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EDITORIAL REVIEW

Renal bone disease 1990: An unmet challenge for the nephrologist

The replacement of excretory kidney function by dialysis or by renal transplantation has not only improved the survival of the patients with end-stage renal failure, but has revealed a variety of other complications which represent a formidable challenge for the nephrologist.

Abnormalities in mineral metabolism and bone are responsible for a considerable part of the morbidity and mortality encountered in these patients. These problems are related either to the failing excretory and/or endocrine functions of the kidney or to side-effects of therapeutic measures calling for reconsideration of formerly widely accepted therapeutic practices.

A rational approach to the treatment of renal bone disease requires a basic understanding of: (1) the anatomic physiology of bone; (2) the pathophysiologic effects of renal failure on mineral metabolism and bone; and, (3) careful assessment of the various available therapeutic modalities.

Anatomic physiology of bone

Functions of bone

The skeleton has a dual mechanical and metabolic function in the body. The hardness and rigidity of bone provide internal support for soft tissue and protection to vital organs and blood-forming tissues. Muscle and tendon insertion on bone transmits the force of muscular contraction.

In addition to these mechanical functions, the microscopic structure of bone, its high mineral content and close contact to extracellular fluid (ECF) allow bone to play an important metabolic role in the homeostatic regulation of calcium concentrations in body fluids and tissues. In a normal individual, approximately 110 nmoles of calcium enter and leave bone daily [1].

There is a dynamic interaction between these two functions. A prolonged demand for calcium will tax the mechanical strength of the skeleton by depleting its mineral content and affecting its hardness. Demineralized bone is at risk for mechanical failure and fracture.

Macroscopic structure of bone

On the macroscopic level, compact or cortical bone is distinguished from trabecular or cancellous bone. Both compact and spongy types are found in nearly every bone. Compact bone accounts for 75% of total bone volume [2]. The strength and rigidity of the long bones of the appendicular skeleton are due to compact bone.

Cancellous bone is found primarily in the axial skeleton, and consists of branched, anastomosed bony trabeculae that create interconnected spaces continuous with the marrow cavity of long bones. The surface area of the trabeculae accounts for approximately 60% of the total surface area of the skeleton. It is the labyrinthine structure of spongy bone that facilitates its central role in mineral metabolism by providing a large surface area for ion exchange.

Biochemistry of bone

Bone consists of an organic intercellular matrix in which a mineral, nonorganic material is deposited. Type I collagen represents 90% of the bone matrix and is associated with an array of non-collagenous proteins, to include: fibronectin, osteonectin, bone Gla-protein (BGP), bone proteoglycan and sialoprotein [3]. Although the physiological role of the non-collagenous proteins is unclear, BGP [4, 5] and osteonectin [6] have been used as markers due to their specificity and the fact that they can be quantified in bone and sera samples.

The mineral phase is formed of crystals of calcium phosphate and carbonate-containing apatite of different size and perfection [7]. The exact mechanisms by which mineralization occurs on and within the collagen matrix is not fully elucidated. However, it is well established that the apatite crystals and more primitive calcium phosphate salts (brushite) provide a huge surface for exchange of bone-seeking elements. In addition to calcium, phosphate and hydroxyl, numerous other compounds can be adsorbed or incorporated into the apatite crystals. Some are normal constituents of the body such as sodium, magnesium, potassium, zinc, fluoride and silicon, while others are toxic or inhibitors of mineralization, to include: aluminum, pyrophosphates, diphosphates, phosphocitrate, and lithium [8, 9].

Tetracycline has been used as a means to assess mineralization status and mineral or bone apposition rate. Tetracyclines are autofluorescent antibiotics and their uptake in bone is seen as bright yellow lines under fluorescent light microscopy (Figs. 1A, 2A, 3, 4). The mineralization rate during a given period of time can be determined by administration of tetracycline at specific intervals and measurement of the width between the resultant areas of labelled bone [10].

Microscopic structure of bone

The amount of organic matrix determines bone volume as assessed by histomorphometry. Normally 80 to 90% of the matrix is mineralized and 10 to 20% is formed of collagen strands soon to be mineralized (osteoid).

Generally, the amount of mineralized matrix determines the mechanical strength of the skeleton. However, in pathological

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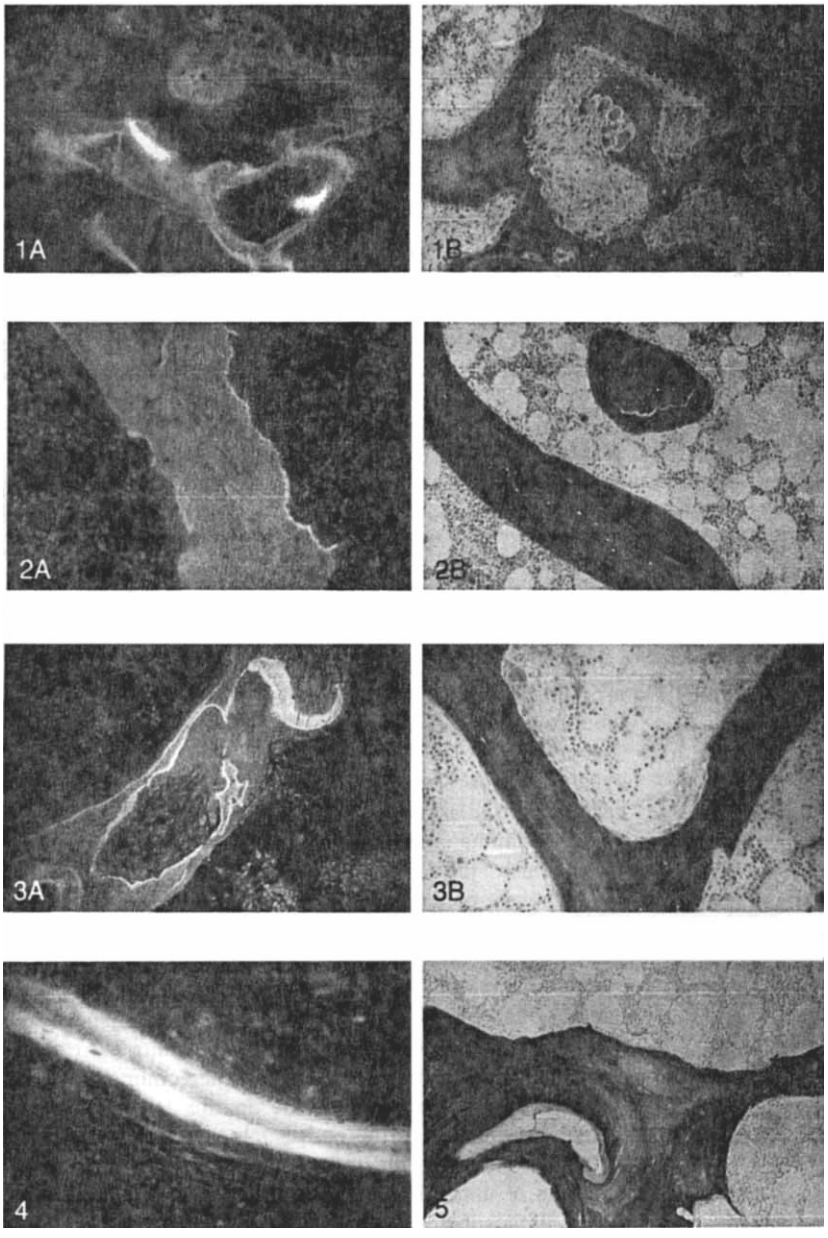

Fig. 1. *Predominant hyperparathyroid bone disease.* **A.** Increased fraction of trabecular surface exhibiting tetracycline uptake. Presence of diffuse intense broad single labels in woven bone and irregular double labels. Undecalcified, unstained 7 μm thick section viewed under fluorescent light microscopy. Original magnification: 12×. **B.** Irregular trabecular surface with increase in osteoid. Abundance of osteoblasts and osteoclasts. Marrow fibrosis. Undecalcified, 3 μm thick section. Modified Masson-Goldner trichrome stain. Original magnification: 8×.

Fig. 2. *Low turnover osteomalacia.* **A.** Thin single labels at the bone-osteoid interface. Absence of double labels. Undecalcified, unstained 7 μm thick section viewed under fluorescent light microscopy. Original magnification: 20×. **B.** Dramatic increase in extent of osteoid covering the trabecular surface, and thick osteoid seams. Absence of osteoblasts and osteoclasts. Undecalcified, 3 μm thick section. Modified Masson-Goldner trichrome stain. Original magnification: 8×.

Fig. 3. *Mixed uremic osteodystophy.* **A.** Coexistence of double and thin single tetracycline labels. Undecalcified, unstained 7 μm thick section viewed under fluorescent light microscopy. Original magnification: 12×. **B.** Increase in osteoid surface and extent of resorption lacunae. Mild peritrabecular fibrosis. Undecalcified, 3 μm thick section. Modified Masson-Goldner trichrome stain. Original magnification: 8×.

Fig. 4. *Double tetracycline labelling.* Two regular distinct labels. The outer golden-yellow label represents incorporation of demeclocycline, the inner green-yellow label tetracycline hydrochloride incorporation. The nonfluorescent zone between the labels represents the amount of bone mineralized during the labelling free interval. Undecalcified, unstained 7 μm thick section viewed under fluorescent light microscopy. Original magnification: 32×.

Fig. 5. *Aluminum deposits in bone.* Linear intense blue aluminum staining at the bone-marrow interface, bone-osteoid interface, at cement lines and within bone. Diffuse light blue aluminum staining within bone. Undecalcified, 7 μm thick section. Modified Solochrome Azurine. Original magnification: 8 ×.

states and especially in renal osteodystrophy, the quality of the bone texture has to be taken into consideration [11]. Lamellar arrangement of mineralized collagen bundles ensures optimal hardness and elasticity of bone. In states of local or systemic high turnover of bone; the collagen fibers are deposited in a loose and randomized manner. The fibrils lack the typical birefringence under polarized light microscopy and display a crisscross, "woven" pattern. In addition to its deficiency in the optimal arrangement of the collagen fibers, mineralization of woven bone is deficient and haphazard, and as a result woven bone is brittle. This explains why some renal patients present with deformities and fractures even though their bone volume or bone density is normal or high. Careful assessment of the effects of therapeutic modalities is essential, as medication may leave unchanged the total osteoid volume and bone mass but may favor one or the other structural pattern, that is, woven or lamellar bone, which can be of biomechanical relevance.

Modelling and remodelling of bone

Bone *modelling* describes the process of bone growth. There are two types of bone growth, longitudinal and appositional. Longitudinal growth occurs by enchondral ossification; appositional growth takes place by periosteal apposition of new bone and endosteal resorption of old bone. The resorbing and formation processes are not coupled and occur at different sites.

The adult skeleton is not a static tissue but undergoes continual *remodelling*, that is, removal of bone and apposition of new mineralized matrix. This dynamic process allows for

removal of older bone whose mechanical competence may be weakened by fatigue damage [12], and formation of new bone with a lower mineral density which can serve as a readily available source of calcium for the organism [13]. Normally, approximately 80% of the bone surfaces is quiescent. The remainder of the surface is the site of active remodelling [11, 14]. The remodelling cycle, which normally lasts from four to eight months [11, 14], encompasses several phases: (a) an activation phase where osteoclasts are recruited and the bone surface prepared; (b) a resorption phase where the osteoclasts contact and erode the bone surface; (c) a reversal phase when resorption ends and osteoblasts start to appear at the site; and, (d) formation and mineralization of bone.

Resorption always precedes and is usually coupled with bone formation. The number of active remodelling sites (bone turnover), the effectiveness and the duration of each phase can vary greatly in pathological conditions and the derangements represent the basis of metabolic bone diseases.

It must be emphasized that the amount of bone resorbed or formed depends not only upon the number of bone cells involved in the process but also their individual activity, the way they interact, and their life span.

Bone cells

There are two primary endogenous bone cell types which have a contrasting and coordinated function. The osteoclasts are responsible for bone degradation, and the osteoblasts are involved in bone formation and mineralization. Two other bone cells are encountered in bone, the lining cells and the osteocytes. Recently, strong evidence has been gathered pointing to the involvement of other cell lines from the bone marrow and the immune system in the regulation of the remodelling process.

Osteoclasts. The osteoclasts are large, usually multinucleated cells. After years of searching for the ontogeny of this cell type, a large body of evidence has been gathered pointing to a monocyte-macrophage lineage [15–17]. Preosteoclasts are thought to be derived from immature mononuclear cells within the hematopoietic system and fuse to form mature osteoclasts.

The morphological specific characteristic of an active osteoclast is the ruffled border surrounded by an organelle-free clear zone containing actin [18]. The ruffled border is in contact with the bone surface and is the site of bone resorption.

Recent work has shown that in addition to the classical theory of acid bone solubilization by activation of lysosomal enzymes and excretion of hydrogen ion [19], additional factors are involved in the cellular mechanisms of bone resorption. The role of carbonic anhydrase, cathepsins and calcium-sodium ion exchange mechanisms have been determined. Moreover, a complete or partial blockage of resorption has been found in vitro and in vivo studies when inhibitors of these substances and mechanisms were administered [20–23]. However, these new potential therapeutic approaches need to be confirmed and tested further.

Osteoblasts. Osteoblasts are mononuclear, cuboidal cells (15 to 20 μm) found on the advancing surface of growing bone. Osteoblasts are rarely seen isolated. They form a monocellular layer arranged in a palisade-like manner and resemble an epithelium. However, they do not display the characteristics of a true epithelium since adjacent cells make contact by gap junctions [24] and a basement membrane is absent. Therefore, there is no continuous barrier between osteoblast and bone marrow [25]. They originate in the bone marrow from stromal fibroblast-like cell precursors and possess a "characteristic repertoire of macromolecular synthetic mechanisms and hormonal receptors" [26].

Osteoblasts produce mineralized bone matrix. They secrete Type I collagen fibers and non-collagenous proteins and are rich in alkaline phosphatase. The mechanisms of action or interaction of this cell type with crystal nucleation and perfection are still not fully elucidated. Osteoblasts may be involved in the removal of inhibitors of nucleation, such as pyrophosphates [27]. However, their ability to transport ionized calcium to the mineralization front has not been proven [28].

Lining cells. The bone surfaces not involved in the remodelling process are covered by a thin, unmineralized layer of collagen fibers, the lamina limitans, and by an envelope of flat, elongated cells, the lining cells. The thin layer of lining cells represent the barrier between bone and marrow. These cells are thought to be of osteoblastic origin representing a terminal or "resting osteoblast" [2]. These cells do not present histological signs of activity and were thought to have little or no role in bone metabolism. Recent evidence suggests that when activated, these cells are involved in the process of preparing the bone surface prior to resorption and may have a role in the coordination between the other bone cells and are implicated in the control of calcium fluxes across the blood-bone barrier (v.i.).

Osteocytes. Approximately 10% of osteoblasts bury themselves into the bone matrix and become osteocytes. The osteocytes are connected to each other and to superficial lining cells through extended cellular processes that traverse bone within thin canaliculi. The osteocytic/lining cell network offers a large surface area for ion exchange and seems to be involved in the rapid mobilization of calcium [29].

Interaction between bone cells. Despite their different origin and function, osteoclasts and osteoblasts are not independent from each other. As previously postulated by Rodan and Martin [30], phenomena or agents stimulating bone resorption do not act directly on osteoclasts but via other cells including osteoblasts and lining cells. The action of "resorbing substances" in cell cultures has been proven inefficient in culture containing only osteoclasts [31]. Signs of activity are obtained only when osteoblasts or other cells are included [32].

Receptors for parathyroid hormone (PTH) and $1,25(OH)_2D_3$ have been isolated in osteoblasts, whereas, it has not been possible until now to demonstrate them in osteoclasts. The wide variety of so-called resorptive agents induce morphological and metabolic changes in osteoblasts in vitro. In vivo, serum levels of PTH display a stronger relationship to the number of osteoblasts than osteoclasts [33]. The practical implication of these new discoveries is that any agent or drug, thought to have a specific action on one type of cell, will probably act on both cell lineages.

Other cells. Other cells are known to participate in the regulation of the remodelling process. Among them, mast cells via heparin production increase collagenase activity and promote bone resorption. It has been shown that protamine administration decreases the resorptive process [34]. The monocyte-macrophage cell line is thought to act as "coordinator" of local or systemic signals through its production of prostaglandin,

interleukin I, $1,25(OH)_2D_3$, growth factors, and lymphoid cells, especially T-lymphocytes via secretion of lymphokines [35, 36]. In practical terms, any derangements of these cell lines or any therapy aimed at controlling them could have an effect on bone metabolism.

Role of bone in mineral homeostasis

Bone is quantitatively the primary calcium reservoir of the body and plays an important role in calcium homeostasis. Even though plasma calcium is maintained within narrow limits, circadian variations exist in humans [37, 38] and animals [39, 40]. Circadian periodicities have also been established for bone cell activity and secretion of PTH, $1,25(OH)_2D_3$, calcitonin and BGP [41]. Based on these findings and experimental data, a new physiological view of in vivo calcium dynamics has been postulated [42, 43]. In this non-linear model of calcium homeostasis or homeokinesis, the target organs, that is, gut, kidney and bone, are dynamically adapted to periodic relationships with the external environment and can even anticipate them. Spontaneous synchronized flux and efflux of calcium (oscillations) exist in the different target organs. For example, net addition of calcium to the ECF through the gut is counterbalanced by simultaneous uptake of calcium by bone, and vice versa. The period, amplitude and phase of these spontaneous oscillations can be adjusted independently and represent an extremely flexible system in response to any alteration in plasma calcium [44]. Therefore, correction of abnormalities in plasma calcium is not solely regulated by feedback loops and cannot be accomplished only by bone formation or resorption [43]. The quiescent surfaces of bone and bone lining cells sensitive to calciotropic hormones are actively involved in the constant transfer of calcium into and from bone. Total calcium flux is approximately 110 nmoles per day of which quiescent surfaces exchange 100 nmoles, ten times the flux exchanged by the remodelling surfaces [44]. The simple calcium phosphate compounds (brushite) represent the primary calcium storage in the superficial layers of bone.

Factors affecting bone

Parathyroid hormone acts (a) as an activator of bone remodelling by increasing the number of osteoblasts and osteoclasts, and (b) as a modulator of the minute-to-minute regulation of calcium fluxes across the blood-bone barrier [11, 28]. Actions of vitamin D metabolites, in particular $1,25(OH)_2D_3$ are multiple and complex [45, 46]. $1,25(OH)_2D_3$ stimulates the differentiation of many cells [47], enhances directly or indirectly the activity of bone cells [48, 49] and facilitates mineralization [28]. The primary known effect of calcitonin on bone is inhibition of osteoclast-mediated resorption [50]. In addition, in vivo and in vitro findings support the notion that calcitonin stimulates osteoblasts and may affect bone formation [51–53]. Moreover, cellular binding sites for calcitonin were described in osteoblasts [54]. Glucocorticoids, sex hormones, thyroid hormones and, possibly, insulin and Vitamin A may also modulate bone turnover [28].

A large variety of local substances participates in the regulation of recruitment and activity of bone cells to achieve continual remodelling of bone [28]. These local factors mediate and/or act in conjunction with systemic factors. These substances can originate from extraskeletal sources, the monocyte-macrophage cell types or bone cells. They belong primarily to the categories of growth factors and the prostaglandins. The osteoblast's ability to secrete $1,25(OH)_2D_3$ directly influences bone remodelling [55]. Local electrical potentials, adenosine, fluoride and pyrophosphate also have a local regulatory effect on bone cell activity.

Pathophysiologic effects of renal failure

A variety of kidney diseases including tubular defects, renal stone disease, nephrotic syndrome, kidney transplantation and oxalosis can induce bone changes. However, the most prominent bone disease occurs in patients with partial or complete loss of glomerular filtration rate (GFR). This review will focus on this aspect.

Effects of renal failure on mineral metabolism

With the progressive loss of excretory kidney function, secondary hyperparathyroidism typically develops early on [56]. Even though a variety of independent and interrelated factors have been identified as influencing the hyperparathyroid state in advanced renal failure, there remains considerable controversy over the sequence of early events leading to the increased serum levels of PTH.

Two related factors seem to play a pivotal role in triggering the excess secretion of PTH: alterations in the excretion of phosphorus by nephrons and deranged vitamin D metabolism.

Despite the progressive loss of nephrons, serum phosphorus levels do not rise before the GFR is reduced to levels of less than 20 to 25% of normal because those nephrons remaining augment their excretion of phosphorus. The increased phosphorus excretion of the remaining nephrons results in reduced activity of renal C_1-α-hydroxylase [57] and, consequently, in deficiency of the active vitamin D metabolite $1,25(OH)_2D_3$.

The relative or absolute deficiency in $1,25(OH)_2D_3$ levels leads to increased synthesis and secretion of PTH [58–61] which, in turn, will stimulate renal production of $1,25(OH)_2D_3$ [62, 63] and, possibly, restore the serum levels of $1,25(OH)_2D$ to normal values. This could, in part, explain why serum levels of $1,25(OH)_2D_3$ in early renal failure have been reported to be either within the normal range [64, 65] or depressed [66, 67].

We advanced the hypothesis that the increase in PTH secretion could act as a compensatory mechanism of nature used to overcome $1,25(OH)_2D_3$ deficiency [11]. What role the extrarenal production of $1,25(OH)_2D_3$ plays in compensating for the failing kidney's inability to produce the active vitamin D metabolite needs further study.

With progression of renal insufficiency, the compensatory effect of PTH on $1,25(OH)_2D_3$ deficiency is defeated, and a relative and, thereafter, absolute deficiency in $1,25(OH)_2D_3$ exists as suggested by the direct relationship between the decrease in GFR and circulating levels of $1,25(OH)_2D$ levels in patients with mild to moderate renal failure [68]. Deficiency of $1,25(OH)_2D_3$ will further stimulate PTH secretion, decrease intestinal calcium absorption [69, 70] and may induce skeletal resistance to the calcemic action of PTH [71, 72].

When the kidney can no longer increase the excretion of phosphorus through the remaining nephrons to compensate for advanced nephron loss, hyperphosphatemia will ensue usually associated with hypocalcemia. This decrease in serum calcium will further stimulate the secretion of PTH. The participation of

hypocalcemia in maintaining high levels of PTH in the advanced stage of renal failure is well established. However, its role in the initial derangement of parathyroid activity is controversial.

It was generally accepted that transient or sustained hypocalcemia, due to phosphate retention and/or decreased activity of $1,25(OH)_2D_3$, was the primary factor in the development of secondary hyperparathyroidism [73, 74]. Even though hypocalcemia represents the appropriate signal for increased activity of the parathyroid glands, some clinical and experimental observations have challenged this concept.

For example, one prospective study found increased circulating levels of PTH and hyperparathyroid bone disease with relatively normal serum calcium levels [75]. Recent experimental studies in partially nephrectomized dogs fed a normal diet, showed that the animals developed sustained, elevated total serum calcium associated with increased PTH levels and overt hyperparathyroid bone disease [76]. In another study, nephrectomized dogs given a diet high in calcium displayed an increase in serum calcium which did not retard the development of secondary hyperparathyroidism, the latter being only prevented by administration of $1,25(OH)_2D_3$ [77]. This can be explained, at least in part, by the elevated set-point for calcium-regulated PTH secretion in renal failure [78, 79]. The suppressive action of $1,25(OH)_2D_3$ on PTH secretion seems to be a direct effect of the vitamin D metabolite since $1,25(OH)_2D_3$ receptors have been isolated in parathyroid glands [80]. In addition, $1,25(OH)_2D_3$ decreases preproparathyroid hormone messenger RNA [61] and decreases basal, maximally-stimulated and maximally-inhibited PTH secretion without altering the set-point for calcium [79].

The increase in bioactive PTH secretion [81] is accompanied by reduced renal clearance and impaired degradation of PTH [82, 83]. However, the retained fragments are thought to be metabolically inactive.

The contribution of metabolic acidosis to the pathogenesis of renal bone disease has not been fully elucidated and awaits further study. The role of calcitonin in the early phase of renal failure is uncertain. In the advanced stage, neither endogenous nor exogenous calcitonin protects against hyperparathyroid bone disease [84]. Absence of catabolism of β_2-microglobulin by the kidney is responsible for deposition of amyloid and may be responsible for severe bone pain, bone cysts and femoral/vertebral fractures, in addition to carpal tunnel syndrome and arthropathy [85, 86].

Instituting various forms of dialysis therapy might alter the spontaneous course of renal osteodystrophy since dialysis techniques may influence circulating levels of calcium and phosphorus. Long-term hemodialysis treatment was reported to be associated with the development of severe secondary hyperparathyroid bone disease [87]. This complication is infrequently observed, however, probably because the negative calcium balance is usually avoided in chronically dialyzed patients.

The extracorporeal circuit and, in particular, cuprophan dialyzer membranes induce activation of the complement [88], coagulation [89] and contact [90] pathways. Although reuse and introduction of non-complement activating membranes have lessened the undesirable reactions, the cumulative effect of dialysis on neutrophils, monocytes, lymphocytes and platelets is not negligible [91]. Release of lyzosomal enzymes by neutrophils, production of interleukin-I by monocytes, and diminished production of interleukin-II by T-lymphocytes could impair the recruitment and activity of bone cells. In addition, cuprophan membranes have been implicated in the increased synthesis of β_2-microglobulins through activation of interleukin-I [91] and may worsen amyloidosis.

Chronic ambulatory peritoneal dialysis bears the risk of progressive protein loss into the peritoneal fluid, in particular DBP-bound $25(OH)D_3$ [92, 93]. Some studies have found indirect evidence of diminished serum binding capacity [94], $1,25(OH)_2D_3$ and $24,25(OH)_2D_3$ [95].

High concentrations of aluminum in the dialysate have been responsible for severe encephalopathy and/or low turnover osteomalacia [96]. The systematic use of reverse osmosis should render this source of aluminum intoxication accidental, that is, related to isolated glitches of RO systems.

Aside from aluminum-contaminated dialysate, additional sources of aluminum have been shown to originate from phosphate binders containing aluminum, milk formulae [97, 98] and medications [99]. Even though a short-term experiment using young, nonuremic dogs [100] suggested that aluminum deposition is an epiphenomenon, numerous other studies point to a direct or indirect effect of aluminum on bone [101] (see **Aluminum-related bone disease**).

Effects of renal failure on bone

Bone is influenced by the cumulative, long-term effects of metabolic derangement. The long-standing alterations in mineral metabolism generated by renal failure have a profound effect on the skeleton and induce severe systemic metabolic bone disease, namely, renal bone disease or renal osteodystrophy. The modes of response of bone to pathologic conditions is limited and virtually every metabolic histological abnormality of bone can be observed in patients with renal failure [11, 26].

Renal bone disease develops in the early stages of loss of excretory kidney function [102–105]. When the GFR falls to 50% of normal, more than 50% of the patients exhibit abnormal bone histology [106]. Bone biopsies show signs of excessive PTH activity on bone with or without mineralization defect. There is an increase in bone turnover characterized by increased forming and resorbing sites. The volume and surface of osteoid are augmented and the number of osteoblasts and osteoclasts is elevated. Woven osteoid appears when the GFR falls below 40 ml/min. Endosteal fibrosis can be seen when GFR is below 30 ml/min. The mineralization status as measured by the uptake of tetracycline is usually within the normal range until the GFR reaches 40 ml/min. At GFR lower than 40 ml/min, some patients exhibit impaired mineralization with a decrease in the fraction of osteoid surface labelled with tetracycline [105].

When end-stage renal failure ensues necessitating chronic maintenance dialytic therapy, nearly all patients have abnormal bone histology, and approximately 5% have some stainable aluminum at the mineralization front—a fraction that increases up to 50% when long-term dialysis patients are studied [106].

Advanced renal bone disease can be subdivided into three major histological groups: predominant hyperparathyroid bone disease, low turnover uremic osteodystrophy (osteomalacic and adynamic renal bone disease) and mixed uremic osteodystrophy consisting of mild to moderate hyperparathyroid bone disease and defective mineralization [11]. Aluminum-related bone changes can be seen to varying degrees in all three groups.

Even though these groups do not represent fully separate entities, and transformation from one form to another can occur, it is useful to distinguish them since therapy can be tailored according to the predominant histologic findings. Prevalence of the different forms of renal bone disease may vary depending on environmental factors, aluminum exposure, therapy with vitamin D metabolites, dietary intake, and dialysis-related factors.

Predominant hyperparathyroid bone disease (Fig. 1). This type of bone disease is encountered when the primary metabolic abnormality is characterized by long-standing, excessive PTH secretion. This disease is seen in approximately 5 to 30% of dialyzed patients and rarely presents before initiation of dialysis.

The disease is characterized by a marked increase in bone turnover. The trabecules are irregular in shape and display numerous abnormal remodelling sites. The bone cells are abnormally high in number, irregular in shape and arrangement. The enlarged osteoclasts are numerous, containing multiple nuclei with prominent nucleoli. The resorption cavities are deep and irregular, frequently dissecting or tunnelling the trabecules.

The osteoblasts have lost their regular cuboidal shape and have become polygonal or spindled-shaped. The nuclei have lost their polarity and occupy random positions within the cytoplasm and contain several nucleoli. The palisade-like monolayer of osteoblasts may be replaced by an atypical multilayered arrangement of cells with variable orientation toward the bone surface (from parallel to perpendicular). These morphological abnormalities of osteoblasts are accompanied by profound perturbations of their function.

There is an overproduction of collagen resulting in an increase in osteoid surface and volume and, sometimes, thickened osteoid seam. The osteoid formed is primarily of the woven, irregular type. The collagen fibers are accumulated toward the bone surface and are deposited between osteoblasts and toward the bone marrow leading to peritrabecular and bone marrow fibrosis. In advanced cases, the bone marrow can be entirely replaced by fibrosis. This reflects both the irregular activity of disorganized groups of osteoblasts and the diminished activity of individual cells [11]. It is conceivable that the cellular hyperplasia might represent a compensatory phenomenon to cellular insufficiency [11]. The number of osteoblasts entrapped in bone is increased resulting in numerous and irregular osteocytic lacunae within woven osteoid and mineralized bone.

The extent and number of mineralizing sites and the mineral apposition rate are notably increased as documented by tetracycline labelling. However, the deposition of calcium in woven osteoid proceeds irregularly, incompletely and diffusely. The findings of thick osteoid seams and irregular, diffuse tetracycline uptake in woven bone are sometimes erroneously diagnosed as osteomalacia.

Usually, the marked increase in bone turnover leads to cancellization of cortical bone causing a net decrease in cortical bone volume, most notably evident in the appendicular skeleton. In cancellous bone, the bone volume depends upon calcium balance. Typically, hyperparathyroid bone disease presents high bone volume; however, bone volume can be markedly reduced in cases of malnutrition, immobilization or other causes [107]. In addition, areas of high bone mass may be adjacent to pseudocysts consisting primarily of fibrotic or hyperplastic bone marrow. In any case, bone strength cannot be equated with high bone mass since the irregular trabeculae may lose their proper three-dimensional architecture and their connectivity. Moreover, they are poorly mineralized and consist mainly of mechanically-deficient woven bone. These characteristics create a particularly fragile bone prone to fractures. Consequently, the use of the term "osteosclerosis" is inappropriate.

In early publications, pathologists impressed by the dramatic hypercellularity of all bone cells associated with fibrosis and pseudocysts named this type "osteitis fibrosa cystica" implying an inflammatory process. This designation is misleading and does not have any pathogenetic relevance. We prefer the term predominant hyperparathyroid bone disease.

Low-turnover uremic osteodystrophy—Osteomalacic and adynamic renal bone disease. The other end of the spectrum of renal osteodystrophy is represented by low-turnover uremic bone disease. The histologic hallmark of this group is a profound decrease in the number of active remodelling sites. Although aluminum overload represents the most frequently observed pathogenetic factor, parathyroidectomy, underlying disease and medications can account for a significant proportion of the cases. Approximately 5 to 25% of patients undergoing chronic maintenance dialysis present with this histological type. It is rarely seen prior to initiation of dialysis [108].

This type is characterized by a dramatic reduction in the number of bone-forming and bone-resorbing cells associated with a significant decrease in bone formation and mineralization. The majority of the trabecular bone is covered by lining cells, and there are few osteoclasts and osteoblasts.

The bone structure is predominantly lamellar and peritrabecular fibrosis is rarely seen. The extent of mineralizing surfaces is markedly reduced and, usually, only few thin single labels of tetracycline are observed. These features reflect the marked decrease in osteoblastic activity.

Depending upon the sequence of events leading to a decline in the number and/or the activity of osteoblasts, two histologic subgroups can be identified. When the reduction in mineralization is coupled with a concomitant and parallel decrease in bone formation, the end result is "adynamic uremic bone disease" where there are few osteoid seams. When the diminution in mineralization precedes or is more pronounced than the inhibition of collagen deposition, an accumulation of unmineralized matrix is seen as a hallmark of "low turnover osteomalacia" (Fig. 2A, B).

The increased lamellar osteoid volume is due to the presence of wide osteoid seams covering a large portion of the trabecular surface. Thus, unmineralized bone represents a sizable fraction of trabecular bone volume. The smooth contour of the osteoid-marrow interface is in striking contrast to the irregular interface between osteoid and mineralized bone which reflects past resorbing activity. Occasionally, woven bone can be seen buried within the trabecules indicating past high bone turnover.

In adynamic uremic bone disease, the bone volume is frequently reduced. In low turnover osteomalacia, total bone volume may vary, whereas, the mineralized bone volume is always low. Osteomalacic bone is prone to deformity and both types are subject to fractures.

Mixed uremic osteodystrophy (Fig. 3A, B). Mixed uremic osteodystrophy lacks a dominant pathogenic cause. Instead, this type of renal bone disease is caused primarily by hyperparathyroidism and defective mineralization with or without decreased bone formation. These features may coexist in varying degrees in different patients. This form is seen in the majority of patients (45 to 80%) on dialysis and in most patients with end-stage renal failure.

The number of osteoclasts is usually increased. The remodelling sites are increased in number and they are heterogeneous. Active foci with numerous cells, woven osteoid seams and peritrabecular fibrosis coexist with adjacent lamellar sites with a more reduced activity. The accumulation of osteoid with normal or increased thickness of osteoid seams is, therefore, due to an increase in production of lamellar or woven osteoid. The active mineralizing surfaces are increased in woven bone with an increase in mineralization rate and diffuse labelling, whereas, in lamellar bone, the mineralization surfaces may be reduced with a decreased mineral apposition rate.

The bone volume is extremely variable in this group and depends upon the dominant pathogenic cause.

Aluminum-related bone disease. In bone, aluminum is deposited linearly at the bone-osteoid interface and within the boney trabecules in a diffuse or linear manner [109–111]. Nephrologists continue to erroneously equate aluminum-related bone disease with low-turnover osteomalacic or adynamic bone disease. In fact, aluminum related bone disease can be superimposed on any of the three previously described histologic groups. This has important implications for the management of patients suffering from renal osteodystrophy.

Approximately 50% of unselected patients with chronic renal failure exhibit aluminum deposition in bone [106]. Although approximately 90% of the patients with low turnover bone disease present aluminum deposits, this particular type of osteodystrophy should be seen as the end result of the effects of aluminum on bone. In addition to this extreme condition, aluminum deposition can be seen in approximately 50% of patients with mixed uremic osteodystrophy and in 10 to 15% of those patients with predominant hyperparathyroid bone disease. Aluminum deposition should not be regarded as an epiphenomenon in hyperparathyroid bone disease, but must be seen as bearing directly upon renal bone disease in light of the long-term direct and indirect effects of aluminum on bone, its distribution within bone and other organs, and its interaction with PTH and $1,25(OH)_2D_3$.

Several effects of aluminum overload on mineral metabolism have been described. Aluminum decreases the secretion of PTH [112], and there is an inverse relationship between plasma PTH levels and bone aluminum content [113] as well as between plasma levels of aluminum and parathyroid gland weight [114]. There is much controversy concerning whether PTH protects [115–123] against aluminum-related bone disease. The occurrence of stainable aluminum at the mineralization front is less frequent in severe hyperparathyroid bone disease than in the other types of renal osteodystrophy [106, 115, 116]. However, high serum levels of PTH seem to augment the uptake of aluminum in bone [117, 119–123]. Indeed, we have found that patients with severe hyperparathyroid bone disease may have a higher bone aluminum content than patients with aluminum related osteomalacia [personal observation, and 124]. In our studies using uremic dogs, we found (unpublished observation) that high PTH levels favor the accumulation of aluminum in a diffuse manner within mineralized bone or at cement lines. In addition, there is some evidence that parathyroidectomy may increase the appearance of stainable aluminum at the mineralization front [122, 125–128]. However, increased total bone aluminum has been associated with elevated PTH levels. This apparent contradiction suggests a redistribution of aluminum in bone after parathyroidectomy [129].

Administration of $1,25(OH)_2D_3$ may induce an increase in serum aluminum levels [130, 131] and a concomitant decrease in liver aluminum [130]. The number of 1,25D receptors in bone and intestinal cells is increased [132, 133] without a concomitant increase in calcium absorption in aluminum intoxicated rats treated with $1,25(OH)_2D_3$ [132]. Our recent acute [134] and chronic experiments in one and 5/6 nephrectomized dogs indicate that the administration of $1,25(OH)_2D_3$ lessens the aluminum accumulation in bone. It is of note that despite successful removal of aluminum from bone with DFO, bone histology does not normalize and exhibits characteristics of increased parathyroid gland activity with or without a concomitant mineralization defect, an abnormality responsive to $1,25(OH)_2D_3$ therapy. Aluminum administration has been shown to decrease the serum levels of $1,25(OH)_2D$ [132, 134, 135], and there is some evidence that aluminum may interfere with the effects of $1,25(OH)_2D_3$ on bone cells [136]. Removal of aluminum after deferoxamine (DFO) therapy might be associated with elevated levels of calcitriol [137].

In addition to its negative effect on serum PTH and $1,25(OH)_2D$, aluminum is known to have a direct effect on crystal growth and maturation [8]. Aluminum interferes with the mineralization process and with cellular metabolism. Even though conflicting data exist regarding the effects of aluminum on osteoblastic proliferation in cell culture contingent upon the doses of aluminum given and cell lines selected [138–140], it has been shown in vivo in uremic patients that there is a strong relationship between the extent of aluminum deposited linearly at the mineralization front and the level of bone turnover and mineralization as assessed by histomorphometry [109]. Other known cellular effects of aluminum are inhibition of enzyme related replication [141] and interference with the enzymatic activities of alkaline and acid phosphatase [136], acetylcholinesterase [141], hexokinase [142], and calmodulin [143].

Renal osteodystrophy in patients on chronic ambulatory or cycling peritoneal dialysis

Conflicting data have been reported regarding the evolution of renal osteodystrophy in adults and children undergoing peritoneal dialysis. One study reports no change in bone disease [144], while others indicate amelioration or worsening of the bone abnormalities, in particular hyperparathyroidism [145, 146].

Recent studies in a larger number of patients [147, 148], revealed that the distribution of the different types of renal osteodystrophy is similar to the distribution found in the hemodialysis population. However, secondary hyperparathyroidism seems to be more difficult to treat in these patients since the doses of $1,25(OH)_2D_3$ needed to suppress parathyroid secretion raise serum calcium in the high normal range [148].

Osteomalacia is usually associated with aluminum accumulation mainly in patients receiving aluminum-containing phosphate binders [148] and occasionally after acute aluminum contamination of dialysate fluid [149]. Osteomalacia without aluminum accumulation can persist however if deficiency in vitamin D is not corrected.

Clinical signs and symptoms

Patients with mild or moderate renal insufficiency are rarely clinically symptomatic. Clinical problems arising from soft tissue and vascular calcifications present prior to orthopedic skeletal problems. Soft tissue or tumoral calcifications, pseudogout and skin calcifications in adult dialysis patients are clearly related to the magnitude of the calcium-phosphate product and are responsive to its reduction. In contrast, vascular calcifications are not related to the calcium-phosphorus product and do not respond to its normalization [150].

The "red eye syndrome" resulting from inflammatory reactions to and irritation from conjunctival calcifications is seen in approximately 10 percent of dialyzed patients. If calcifications occur in the cornea, band keratopathy can be demonstrated by slit-lamp examination.

Patients in end-stage renal disease requiring dialysis are prone to mechanical skeletal problems, to include: fractures of tubular bones, crush fractures of the vertebrae and rib fractures. In long-term dialysis patients, carpal tunnel syndrome and chronic arthralgias are often associated with β_2-microglobulin amyloid deposition in articular and periarticular structures. The arthralgias are usually bilateral and affect primarily the shoulders and other joints such as knees, wrists, and small joints of the hands. Femoral neck fractures due to bone cysts can occur. There is no uniformly effective therapy; renal transplantation might be helpful [151].

Approximately 20% of dialyzed patients have bone pain, pseudogout, and/or extraosseous calcifications [150]. Proximal myopathy and muscle weakness are often seen in conjunction with bone pain. The kidney's impaired endocrine function may affect the hormonal target organ, striated muscle, where there are receptors for PTH and $1,25(OH)_2D_3$ [152, 153]. Muscle weakness may be aggravated by aluminum's perturbation of muscle metabolism [154].

Intractable pruritus, periarticular calcifications, soft tissue calcifications and rupture of the quadriceps are typically seen in patients with predominant hyperparathyroid bone disease, whereas, loss of height and spontaneous fractures occur primarily in patients with low turnover osteomalacia. There is a relationship between low turnover osteomalacia and encephalopathy. The encephalopathy may be sporadic or endemic. Sporadic encephalopathy is thought to be caused by aluminum toxicity due to prolonged therapy using phosphate binders containing aluminum. Endemic encephalopathy may be due to insufficient water treatment.

Renal osteodystrophy in children and growing individuals may present with a different clinical picture. Although bone pain, pseudogout, soft tissue calcifications, conjunctival calcifications and serum biochemical changes are generally similar to those seen in adults, vascular calcifications are quite infrequent in children on chronic maintenance dialysis. Children usually present with growth retardation and may have epiphysiolysis characterized by roentgenologicaly slippage of epiphyses due to impaired transformation of growth cartilage into metaphyseal spongiosa.

Diagnostic tools

Biochemical parameters

Serum biochemical parameters are of limited diagnostic value. The parameters are relatively poor predictors of the type and severity of bone disease. However, they are somewhat more reliable as a means to identify high- or low-bone turnover states.

Serum calcium is homeostatically controlled and the integrity of bone may be sacrificed to maintain serum calcium within the normal range. Consequently, serum calcium is a poor predictor of histological features and is not indicative of bone resorption in renal patients. Spontaneous hypercalcemia or hypercalcemic episodes during vitamin D therapy are seen in patients with severe hyperparathyroidism as well as those with aluminum-related bone disease.

Generally, phosphorus concentrations are not indicative of the type or severity of renal bone disease. However, patients with hyperparathyroid osteodystrophy tend to have higher serum phosphorus because for these individuals the source is twofold. Phosphorus is derived from intestinal absorption and released at a higher rate from bone due to the accelerated bone turnover characteristic of hyperparathyroid bone disease [11]. This may explain why elevated serum phosphorus levels persist in some individuals despite administration of high doses of phosphate binders.

The interpretation of levels of total serum alkaline phosphatase is limited. Care must be taken to avoid misinterpretation of normal total alkaline phosphatase levels as indicative of normal bone turnover or mineralization status. In addition to problems related to the dual origin of this enzyme (liver and bone), elevated serum alkaline phosphatase can be seen in patients with hyperparathyroidism and its characteristic high-bone turnover state and in patients with low turnover osteomalacia and rickets, diseases with profound mineralization defect. Measurement of bone alkaline phosphatase is more sensitive but not widely available. Levels are often elevated, while total alkaline phosphatase concentrations are normal since bone alkaline phosphatase represents only 20 to 30% of the total alkaline phosphatase activity in patients with renal failure.

Parathyroid hormone levels are a relatively good index of bone remodelling. Parathyroid hormone correlates better with osteoblastic parameters than osteoclastic indices [33]. Parathyroid hormone levels are higher in severe hyperparathyroid bone disease than in low-turnover uremic osteodystrophy. However, there is a considerable overlap in PTH concentrations between the different histological types of renal osteodystrophy. Radioimmunoassays recognizing the N-terminal fragment have a superior diagnostic value than assays detecting M or C fragments [33, 155]. Optimal interpretation of serum PTH levels requires concomitant measurement of serum calcium and validation of the assay by bone histomorphometry. Techniques for determinations of bioactive PTH levels using a cytochemical bioassay [156, 157] or a guanyl nucleotide-amplified renal adenylate cyclase assay [158] have been developed. The utility of these assays as a predictor of histological types is unknown.

Bone Gla-protein or osteocalcin is a good predictor of the number of osteoblasts in bone and permits a distinction between high and low turnover state of bone [159]. However, serum levels of BGP lack the sensitivity needed to distinguish mixed uremic osteodystrophy from the other forms of renal bone disease.

The levels of 25(OH)D are usually normal in renal patients receiving standard multivitamin supplementation. Only in cases of reduction in exposure to sunlight, malnutrition, melanosis cutis, heavy proteinuria, phenobarbital intake, alcoholism or advanced liver disease are 25(OH)D levels low and may contribute to bone disease [160]. Levels of $1,25(OH)_2D$ are low or in the low normal range and are of no diagnostic value except that they may reflect the severity of the bone disease.

Plasma levels of calcitonin have not been proven to be of any use in predicting renal osteodystrophy [84]. This may be due, at least in part, to the lack of specificity and sensitivity of most radioimmunoassays employed.

Osteonectin [6], serum procollagen carboxyterminal extension peptide [161] and plasma tartrate-resistant acid phosphatase [162] have not been extensively assayed in patients with renal failure and their potential diagnostic value is unknown.

The aforementioned biochemical parameters give information about bone turnover and/or bone formation, but none indicate directly aluminum-related bone changes. Diagnostic tools used to study aluminum-related bone changes include: (1) measurement of random serum aluminum levels; (2) deferoxamine mesylate (Desferal^R) infusion test (DFO test) [163]; and, (3) DFO test combined with measurements of serum PTH levels [164, 165]. Even though correlations exist between random serum aluminum levels and the extent of stainable aluminum in bone, no threshold value has been determined allowing a clear-cut distinction between patients with and without aluminum-related bone disease. The DFO test alone, or in combination with PTH measurement, may be used as a screening test. However, only 14% of patients with stainable aluminum at more than 10% of the trabecular surface can be diagnosed accurately [166]. Due to the DFO test's large number of false negative results, bone biopsies are the only reliable means for unequivocal diagnosis of aluminum deposition in bone.

There is no non-invasive tool to ascertain the diagnosis of amyloidosis. At the present time, confirmation of diagnosis requires histological examination of deposition of amyloid fibriles in the involved organs [151].

Radiologic features and bone densitometry

Information obtained from skeletal X-rays is limited and often misleading. Radiologic landmarks appear late in the course of renal osteodystrophy and X-ray techniques focus on cortical bone while the early abnormalities of renal bone disease pertain to cancellous bone. The comparison of X-ray findings and bone histology indicates that most radiologic signs considered to be pathognomonic of severe hyperparathyroid bone disease can be found in any of the three histological types. The radiologic features suggestive of renal bone disease include erosion of cortical bone evidenced by subperiosteal, periosteal and endosteal resorption, cortical striation and cortical thinning. Other characteristics include cortical defects in the skull ("pepper pot skull"), acroosteolysis of the clavicula and erosion of the terminal finger phalanges. Changes in cancellous bone are indicated by the rugger jersey appearance of the spine and ground glass aspect of the skull, ribs, pelvis and metaphysis of long bones.

These findings indicate that there is, or was, a marked hyperparathyroid component with increased osteoclastic resorption. That is, no unequivocal information about the current status of the patient can be obtained. In particular, superimposed osteomalacia can be overlooked because resorption cavities will have been replaced by radiolucent osteoid. Looser zones are not pathognomonic of osteomalacia since similar landmarks can be found in fatigue or stress fractures in osteopenic bone, although, in renal patients they are highly suggestive of a severe, advanced mineralization defect. In long-standing cases of hyperparathyroidism, pseudocysts and brown tumors can be visualized on X-rays. Large cystic formations can be seen in severe amyloidosis, especially in the shoulder and hips [151]. The association of carpal tunnel syndrome and lytic lesions of carpal bones is highly suggestive of amyloidosis.

Bone volume is poorly evaluated by standard X-rays. Bone density and mineral content of the spine measured by dual-photon absorptiometry (DPA) and CT-scan have been shown to correlate with cancellous bone mass in iliac bone as evaluated by histomorphometry [167]. However, it is of note that both CT-scan and DPA measure bone mineral density and not bone mass directly, that is, mineral density may be abnormal without a corresponding change in total bone mass. This explains why DPA and CT-scans cannot necessarily distinguish patients with osteopenia (decrease in bone mass with normal mineral density per unit volume of bone) from those with osteomalacia (normal or increased bone mass with diminished mineral density per unit volume of bone).

Although there is a need for more sensitive, non-invasive diagnostic methods, baseline bone biopsies in conjunction with a biochemical profile, X-ray findings, densitometry, and clinical manifestations, followed by sequential assessment of non-invasive parameters, provide a means to follow the effectiveness of any given therapy.

Bone biopsy and mineralized bone histology

At the present time, bone biopsies and mineralized bone histology still represent the only unequivocal means to evaluate the severity and the type of renal osteodystrophy. Labelling of bone with tetracycline prior to biopsy will dramatically improve the quality of the information provided by histological analysis and will give information on the mineralization status (Fig. 4). Processing the bone sample without removal of the mineral allows distinction between osteoid and mineralized bone. Viewing the slides under polarized light allows one to distinguish between the relative amount of lamellar and woven bone and/or osteoid. In addition to routine staining procedures [11] using Masson-Goldner trichrome, Hematein and Eosin, and solochrome-cyanin, additional stains are used to detect aluminum (Fig. 5) [168, 169] and iron. Congo red stains are used for detection of amyloid deposits. Bone specimens can also be used to measure the mineral content of bone, toxins, and trace elements, in particular, aluminum.

Bone histomorphometry represents an invaluable research tool for investigation of pathogenetic factors and documenta-

tion of the effects of therapies. It is our opinion that the interpretation of numerical results alone is insufficient for interpretation of bone changes. Thorough diagnostic assessment of bone and bone marrow by an experienced bone histopathologist is essential with or without the additional information provided by histomorphometry.

For research purposes, the quantitative evaluation of parameters of bone structure, formation, resorption and dynamics [11] documents the nature and the amplitude of morphological changes. Quantitative evaluation of parameters is best achieved using computerized assisted method [170, 171].

Therapeutic modalities

Long-standing renal osteodystrophy leads to morbidity and mortality and is not easily amenable to treatment. Because the effects of renal failure on bone can be observed at a GFR of approximately 60 ml/min and renal osteodystrophy progresses insidiously for several years before patients become symptomatic, the need to initiate early preventive measures cannot be overemphasized and represents the most effective approach. Preventive measures should be aimed at correcting the early consequences of the failure of excretory and endocrine kidney function leading to secondary hyperparathyroidism. This entails the maintenance of normal serum phosphorus and calcium, and supplementation of the deficient hormone $1,25(OH)_2D_3$, keeping in mind that these abnormalities are related. Ideally, these measures should be initiated prior to chronic maintenance dialysis and continued after dialysis has begun.

Control of phosphorus

Dietary phosphate restriction. Patients with early renal failure typically have normal or low levels of serum phosphorus. This is misleading, in that their PTH concentration is elevated and as a result tubular reabsorption of phosphorus is decreased. Experimental dietary phosphorus restriction was shown to decrease serum PTH levels, and to increase plasma levels of $1,25(OH)_2D$ [172, 173], total urinary excretion of calcium [173], intestinal calcium absorption and, occasionally, total and ionized serum calcium concentrations [172].

Serum phosphorus usually rises when the GFR is 25% of normal [174]. Therefore, restriction of phosphate intake appears logical at this stage. This requires a thorough dietary assessment and advice from a skilled dietician. A regimen of less than 500 mg of phosphorus per day has been advocated for prophylaxis [175], but may be nutritionally too restrictive and inadequate for most patients due in part to concomitant low protein intake and the risk of phosphorus depletion which may, in turn, induce osteomalacia. Usually, a daily intake of phosphorus of approximately 800 mg should be acceptable with careful monitoring of phosphate balance.

Phosphate-binding. When the use of intestinal phosphate-binders is required, the nephrologist is confronted with a dilemma because the ideal compound has yet to be discovered.

Recently introduced alginate phosphate-binders have yet to be proven safe and efficient [176]. The efficacy of magnesium salts is controversial. Some reports show that magnesium carbonate can be effective, while magnesium oxide and trisilicate were ineffective [177–179]. It is of note that magnesium salts may have deleterious effects on bone mineralization and the central nervous system. Clinicians choose mostly between aluminum gels and calcium salts.

The most potent phosphate binders (hydroxide or carbonate) are those containing aluminum, but one bears the risk of aluminum intoxication when given at high doses for an extended period of time. Used in low doses with careful monitoring of serum aluminum levels, these compounds may have a beneficial effect when given alone or in conjunction with other phosphate-binders.

Substitution of calcium salts for drugs containing aluminum is in current practice. Several salts have been introduced in a more or less empirical manner and found able to bind phosphorus [180–182]. (a) Calcium salts such as lactate or gluconate are not palatable and require an excessive fluid ingestion [183]. (b) Calcium carbonate is more tolerable and has the potential beneficial effect to correct hyperphosphatemia, hypocalcemia and metabolic acidosis [182]. (c) Calcium citrate bears the risk of increasing aluminum absorption when administered together with aluminum gels [184–186]. (d) Calcium acetate has recently been found superior to the other calcium salts for the in vitro and in vivo binding of phosphorus [187]. Additional studies are needed to confirm this in renal patients.

Calcium salts are less potent than aluminum phosphate-binders in decreasing phosphorus levels, and increase the risk of hypercalcemia and extraosseous calcifications, especially when given with $1,25(OH)_2D_3$ therapy.

A recent controlled study using calcium acetate has proven the empiric clinical notion that phosphate-binders should be given with meals, either immediately before or after a meal or either at half dose [181]. Ideally, the dose should be tailored to the phosphorus content of each meal. This approach assures minimal dietary intake of phosphorus and avoids unnecessary administration of binder. Studies indicate that ketovalin binds phosphate as efficiently as calcium carbonate [188]. The therapeutic efficacy of phosphate binders with low calcium content needs further study. It has also been suggested that a combination of calcium carbonate and ketovalin might be of clinical value because of the optimal phosphate binding of the two substances at different pH values [188].

With stringent monitoring of serum aluminum and calcium, low doses of aluminum gels prescribed in tandem with calcium salts may currently represent the best approach available until better phosphate binders are found.

The level of serum phosphorus should be kept in the range of 4.5 to 6 mg/dl. Sustained hyperphosphatemia is not necessarily related to insufficient dosage of phosphate-binders or noncompliance of the patient, but can be secondary to release of phosphate from bone in severe hyperparathyroid bone disease.

Removal of phosphorus by dialysis

The dialyzer clearance of phosphorus depends upon the blood flow and duration of dialysis. The clearance of the commonly used membranes is relatively poor in hemodialysis and somewhat superior with peritoneal dialysis. Enhancement of phosphorus clearance by new dialysis membranes might be beneficial.

Control of calcium

Prior to initiation of dialysis, the patient's tendency to hypocalcemia can be controlled by manipulation of serum levels of phosphorus and/or $1,25(OH)_2D_3$ administration.

In dialysis patients, serum calcium levels can be controlled by manipulation of the dialysate calcium concentration. The profession's view of optimal dialysate calcium concentration has changed over time. Initially, low calcium concentrations (50 to 60 mg/liter) were used. As evidence for secondary hyperparathyroid bone disease accumulated, calcium concentrations were increased [189]. Relatively high concentrations became the norm. We found that chronic positive calcium balance without vitamin D therapy seemed to increase soft tissue and vascular calcification [190]. At the present time, lower dialysate calcium concentrations are coordinated with high doses of oral calcium salts used to bind phosphate. Even though this approach appears to solve the problems associated with therapy using calcium salts as a phosphate binder, one should bear in mind that if the balance between calcium removal during dialysis and oral administration of calcium salts between dialysate treatments is poorly maintained, the patient risks either transient, increased parathyroid gland activity or extraosseous calcifications.

The approach of using a calcium-free dialysate with intravenous calcium infusion represents a clinical experiment which, if further tested, might be an option for the exceptional patient with extreme difficulties in controlling serum calcium [191].

$1,25(OH)_2D_3$ supplementation

The prevention of renal osteodystrophy using renal hormone $1,25(OH)_2D_3$ supplement has been in use since 1972.

From 1972 through August 1989, approximately 330 patients with mild to moderate renal insufficiency have been treated with $1,25(OH)_2D_3$. Beneficial effects on prevention of renal bone disease, reversal of secondary hyperparathyroidism and increased growth velocity in children have been observed [192, 193].

However, the cost of the metabolite and concern regarding a potential negative effect on renal function has hampered its widespread prophylactic use. The studies that suggested a deleterious effect on kidney function (decreased GFR) were uncontrolled prospective studies using high doses of $1,25(OH)_2D_3$ [194–198]. Double-blind placebo controlled trials or prospective studies using smaller doses failed to demonstrate this deleterious effect [199–201] when hypercalciuria and hypercalcemia were closely monitored. However, it has been found that even low doses of $1,25(OH)_2D_3$ given for one year may suppress bone turnover in some patients [201], a finding that calls for lower doses and/or intermittent therapy as an alternative.

In dialyzed patients, approximately 170 reports (850 patients) have been published on the effects of $1,25(OH)_2D_3$ given at doses varying from 0.027 to 3.5 μg/day in adults and 0.375 to 62 ng/day in children. Duration of therapy ranged from four days to ten years. These studies were usually designed as prospective or retrospective, and few were double-blind placebo controlled. In addition, most studies were conducted before aluminum was recognized as a pathogenetic factor for renal osteodystrophy, and, therefore, information on aluminum in serum, dialysate or bone is given in only a few reports.

Most studies revealed a beneficial effect of $1,25(OH)_2D_3$ on biochemical, radiological and histological signs of hyperparathyroid bone disease [202, 203]. The drug's effect on the osteomalacic component of renal osteodystrophy is somewhat difficult to establish because of the uncertain contribution of aluminum.

Hypercalcemia is a rather common side-effect of daily $1,25(OH)_2D_3$ therapy. Alternative approaches such as "pulse therapy" with high doses given twice weekly at the end of dialysis [204] or modulation of calcium supplement, dialysate calcium, along with doses of $1,25(OH)_2D_3$ [205], were shown to be efficient in decreasing PTH secretion with less hypercalcemia.

Studies suggest that the route of administration bears directly upon the efficacy of drug therapy. Intraperitoneal administered calcitriol has been advocated [206] but does not seem to be more advantageous than orally administered calcitriol [207]. Intravenous administration of $1,25(OH)_2D_3$ suppresses the levels of PTH with decreased incidence of hypercalcemia [208]. Higher peak levels and/or greater bioavailability of intravenous calcitriol may account for an enhanced biologic effect of the intravenous administered $1,25(OH)_2D_3$.

Few long-term controlled studies have been reported on selected patients with predominant hyperparathyroid bone disease who became hypercalcemic with oral $1,25(OH)_2D_3$ therapy [207, 209–211]. The anecdotal clinical observation of rapid metastatic calcification with intravenous calcitriol occurring with a calcium and phosphorus product above 80 [212] indicates that similar precautions are needed for i.v. and oral calcitriol administration. Clearly, further studies are needed to assess the efficacy and safety of i.v. $1,25(OH)_2D_3$ in patients with renal failure, and to answer whether the beneficial effect on hyperparathyroidism might be limited when severe "autonomous" hyperparathyroidism with increased parathyroid cell mass prevails.

In addition, recent reports of in vitro experiments that suggest a potential effect of calcitriol on lipid accumulation in human monocyte derived macrophages [213, 214] deserve further in vivo studies to prove or disprove this potentially disturbing side effect.

Because $24,25(OH)_2D$ was alleged to play a role in calcium metabolism [215, 216], clinical trials and experimental studies using $24,25(OH)_2D$ alone or in combination with $1,25(OH)_2D_3$ were undertaken [217–220]. The results of these studies do not support the notion that $24,25(OH)_2D$ has a prophylactic or therapeutic effect on renal osteodystrophy. However, it was found that when administered with $1,25(OH)_2D_3$, the occurrence of hypercalcemia decreased and the serum level of $1,25(OH)_2D$ fell [219, 221].

The hypothesis that $24,25(OH)_2D$ increases the $1,25(OH)_2D_3$ receptor occupancy and, therefore, enhances its physiologic activity has been at least partially disproven. Recent findings point to a $24,25(OH)_2D$ mediated increase in the metabolic renal clearance rate of calcitriol [222]. Therefore, the effect of $24,25(OH)_2D$ on serum concentrations of $1,25(OH)_2D$ appears to result from an increased degradation.

The most promising future approach would be to isolate the positive effect of $1,25(OH)_2D_3$ on osteoblastic receptors from those on intestinal receptors. Our experience in testing new vitamin D metabolites suggests that the ideal compound should

have: (1) a positive effect on bone while avoiding a profound decrease in bone turnover, as well as (2) a moderate effect on parathyroid glands and intestinal calcium absorption.

We do not think that prevention or treatment of hyperparathyroidism and avoidance of aluminum accumulation will completely eliminate renal bone disease, since we have shown that bone cells do not function properly in the presence of normal levels of parathyroid hormone and low levels of 1,25 Vitamin D [223]. Further studies are needed to determine whether alterations of the various hydroxyl groups of the vitamin D sterol can accomplish this.

The recent study using 22-oxa-calcitriol [224] revealed a profound suppressive effect on parathyroid gland secretion and calcium absorption and no or little in vitro effect on bone. This compound could therefore be useful in the short-term management of severe hyperparathyroidism. However, the dramatic decrease in parathyroid hormone production with a concomitant decrease in $1,25(OH)_2D$ would lead, over time, to a profound decrease in bone turnover and to adynamic bone disease.

The discovery of partial control of parathyroid secretion by β blocker and H2 antagonists has stimulated clinical trials using these substances [225, 226]. Available long-term results are not convincing.

Removal of aluminum

Several methods are available for removal of aluminum from bone. Any therapeutic maneuver that lowers plasma aluminum levels and creates a concentration gradient across the bone-extracellular fluid membrane will be able to move aluminum from bone to blood

In plasma, approximately 20% of the aluminum is non-protein bound and ultrafiltrable. In hemodialyzed patients, this means that a plasma level of at least 50 μl/liter is needed to reach an osmotic gradient between blood and dialysate [227, 228] since dialysate may contain 5 to 10 μg/liter of aluminum after reverse osmosis.

The simplest method seems to be to completely withdraw the aluminum containing phosphate binders and to replace them with calcium salts. However, frequent hypercalcemia is encountered necessitating a lowered calcium dialysate that may in itself cause problems (vide supra). The elimination of excessive aluminum from bone through normal turnover, that is, without chelation, would take years. Certain hemodialysis membranes, such as polysulfone or polyacrylonitrile membranes, may have higher aluminum clearances than others. Aluminum clearances achieved with peritoneal dialysis may be greater than with hemodialysis due in part to loss of protein-bound aluminum [229]. At present, it is not known whether CAPD is preferable to hemodialysis in removing aluminum.

The use of a chelator increases the complex bound fraction of aluminum and facilitates its removal through dialysis. A highly specific and entirely safe chelator of aluminum does not exist. EDTA lacks specificity and binds calcium. Deferoxamine (Desferal^R, Ciba Geigy, Summit, New Jersey, USA) is presently the best chelator of aluminum available.

Deferoxamine has been proven relatively safe but rare ocular complications such as cataracts, altered color vision, night blindness or scotoma have been reported [230]. Episodes of hypotension can occur during therapy and are usually easily reversible; in some cases, however, they have been accompanied by angina. The association between Deferoxamine therapy and infections has been the subject of an abundant and controversial literature during the last few years. Deferoxamine is thought to act as siderophore and therefore promotes bacterial and fungal infections [231, 232]. Although numerous case reports of bacteremia and mucormycosis occurring with Deferoxamine (DFO) therapy have been published, recent large surveys did not confirm that DFO increases the risk of bacteremia in dialysis patients [233], and in vitro studies did not find any stimulative effects of DFO with or without iron and aluminum on the growth of Mucorales [234]. The relationship between DFO therapy and infections certainly requires further investigation. Consequently, careful documentation of aluminum overload is required before long-term DFO therapy is begun.

After initiation of DFO therapy, increases in serum aluminum levels are observed indicating the translocation of aluminum from bone and other organs into the blood. With continuation of chronic intermittent therapy, a saw tooth pattern of blood aluminum levels before and after infusion is customarily observed, with a trend toward baseline values after three to twelve months depending upon the extent of initial aluminum overload [163]. When no further increases in serum aluminum levels are seen and, more importantly, a zero dialysance is observed, therapy should be discontinued to avoid chelation of other trace metals [235].

During DFO therapy, parathyroid hormone levels may rise [163], or be higher at any given serum calcium (change in calcium set-point and maximum PTH inhibition) [236]. Deferoxamine seems, therefore, to enhance the PTH secretion per individual parathyroid cell [236].

At this point, bone biopsies are helpful for documentation of removal of aluminum from bone. Biopsies assist the clinician in diagnosis of the new underlying renal osteodystrophy since low turnover bone disease can be transformed into mixed uremic osteodystrophy or the latter into predominant hyperparathyroid bone disease.

Muscle pain and weakness are usually the first symptoms to improve followed by improvement in bone pain. Usually, serum PTH and alkaline phosphatase levels increase. Development of pruritus is not unusual paralleling the increase in PTH levels.

Transient episodes of hypocalcemia or diminished serum calcium levels may be encountered necessitating administration of $1,25(OH)_2D_3$. The most frequently encountered side-effect is transient hypotension due to the histamine-mediated vasodilatory effect of the drug and an infusion rate exceeding 15 mg/kg body wt/hr. Nausea, vomiting and neuromuscular excitability are usually transient.

Although more long-term placebo controlled studies are necessary, it is obvious that DFO therapy is efficient in most cases in removing aluminum and is acceptably safe. However, considerable controversy exists regarding the dose, time, route and frequency of infusions of DFO. The optimal dose is 15 to 20 mg/kg body wt infused over a two hour period, three times per week. Infusions of DFO at the end of dialysis are potentially more efficient since it allows the chelator to act longer. However, this bears the risk of inducing long-standing high levels of blood aluminum which could be redistributed to the brain causing acute encephalopathy. Intramuscular injections of 1 g

of DFO 12 hours before dialysis once weekly have also been suggested [237]. In high risk patients, the dose and the frequency of injections might have to be reduced.

It is not known if aluminum can reaccumulate in bone after successful chelation therapy despite low dose (or absence of) administration of aluminum-containing phosphate binders, and whether other substances are removed during chelation therapy inducing insidious deficiencies.

Trials using hemofiltration without dialysis, plasma exchange or sorbent hemoperfusion have been disappointing when employed without additional systemic or extracorporeal DFO therapy. The added expense and the logistical problems of using special cartridges with microencapsulated carbon (Alucart^R; National Medical Care, Rockleigh, New Jersey, USA) [238, 239] or DFO coating (Al/Fe Clark^R Specific; Clark Research and Development, Inc., Folsom, Louisiana, USA) limits their application to severe aluminum toxicity where time is of the essence.

Parathyroidectomy

In the past, the surgical reduction of parathyroid glands has been overzealous. High levels of PTH (especially C or M terminal) and hypercalcemia should not prompt the clinical nephrologist to recommend parathyroidectomy. The threat to fragile patients posed by anesthesia is calculable and well known. Parathyroidectomy should represent the treatment of last resort and should always be preceded by a careful assessment of aluminum loading and histological verification of the diagnosis by bone biopsy. Its indications must be restricted to refractory calciphylaxis, idiopathic disseminated skin necrosis, and marked sustained hypercalcemia without other identifiable causes (in particular, sarcoidosis). Only when all available therapeutic modalities have failed should parathyroidectomy be recommended.

There is much controversy regarding the optimal choice of the type of parathyroidectomy to be performed [240, 241]. Three surgical modalities are currently used: subtotal and total parathyroidectomy and total parathyroidectomy with autotransplantation.

Although all three surgical approaches are usually followed by short-term clinical and biochemical improvement, persistent severe hyperparathyroidism can be encountered due to failure to resect all parathyroid gland tissue. Long-term results show a non-negligible incidence of recurrent hyperparathyroidism, especially with subtotal and total parathyroidectomy with autotransplantation. In these instances, localization of the hyperactive parathyroid fragment can become challenging. Malignant transformation of residual or transplanted tissue has also been described especially in cases of prior neck irradiation [242]. Long-standing severe hypoparathyroidism remains a major risk chiefly after total parathyroidectomy. Long-term supplementation in calcium and/or $1,25(OH)_2D_3$ is then required and a dramatic decrease in bone turnover can occur leading to adynamic bone disease and increased risk of extraosseous calcifications.

Development of alternative, less invasive approaches, such as reduction of parathyroid gland cellular mass by percutaneous injection of absolute ethanol with assisted localization of parathyroid gland by ultrasound, seem promising [243, 244]. In any event, particular, careful post-surgical follow-up is needed as clinical reports show that patients appear particularly prone to accumulate aluminum in bone after parathyroidectomy [127, 128, 245, 246]. Institution of postsurgical $1,25(OH)_2D_3$ therapy should be delayed if widespread extraosseous calcifications are present. Maintenance of serum calcium with individually dosed calcium supplements following surgery should help mobilize extraosseous calcifications and facilitate improved function of the transplanted gland cells.

Despite the recent advances in the understanding of pathogenetic mechanisms and the introduction of new, potentially helpful therapeutic regimen, there is no uniformly accepted management of the metabolic bone disease(s) of patients with chronic renal failure. This review provides a rational therapeutic approach. However, it should be noted that some of the drugs recommended and used by nephrologists have not been approved by the Food and Drug Administration for the given indication. New therapeutic approaches should not be advanced hastily, and experimental animal studies and long-term prospective controlled trials in patients are imperative before general recommendations can be given. Any therapeutic regimen should be tailored to the clinical, biochemical and histological derangements of the individual patient, and careful follow-up is needed.

Prophylactic measures should be the first priority in management of renal osteodystrophy. Long-term studies on the effects of prophylaxis will show whether the quality of life and longevity of dialysis patients improve.

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