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Definition and Classification of Renal Osteodystrophy

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Abstract

One of the major complications that arise as a result of chronic kidney disease is that of 'renal osteodystrophy.' It is believed to be a multifactorial disorder of altered bone modeling. Bone biopsy occupies a central role in the differentiation of the various kinds of renal osteodystrophy based on histological findings. However, due to its limitations of being a rather invasive and costly procedure, it is performed rather infrequently. Therefore, scientists started to focus on alternative measures of classifying the various types, e.g., the parathyroid hormone (PTH). PTH has been used as an indicator of bone turnover, thereby dividing the diseases into those of high turnover and low turnover. To further our understanding of this particular disease entity, a unified definition and classification was formulated and adopted by well-renowned experts from both local and international scenes, and this is presented in some detail in this chapter. It is hoped, that such unification will enhance communication, facilitate clinical decision making, and promote the evolution of evidence-based clinical practice guidelines worldwide. (2)

Key Words: renal, osteodystrophy, osteoblast, osteoclast, osteitis fibrosa, osteomalacia, histomorphometry, osteoid, peritrabecular

Traditionally, disturbances of bone and mineral metabolism, commonly seen in patients with chronic kidney disease (CKD), have been referred to as "renal osteodystrophy." Similarly, its classification was primarily based on bone biopsy findings.

In 2003, during the National Kidney Foundation Controversies Conference on Mineral Metabolism and Bone Disease in CKD, it was proposed that renal osteodystrophy be defined as: *A constellation of bone disorders present or exacerbated by chronic kidney disease that lead to bone fragility and fractures, abnormal mineral metabolism, and extraskeletal manifestations* (1).

Such definition, however, failed to gain acceptance by the majority of experts.

In 2005, the second Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference on the "Definition, Evaluation and Classification of Renal Osteodystrophy" was held in Madrid, Spain. By consensus, renal osteodystrophy is now defined as: *An alteration of bone morphology in patients with CKD*.

Another entity called Chronic Kidney Disease-Mineral Bone Disorder (CKD-MBD) was defined as: *A systemic disorder of mineral and bone metabolism due to CKD manifested by either one or a combination of the following: abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism; abnormalities in bone turnover, mineralization, volume, linear growth, or strength; and, vascular or other soft-tissue calcification* (2).

With these definitions, renal osteodystrophy is now considered to be only one of the various bone and mineral disorders that occur secondary to CKD.

Furthermore, a bone biopsy is required to establish the definitive diagnosis of renal osteodystrophy. Using bone histomorphometry, there are several parameters that have traditionally been

TABLE 1. *Histomorphometric diagnosis of renal bone disease*

Parameters	Abbreviation and units[a]	Normal values[b]	Osteitis fibrosa	Mixed osteopathy	Mild lesion	ABD		Osteomalacia	
						Al+	Al−	Al+	Al−
Bone volume	BV/TV % of total volume	21 ± 5	N – ↗	N – ↗	N	↘	N	N	N
Osteoid volume (or area)	OV/TV % of total volume	1.8 ± 0.4	↗	↗↗	N	N ↘	N ↘	↗↗	↗↗
Osteoid surface	OS/BS % of total surface	11 ± 3	↗	↗↗	↗	N ↘↗	N↘↗	↗↗	↗↗
Osteoid thickness	μm	6.3 ± 1.5	N	N	N	N ↘	N ↘	↗↗	↗↗
Osteoblastic surface	OblS/BS % of total surface	3.6 ± 1.2	↗↗	↗ –N	N	↘	↘	↘	↘
Eroded surface	ES/BS % of total surface	3.5 ± 1.5	↗↗	↗	N	N	N	N	N
Osteoclast surface	OCS/BS % of total surface	0.5 ± 0.2	↗↗	↗	N	N ↘	N ↘	N ↘	↘ N
Osteoclast number	NOC/T.Ar n/mm^2	0.2 ± 0.1	↗↗	↗	N	↘	↘	↘	↘
Medullary fibrosis	% of medullary and bone area	<0.5	>0.5	>0.5	N	N	N	N	N
Mineral apposition rate	MAR μm/day	0.62 ± 0.22	↗ –N	↗ –N	N	↘	↘	↘	↘
Double labeled surface	DLS/BS % of total surface	5.2 ± 1	↗	N– ↗	N	↘	↘	↘	↘
Bone formation rate at tissue level	BFR/BS	See footnote[c]	↗↗	↗	N	↘	↘	↘	↘
Aluminum staining: of cement lines		0	±	++	±	+	–	+	–
of osteoid/calcified bone interfaces		0	0	+	0	+	–	+	–

[a] Bone histomorphometry: Standardization of nomenclature. Parfitt AM. *Bone Min* 1988;4:1–5.
[b] Garcia Carasco and MC de Vernejoul. *Calcif Tissue Int* 1988;42:13–7.
[c] The normal values vary according to age, sex, race, units used by authors. They have been summarized in Table 1 of Fournier et al. Adynamic bone disease. In: Wichtig D, ed. *Issues in Nephrosciences.* Milan, Italy, 1996: Uremic Osteoarthropathy.
The major criteria have been put in boxes.
(Reprinted with permission from: Fournier A, Oprisiu R, et al. Renal osteodystrophy in dialysis patients: diagnosis and treatment. Artif Org 1998;22;7:530)

used to classify the various types of renal osteodystrophy (Table 1).

The American Society for Bone and Mineral Research (ASBMR) has recommended a standardized nomenclature for reporting the findings on bone histomorphometry, for both clinical and research purposes. The three key histologic descriptors that are used in this new classification include bone turnover, mineralization, and volume (TMV Classification System) (Table 2).

Turnover refers to the rate of bone remodeling, reflecting the processes of bone resorption and bone formation. It is determined by dynamic measurements of osteoblast function, using double-tetracycline labeling *(2)*. Mineralization, on the other hand, reflects how well bone collagen is calcified. It is determined by dynamic measurements of mineralization lag time and osteoid maturation time, using double-tetracycline labeling methods; static measurements of osteoid volume and osteoid thickness are also used *(2)*. Lastly, volume refers to the amount of bone per unit volume of tissue. This is determined by static measurements of bone volume in cancellous bone *(2)*.

Table 2. TMV classification system for renal osteodystrophy

Turnover	Mineralization	Volume
Low		Low
	Normal	
Normal		Normal
	Abnormal	
High		High

TMV, boneturnover, mineralization, and volume.
(Reprinted with permission from: Moe SM, Drueke T, et al. Definition, evaluation and classification of renal osteodystrophy: A Position Statement from Kidney Disease: Improving Global outcomes (KDIGO). Kidney Int 2006.69;1947)

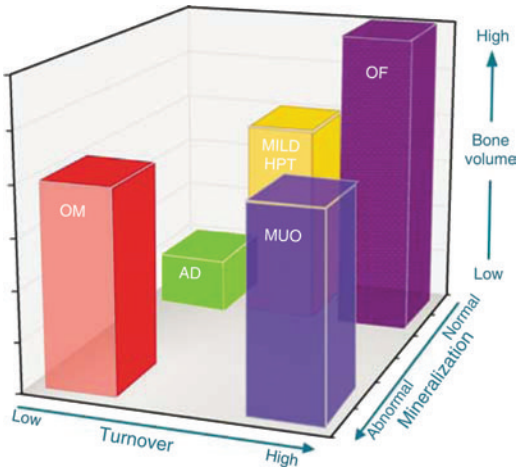


Fig. 1. TMV classification system for bone histomorphometry. The figure is a graphical example of how the TMV system provides more information than the present, commonly used classification scheme. Each axis represents one of the descriptors in the TMV classification: turnover (from low to high), mineralization (from normal to abnormal), and bone volume (from low to high). Individual patient parameters could be plotted on the graph, or means and ranges of grouped data could be shown. For example, many patients with renal osteodystrophy cluster in areas shown by the bars. The red bar (OM, osteomalacia) is currently described as low-turnover bone with abnormal mineralization. The bone volume may be low to medium, depending on the severity and duration of the process and other factors that affect bone. The green bar (AD, adynamic bone disease) is currently described as low-turnover bone with normal mineralization, and the bone volume in this example is at the lower end of the spectrum, but other patients with normal mineralization and low turnover will have normal bone volume. The yellow bar (mild HPT, mild hyperparathyroid-related bone disease) and purple bar (OF, osteitis fibrosa or advanced hyperparathyroid-related bone disease) are currently used distinct categories, but in actuality represent a range of abnormalities along a continuum of medium to high turnover, and any bone volume depending on the duration of the disease process. Finally, the blue bar (MUO, mixed uremic osteodystrophy) is variably defined internationally. In the present graph, it is depicted as high-turnover, normal bone volume, with abnormal mineralization. In summary, the TMV classification system more precisely describes the range of pathologic abnormalities that can occur in patients with CKD.
(Reprinted with permission from: Moe SM, Drueke T, et al. Definition, evaluation and classification of renal osteodystrophy: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 2006, 69:1949)

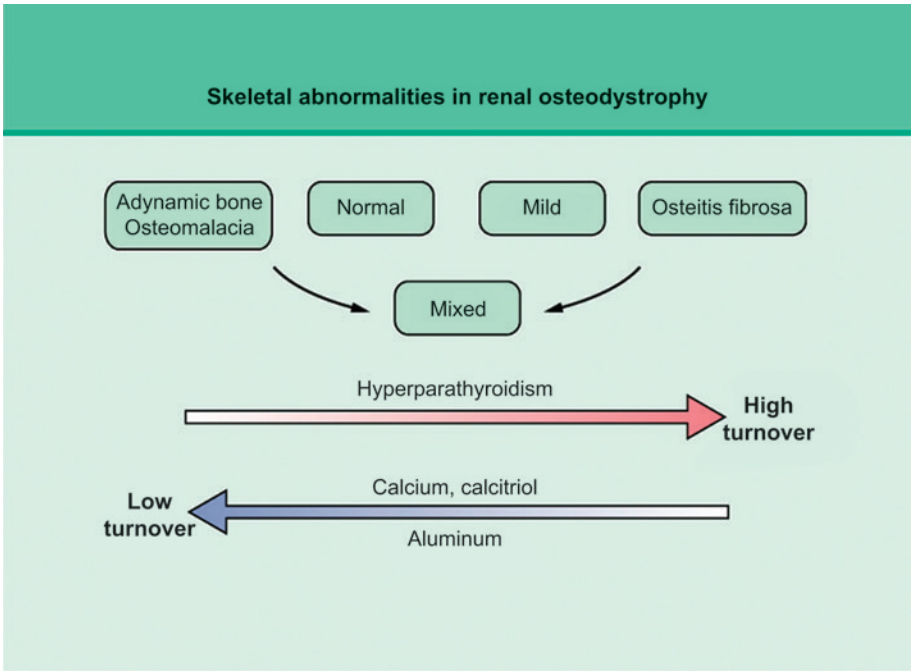


Fig. 2. The Spectrum of Renal Osteodystrophy. The range of skeletal abnormalities in renal bone disease encompasses syndromes with both high and low bone turnover. (Reprinted with permission from: Gonzalez EA, Martin KJ. Bone and Mineral Metabolism in Chronic Renal Failure. In: Johnson RJ, Feehally J, eds. Comprehensive Clinical Nephrology. 2nd Edition. Mosby/Elsevier Limited; 2003:873.)

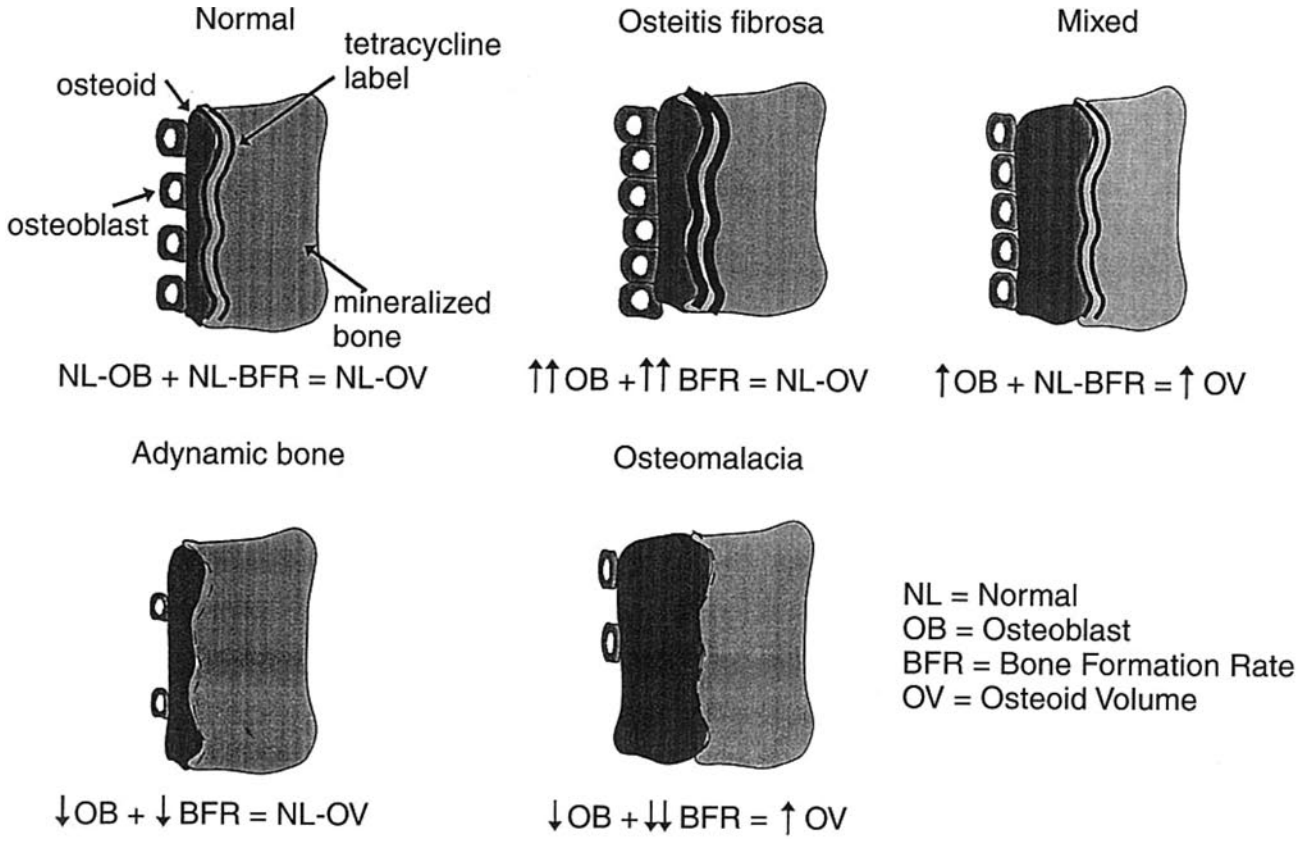


Fig. 3. A schematic diagram of the different forms of renal osteodystrophy. Shown are schematic diagrams of the different forms of renal osteodystrophy. The amount of osteoid accumulation depends on the rate of osteoid deposition by osteoblasts and the rate that bone is mineralized or formed (bone formation rate). In osteitis fibrosa, both the rate of osteoid deposition is increased and the rate of bone formation (represented by the two tetracycline labels) are equally increased; thus osteiod accumulation does not occur. In mixed osteitis fibrosa—osteomalcia, the rate of osteiod deposition (greater than normal) exceeds the rate of bone formation (normal) and as a result, osteoid accumulation is observed. In adynamic bone, the rate of osteoid deposition and the rate of bone formation are proportionally reduced so that osteoid osteoid accumulation is not present. In osteomalacia, the rate of osteiod deposition and the rate of bone formation are reduced; however, the rate of bone formation is reduced more than of osteoid deposition and as a result, osteoid accumulation is observed. (Reprinted with permission from: Felsenfeld AJ, Torres A. 2001 Osteitis fibrosa, osteomalacia, and mixed bone lesions. In: Drueke T, Salusky IB (eds) The Spectrum of Renal Osteodystrophy. Oxford University Press, 2001;192)

Based primarily on histologic features (Table 3), renal osteodystrophy is traditionally divided into four types, namely osteitis fibrosa, mixed uremic osteodystrophy, osteomalacia, and adynamic bone disease. Using the new TMV classification, it can be divided into (1) high turnover – osteitis fibrosa and mixed osteodystrophy and (2) low turnover – osteomalacia and adynamic bone disease.

Normal Bone

To fully understand the concept of differentiation of the various categories of renal osteodystrophy, one must be fully versed with normal bone remodeling (Fig. 1).

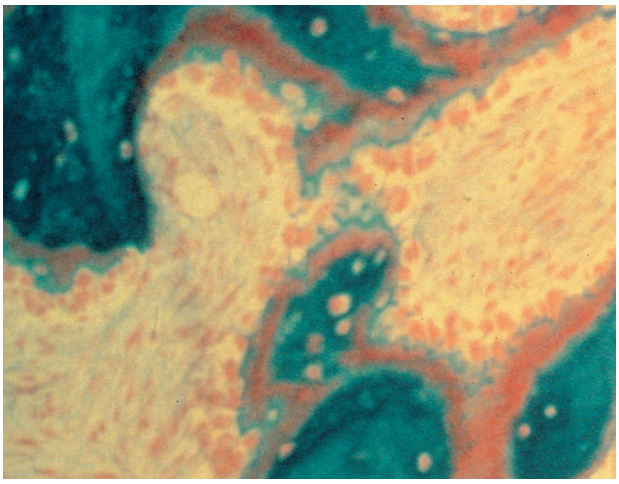
Normal bone is considered a "dynamic" tissue. It continuously undergoes a so-called remodeling process, whereby old bone is continuously replaced by new bone. This process, which usually lasts 4–8 months, is conveniently divided into four phases (3):

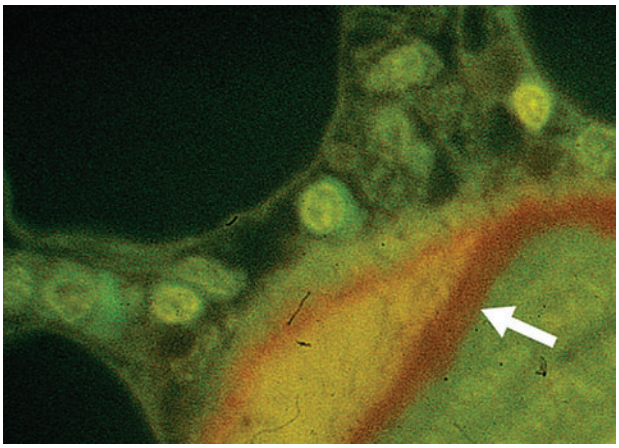
1. Activation phase: osteoclasts are recruited and the bone surface is prepared.
2. Resorption phase: osteoclasts contact and erode the bone surface.
3. Reversal phase: osteoblasts appear at the site.

Table 3. Histologic Classification of Renal Osteodystrophy.

Disorder	Description	Pathogenesis
Osteitis fibrosa	Peritrabecular fibrosis, increased remodeling — resorption and formation	Secondary hyperparathyroidism, secondary role of cytokines and growth factors
Osteomalacia	Increased osteoid, defective mineralization	Aluminum deposition, plus unknown factors
Mixed disease	Features of both osteitis fibrosa and osteomalacia	Secondary hyperparathyroidism and aluminum deposition, plus unknown factors
Mild disease	Slightly increased remodeling	Early or treated secondary hyperparathyroidism
Adynamic renal bone disease	Hypocellular bone surfaces, no remodeling	Aluminum deposition, parathyroid hormone suppression, and other factors (deficiency of bone growth factors or increased suppressors of bone remodeling)

(Reprinted with permission from: Hruska KA, Teitelbaum SL. Renal Osteodystrophy. N Engl J Med 1995; 333:167)





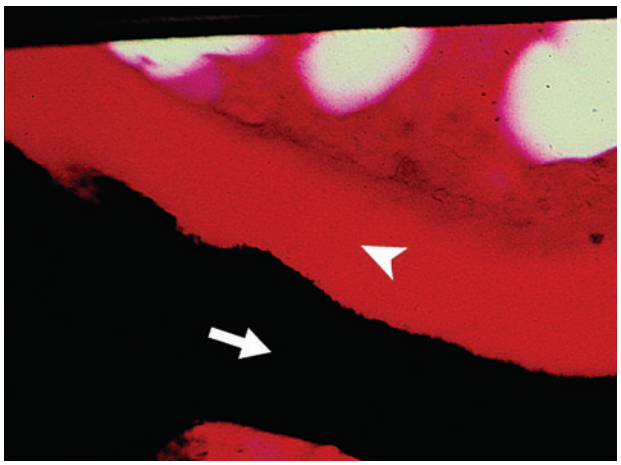


Fig. 4A. Osteitis fibrosa: characteristic manifestations of severe hyperparathyroidism with increased osteoclast and osteoblast activity and peritrabecular fibrosis. Fig. 4B. Osteomalacia: marked excess of unmineralized osteoid stained red (arrowhead) surrounding the mineralized bone stained black (arrow). Fig. 4C. Aluminum bone disease: specific red staining shows the deposition of aluminum at the mineralization front (arrow).
(Reprinted with permission from: Gonzalez E. A., Martin, K. J. Bone and Mineral Metabolism in Chronic Renal Failure. In: Johnson R. J., Feehaly J, eds. Comprehensive Clinical Nephrology. 2nd Edition. Mosby/Elsevier Ltd., 2003, 881)

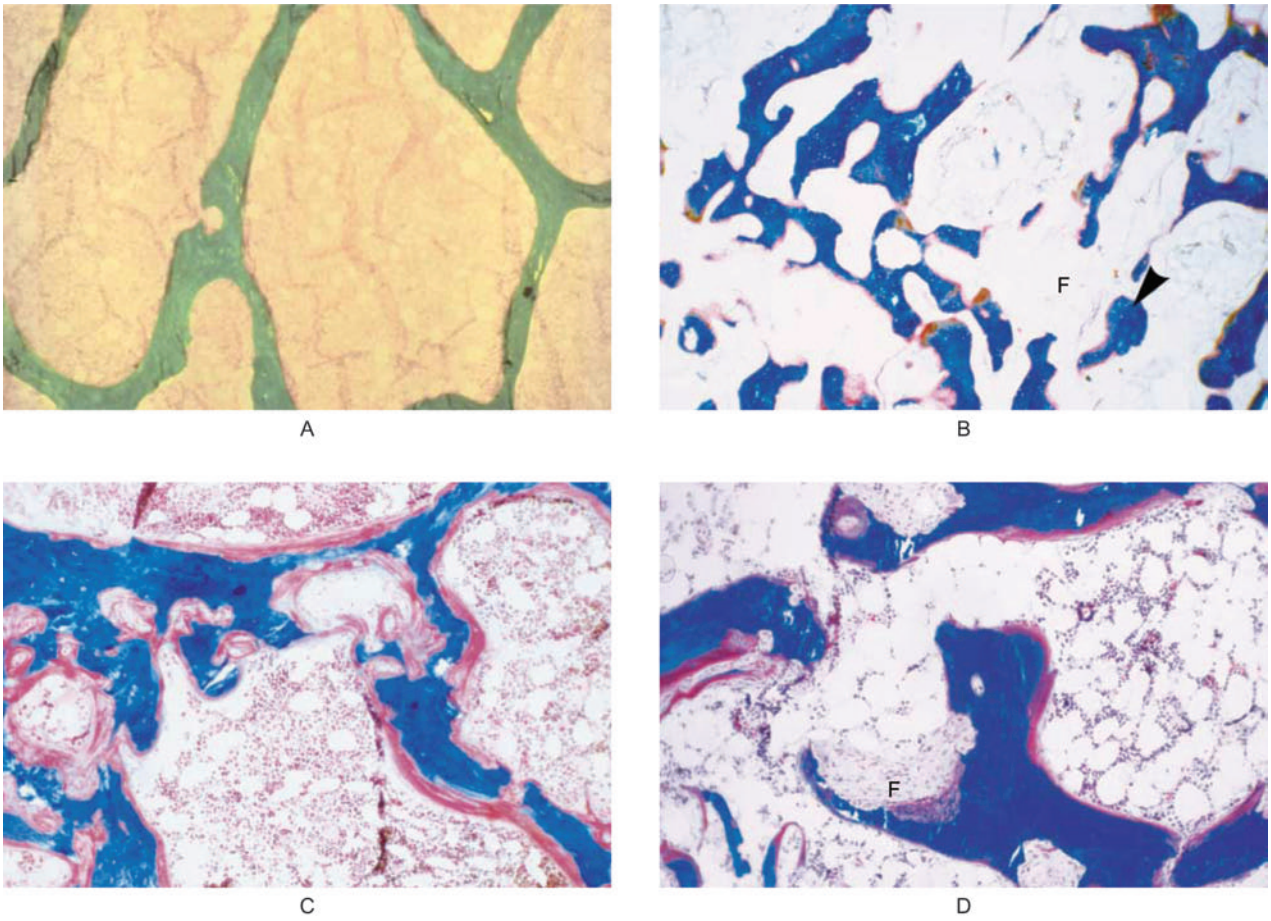


Fig. 5. Specimens of Normal Trabecular Bone and Trabecular Bone Showing the Histologic Types of Renal Osteodystrophy. Nondecalcified iliac-biopsy specimens from patients with endstage renal disease were fixed in Millonig's fluid and stained with a modified Masson stain (X40). Panel A shows normal trabecular bone. The trabeculae consist of lamellar bone and are connected in a meshwork. The marrow spaces are occupied by normal hematopoietic and mesenchymal cells. At a higher magnification (not shown), lining cells, osteoblasts, and osteoclasts can be seen in normal numbers. Tetracycline labeling confirmed normal dynamic indexes of bone formation (not shown). Panel B shows osteitis fibrosa with prominent peritrabecular fibrosis (F), which is the hallmark of this disease. Increased rates of bone remodeling are demonstrated by numerous resorption lacunae, resulting in scalloped trabeculae, loss of trabecular connections, and the appearance of bone islands (arrowhead). At a higher magnification, more osteoclasts and osteoblasts would be seen. Increased bone formation is suggested by the amount of osteoid (red areas) and indexes of formation derived from tetracycline labeling (not shown). Panel C shows osteomalacia with increased unmineralized bone matrix (osteoid, red). Decreased rates of remodeling are suggested by the decreased activity and number of osteoclasts. Tetracycline labeling (not shown) demonstrated poorly organized and diminished mineralization fronts. The osteoid accumulates and is poorly resorbed. Panel D shows mixed disease, characterized by areas of fibrosis (F) and increased remodeling activity adjacent to areas of increased osteoid deposition, with poor mineralization and remodeling. Panel E shows adynamic bone disease, characterized by an absence of remodeling activity. The number of bone cells (osteoblasts and osteoclasts) is decreased, and there is minimal evidence of osteoid production. (Reprinted with permission from: Hruska KA, Teitelbaum SL. Renal Osteodystrophy. N Engl J Med 1995; 333:167)

4. Bone formation by osteoblasts as unmineralized matrix (osteoid), followed by mineralization.

Normally, bone resorption is minimal (<10%), and osteoclasts are present on a small percentage of the bone surface (<2%). Osteoid is lamellar and is present on a modest amount of the bone surface (<25%)and some of the osteoid is covered with mature osteoblasts (20–40%) *(3)*.

High Bone Turnover Diseases

Osteitis Fibrosa

The primary abnormality in this disease is the chronic elevation of PTH, which leads to a marked increased in bone turnover: increased osteoclasts and bone resorptive surfaces, increased number and activity of osteoblasts with wide osteoid surfaces, as well as peritrabecular fibrosis. This is the form most commonly seen in patients with CKD.

Mixed Osteodystrophy

This is similar to osteitis fibrosa with the exception of greater degree of unmineralized osteoid.

Low Bone Turnover Diseases

Osteomalacia

This form is secondary to defective mineralization. Both osteoblasts and osteoclasts are reduced in number, and there is increased volume of unmineralized bone (osteoid). It has commonly been associated with aluminum intoxication secondary to use of aluminum-containing phosphate binders. Aluminum accumulates in the bone, thereby causing defective mineralization with increased synthesis of bony matrix (osteoid). Patients usually present with bone pain, fractures, and musculoskeletal symptomatology.

Adynamic or Aplastic Bone Disease

This is the form most commonly seen in patients on continuous ambulatory peritoneal dialysis (CAPD). Similar to osteomalacia, there is decreased bone turnover, but there is no increase in formation of unmineralized bone (osteoid). Excessive suppression of the parathyroid glands (by calcitriol and calcium-based phosphate binders) is the cause in the majority of cases.

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