsy specimen (1).

Patients with renal osteodystrophy usually tend to be asymptomatic. For those with symptoms, they tend to be generally vague and nonspecific. They may complain of bone pain involving the lower back, hips, and lower extremities, which is a common symptom. Weight bearing activities commonly aggravate such symptoms.

Generalized pruritus is also common, especially in those already on maintenance renal replacement therapy. It has been postulated that calcium phosphate deposition in the skin may play a major role in its causation.

To subject patients who may either be asymptomatic or with such vague symptoms to a bone biopsy is rather invasive and impractical.

Over the past two decades, alternative methods of diagnosis have been the subject of much research and discussion. These include serum tests that may reflect either bone formation or bone resorption (Table 1) (2), bone mineral densitometry, and bone radiography.

Laboratory Tests

Parathyroid Hormone (PTH)

Because PTH plays a central role in the regulation of bone turnover and cellular activity, measurement of PTH levels has gained popularity as the principal

Table 1. Circulating biochemical markers of bone remodeling

Bone formation
Total alkaline phosphatases (tAP)
Bone-specific alkaline phosphatase (bAP)
Osteocalcin
Procollagen type-I carboxy-terminal extension peptide (PIPC)
Insulin-like growth factor-I (IGF-I)
Bone resorption
Tartrate-resistant acid phosphatase (TRAP)
Pyridinoline (PYD)
Deoxypyridinoline (DPD)
Procollagen type-I cross-linked carboxy-terminal telopeptide (ICTP)
β2-microglobulin (β_2m)
Bone sialoprotein
Advanced glycatation end-products (AGEs)
Advanced oxidation protein products (AOPP)
Cytokines (IL-1, IL-6, IL-11, TNFα, TGFβ, IFNγ,)
Growth factors (MCS-F, GMCS-F)
Other potential markers
Osteopontin
Osteonectin
Fibronectin
Bone morphometric proteins (BMPs) and their soluble receptors
Prostaglandin E_2
Plasminogene activator factor (PAF)
Inhibitor of the plasminogene activator factor (PAF-I)
Cathepsins
Integrins
Nitric oxide

(Reprinted with permission from Urena P, Vernejoul M. 1999 Circulating biochemical markers of bone remodeling in uremic patients. Kidney Int 55:2141)

biochemical marker in the diagnosis and classification of renal osteodystrophy, but this is not without controversy. To date, several assays have been developed with the primary goal of accurately measuring the PTH level.

In order to better understand the issues at hand, Martin et al (3) published an extensive discussion of this controversial topic and provided a listing of definitions of terms used in the various assays (3).

To date, the second generation assays for PTH (more specific) are not widely available, therefore, "intact PTH" assays of the first generation type continue to be used in clinical practice guidelines.

Some guidelines recommend using intact PTH levels in classifying the various types of bone disease (4): intact PTH levels <100 pg/mL are associated with an increased incidence of adynamic bone disease and a decreased likelihood of osteitis fibrosa; intact PTH levels >450 pg/mL is typically associated with an increased incidence of high bone turnover diseases, such as hyperparathyroid (osteitis fibrosa) bone disease and/ or mixed/ renal osteodystrophy; and intact PTH levels between 100 and 450 pg/mL may be associated with various degrees of bone remodeling, whether increased or decreased, or even normal. Intact PTH levels <200 pg/mL are associated with increased risk of fractures.

Note that such assays for measuring intact PTH are used for both diagnostic as well as in the therapeutic guidance of management of renal osteodystrophy.

Calcium and Phosphorus

Levels of serum calcium and phosphorus are not very useful in diagnosing specific types of bone disease, especially when used alone. In advanced stages of chronic kidney disease (CKD), serum calcium tends

Table 2. Glossary of PTH Terminology

Intact PTH, usually refers to PTH measured by a 2-site immunometric assay. If radioactive reagents are used, the term immunoradiometric assay (**IRMA**) would apply, while if chemiluminescent reagents are used, the term immunochemiluminescence assay (**ICMA**) would apply. Initial assays were called "second-generation PTH assays" as a comparison to the older mid-region and n-terminal assays. However, the widely used intact assay is a first generation of *intact* assays whereby 2 antibodies are used to simultaneously detect the N-terminal and C-terminal. However, it is now known that many, if not all, such assays also measure C-terminal PTH fragments such as PTH 7-84, which are of unclear biologic significance. As a result, new "second-generation intact" assays such as the bio-intact and whole PTH assays have been developed.

Bio-Intact PTH is a 2-site chemiluminescence assay specific for PTH 1-84 developed by Nichols Institute Diagnostics.

Whole PTH is also a 2-site immunoradiometric assay specific for PTH 1-84 developed by Scantibodies, Inc. Since PTH 1-84 mediates its biological effects by increasing the activity of adenylate cyclase, this assay is also know as **CAP** (cyclase-activating PTH).

Since **PTH 7-84** does not stimulate adenylate cyclase, the measurement of PTH 7-84 is known as **CIP** (cyclase-inactive PTH). PTH 7-84 can be measured by subtracting values for PTH 1-84 from values obtained with the older " intact" PTH assays.

(Reprinted with permission from: Martin KJ, Olgaard K, Coburn JW, et al. Diagnosis, assessment and treatment of bone turnover abnormalities in renal osteopystrophy. Am J Kidney Dis 2004;43:560)

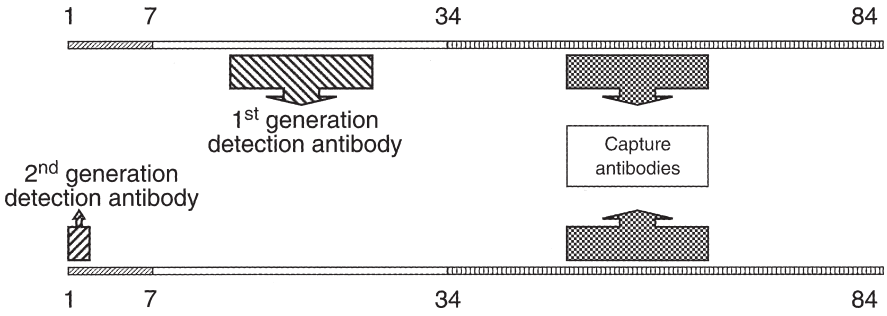

Fig. 1. A comparison of technical aspects of first- and second- generation immunometric assays for parathyroid hormone (PTH). (Reprinted with permission from: Goodman WG, Juppner H, Salusky IB, Sherrard DJ. Parathyroid Hormone (PTH), PTH-Derived Peptides, and new PTH assays in renal osteodystrophy. Kidney Int. 2003; 63: 5.)

to be low, whereas serum phosphorus is usually elevated as a result of primary renal retention of phosphate. They are however useful, in guiding management of renal osteodystrophy. On the other hand, hypercalcemia can be secondary to concomitant use of calcium- containing antacids and phosphate binders.

Alkaline Phosphatase

This can be measured either as bone-specific or total alkaline phosphatase. Alone, such levels provide an index of osteoblast activity, especially in patients with CKD. More importantly, they provide useful information in the diagnosis of renal osteodystrophy, especially when used concomitantly with intact PTH measurements. When taken together, both serum alkaline phosphatase and intact PTH levels can be useful in classifying low or high turnover disease: a low serum alkaline phosphatase (< 7 ng/mL) combined with low intact PTH, points to low turnover diseases (2), such as osteomalacia or adynamic bone disease. Conversely, a high serum alkaline phosphatase (> 20 ng/mL) combined with an elevated intact PTH (> 200 pg/mL), is highly sensitive and specific for the high turnover diseases (5).

Osteocalcin

This is another marker of osteoblastic activity but is not considered superior to alkaline phosphatase in the diagnosis of renal osteodystrophy.

There are several limitations to its use in renal osteodystrophy, such as the following: it is rapidly degraded into various active and inactive fragments that accumulate in the presence of renal failure, and it is released from bone during matrix degradation.

Others

Still investigational at this time, other known markers of osteoclastic activity such as tartrate-resistant acid phosphatase (TRAP) and collagen degradation products (CDP), such as pyrodinoline (PYD) and dihydro-pyrodinoline (DPD). A significant limitation of CDP is that they are eliminated via the renal route such that, in patients with underlying CKD, they tend to accumulate. See Table 1.

Imaging Studies

As far as radiographic findings in renal osteodystrophy, such bony changes can also be classified into four, namely: osteitis fibrosa, osteomalacia, osteosclerosis as well as soft-tissue calcification.

Osteitis Fibrosa

The classic radiographic finding in hyperparathyroidism is subperiosteal resorption (Fig. 2) of bone, believed to be because increased osteoclastic activity secondary to the elevation of PTH levels. Such "subperiosteal resorption," is commonly observed along the radial aspect of the phalanges.

In the facial bones, especially the mandibular area, as well as long bones, clavicles, and digits, focal collections of giant cells referred to as "brown tumors" are usually seen. On the other hand, the most common radiographic finding is the "salt and

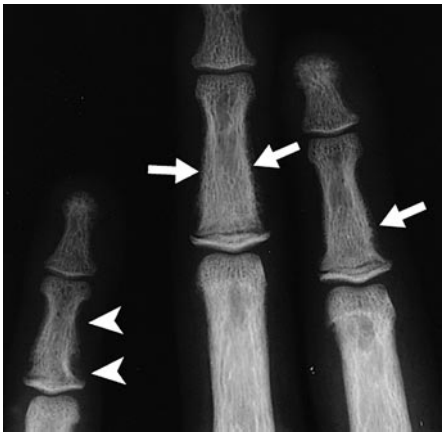

Fig 2. Subperiosteal erosions in hyperparathyroidism. Severe subperiosteal erosions as a manifestation of hyperparathyroidism (arrows). The extensive scalloped appearance of the middle phalanx on the left (arrow heads) represents a small brown tumor. (Reprinted with permission from: Gonzalez, E. A., Martin, K. J. Bone and Mineral Metabolism in Chronic Renal Failure. In: Johnson, R. J., Feehally, J, eds. Comprehensive Clinical Nephrology. 2nd Edition. Mosby/Elsevier LTD.; 2003:880)

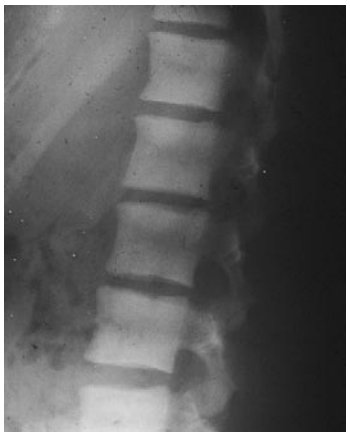

Fig 3. Rugger-jersey spine' in hyperparathyroidism. Vertebral bodies show the increased density of the ground plates and central radiolucency, which gives the appearance of a "rugger-jersey". Reprinted with permission from: page 878.

pepper" appearance to the skull, referring to the mottling areas of varying density.

Osteomalacia

Radiographically, one may characteristically see "Looser's zones," also referred to as "pseudofractures." Commonly seen in the ischial and pubic rami of the pelvis, they appear as thin, radiolucent lines perpendicular to the cortex. Such zones are believed to represent areas of incomplete fractures owing to decreased mineralization that may potentially progress to true pathologic fractures. They are also commonly seen in the neck, posterior and axillary margins of the scapula, as well as the lesser trochanter of the femur (6).

Osteosclerosis

Osteosclerosis commonly involves the spine, pelvis, and ribs. "Rugger-jersey spine" (Fig. 3) is its radiographic correlate.

Soft-Tissue Calcifications

Extra-skeletal (Fig. 4) calcifications are usually seen in association with secondary hyperparathyroidism. Corneal and conjunctival calcifications are commonly seen in patients who have been maintained on long-term hemodialysis.

Dual-Energy X-Ray Absorptiometry (Dexa)

This test is primarily used to measure bone mineral density (BMD). It is widely used in the diagnosis of osteoporosis. However, in renal osteodystrophy, its use is significantly limited because of the inconsistent correlations between BMD measurements obtained by DEXA and actual bone histology patterns. Such variability is brought about by extra-skeletal calcifications, steroid therapy, and so on.

It is also noted that majority of patients on hemodialysis have a reduced BMD (7), making this test less useful in this population.

The most recent K-DOQI Guidelines recommend BMD evaluation only in CKD patients with fractures or pre-existing osteoporosis (steroid-induced) (8).

Deferoxamine Challenge Test (DFO)

The deferoxamine challenge test (DFO) has been used to primarily exclude aluminum-related bone diseases. In general, a low DFO test combined with an elevated intact PTH level mitigates against the diagnosis of aluminum related bone disease (9).

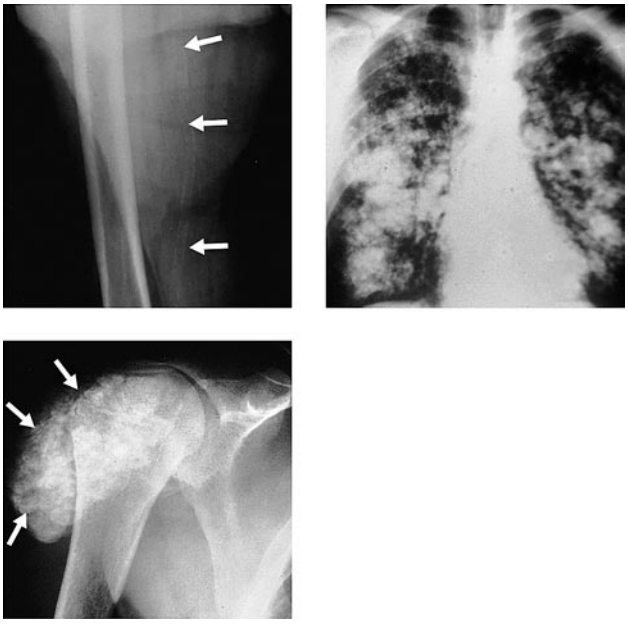

Fig. 4A. Extra-skeletal calcification in CKD: Arterial calcification (arrows). Fig. 4B. Extra-skeletal calcification in CKD: Pulmonary calcification. Fig. 4C. Extra-skeletal calcification in CKD: Periarticular calcification (arrows). (Reprinted with permission from page 878: Gonzalez, E. A., Martin, K. J. Bone and Mineral Metabolism in Chronic Renal Failure. In: Johnson, R. J., Feehally, J, eds. Comprehensive Clinical Nephrology. 2nd Edition. Mosby/ Elsevier LTD.; 2003:880).

Bone Biopsy

Bone biopsy is the gold standard for establishing the type of renal bone disease, since no combination of biochemical parameters is sufficiently accurate (10).

Definitive and quantitative diagnosis of various types of bone disease is established by direct bone biopsy and then using double tetracycline labeling of undecalcified areas.

As a result of its rather invasive nature, bone biopsy is not routinely recommended in the evaluation of bone disease. The specific indications for doing a bone biopsy in patients with CKD include (11):

- Inconsistencies among biochemical parameters, thereby preventing definitive interpretation;
- Unexplained skeletal fracture or bone pain;
- Severe progressive vascular calcification;
- Suspicion of overload or toxicity from aluminum and/ or other metals;
- Prior to parathyroidectomy, if there was a clnical history of aluminum exposure or if the biochemical determinations are inconsistent with advanced secondary or tertiary hyperparathyroidism; and
- Consideration prior to beginning treatment with bisphosphonates.

The principal site of bone biopsy is the iliac crest. There are two generally accepted techniques in obtaining tissue sample, namely the transiliac approach or the vertical biopsy.

One of the most important resources for interpreting events within bone is tetracycline labeling. Tetracycline is incorporated into mineralizing bone and other calcified tissues, and in ultraviolet light, it fluoresces green to yellow. If given to a patient prior to biopsy, it can be seen as a yellow-green line when unstained sections are viewed in ultraviolet light. This line can be used as a marker of mineralization. If two or more doses of tetracycline are given at specified intervals, parallel lines of fluorescence can be separated by unlabeled bone. The separation between the lines is a measure of the rate of mineralization and, in steady bone deposition states, the rate of bone formation (12).

Typically, two 3-d tetracycline-labeling periods, separated by 21 d are required. The second labeling period must be completed at least 2 d before the actual biopsy is performed. Most centers prefer to use two different types of drugs (for the two labeling periods) belonging to the tetracycline family.

Once the tissue sample is obtained, it is stained for aluminum and iron.

In interpreting the findings in the tissue sample obtained, the TMV Classification nomenclature is recommended by the American Society of Bone and Mineral Research.

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