Renal Osteodystrophy

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It is well established that the kidneys play a pivotal role in maintaining mineral homeostasis and hormonal balance. Reductions in renal excretory and endocrine functions have a profound impact on divalent ion metabolism, calciotropic hormones, and thus on bone metabolism, resulting in renal osteodystrophy (ROD). The earliest histologic abnormalities of bone are seen after a relatively mild reduction in glomerular filtration rate (GFR) (creatinine clearances between 70 and 40 mL/min) [1]. Histologic changes are found in virtually all patients with end-stage renal failure (ESRD) [2].

The importance of renal bone disease extends beyond histologic, radiologic or biochemical abnormalities. Thirty years ago, it was reported that approximately 25% of patients with chronic renal failure (CRF) had symptomatic manifestations of ROD, such as bone pain and fracture and extraskeletal calcifications, with 10% of these presenting with severe symptoms [3]. With improvement in dialytic therapies, one could expect better control of divalent ions and bone homeostasis. However, adequate dialysis, per se, does not prevent the development of ROD [4] and while prolonging the life of uremic patients, long-term dialysis therapy is accompanied by more severe forms of ROD [3, 5, 6]. Indeed, more recently, it has been reported that bone pain was found in 36% and fractures in 10% of 259 dialysis patients [7]. Moreover, clinical manifestations of ROD, together with other long-term complications of dialysis, such as myopathy and amyloid bone disease, impact greatly the functional and psychosocial capacities of patients with ESRD and are responsible for a great part of morbidity and mortality. In a large study including 428 dialyzed patients, only 45% had normal physical activity scores [8] and in another survey, not more than one-third of the dialysis patients were considered able to work [9]. Since the incidence of ESRD in the United States is 68,870 patients/year (253/million/year) and the prevalence is 257,266 patients (967/million) [10], ROD is becoming a critical socioeconomic health problem.

ROD is not a uniform disease, and a large spectrum of systemic and histologic abnormalities can be observed, requiring different therapeutic approaches. Moreover, transformation from one form to another is not unusual [2]. Over the last decade, many factors have contributed to these changes, and correction of one abnormality can often lead to the aggravation of another. Bicarbonate dialysate became standard practice, calcium (Ca) salts replaced aluminum gels, and biocompatible membranes were introduced. Currently, dialysate Ca concentration is reduced and vitamin D metabolites are more widely used. Peritoneal dialysis (PD) is now an acceptable alternative to hemodialysis (HD). Finally, diabetic and aging patients comprise a large proportion of the dialysis population. These significant changes may have contributed to new trends seen in the spectrum of ROD [5, 11, 12]. These trends include the emergence, and

later decrease, in aluminum-related bone disease and the appearance of adynamic bone disease and β_2-microglobulin amyloidosis. Therefore, preventive or therapeutic approaches to patients with ROD remain an ongoing challenge for nephrologists [13].

A rational approach to the treatment of ROD requires a basic understanding of bone and divalent ion metabolism.

Functional Organization of Bone

The skeleton has a dual mechanical and metabolic function. The rigidity of the skeleton is responsible for maintenance of the human body configuration, protection of soft organs, and mobility through transmission of forces originated by muscle contraction. It is also the main reservoir for Ca, phosphate, and bicarbonate; thus, the skeleton contributes to the minute-to-minute regulation of extracellular fluid. Each bone consists of bone tissue, hematopoietic marrow, vasculature, and peripheral nerves. Bones from the axial skeleton include the skull, spine, thorax, and pelvis, whereas bones from the extremities comprise the appendicular skeleton. Pathologic processes and therapies can affect these skeletal sites in different ways [14].

Cortical and Cancellous Bone

Cortical or compact bone can be distinguished macroscopically from cancellous or trabecular bone. Cortical bone is a dense tissue that contains < 10% soft tissue. Cancellous or spongy bone is made up of trabecules shaped as plates or rods interspersed between bone marrow that represents > 75% of the cancellous bone volume. Cortical bone forms the external layer of all bones but is found predominantly in the appendicular skeleton, particularly in diaphysis of long bones. Cancellous bone is found mainly in the axial skeleton, located between the cortices of smaller flat and short bones such as scapulae, vertebrae, and pelvis. It is also present in limited amounts in the juxta-articular extremities of the appendicular skeleton. Cortical bone represents 80% of the skeletal mass and therefore supports most of the mechanical function [15]. Cancellous bone is only 20% of the skeletal mass but is metabolically 4 times more active per unit volume than cortical bone. Thus, the metabolic function is equally distributed between cortical and cancellous bones [15].

Bone Envelopes, Bone Surfaces, and Bone Structural Unit

The periosteal envelope represents the outer layer of connective tissue that encloses both hard and soft tissue and separates bone from other organs. The inner or endosteal envelope surrounds all soft tissue within the bone (except osteocytes) and is the boundary between soft tissue, mainly bone marrow, and bone tissue. Within the endosteal envelope, 3 distinct but continuous surfaces are observed: the intracortical, including the Haversian and Volkmann canals, the endocortical, and the trabecular surfaces. Modeling and remodeling activities take place on bone surfaces. However, the levels of activity vary from one surface to another and can be affected differently by physiological or pathological events as well as by therapeutic agents.

Between the periosteal and endosteal envelopes, bone is further organized in several structural elements, the bone structural units (BSU). The spatial arrangement of these smallest, individual units of bone and their cohesion are responsible for bone strength.

In cortical bone, BSU is represented by the osteon or Haversian system. Each osteon consists of a 200 – 250 μm wide cylinder running parallel to the long axis of cortical bone. The osteon center is occupied by a 40 – 50 μm "Haversian" canal containing blood vessels, nerves, and connective tissue. The Haversian canals of adjacent osteons are linked transversally by Volkmann canals, creating an intracortical network, which is also connected with the periosteum and bone marrow. The central Haversian canal is surrounded by concentric layers of 20 – 30 osseous lamellae, making the osteon wall approximately 70 – 100 μm thick. Osteons are densely packed and separated only by interstitial lamellae, which are the remains of incompletely resorbed osteons.

In cancellous bone, BSUs are flat and can be envisioned as longitudinally cut and unfolded osteons. They appear as semilunar packets roughly parallel to the central axis of the trabecule. The trabecular surface corresponding to the open Haversian canal follows the shape of the trabecule and is in contact with bone marrow. Within trabecules, the BSUs are separated from each other by interstitial bone, which, as in cortical bone, represents the remainder of older, incompletely resorbed packet.

Lamellar and Woven Bone

Each BSU consists of a specialized connective tissue, the osseous tissue, made of a mineralized protein matrix. At the microscopic level, 2 different types of bone can be identified by the arrangement of collagen bundles.

In the normal mature skeleton, bone is of the lamellar type. In this bone, the orientation of collagen fibers alternates regularly from layer to layer. Each layer is approximately 3 μm thick, with all collagen fibers deposited in the same direction. The deposited collagen exhibits an orderly lamellar pattern as circular layers alternating with longitudinal ones. The change in collagen fiber direction from layer to layer is responsible for the birefringence of bone under polarized light microscopy.

Contrasting with the regularity of lamellar bone, woven bone is composed of loose and randomly arranged collagen bundles. Woven bone is formed by irregular and unpolarized extrusion of protocollagen by osteoblasts. This matrix consists of an unordered, crisscross texture that lacks the birefringence typical of lamellar bone under polarized light. Woven bone is present in embryonic skeleton and in both cortical and cancellous bones during stages of rapid growth. After completion of bone growth, woven bone is replaced by lamellar bone in the normal skeleton. However, woven bone is also observed in certain pathologic conditions, such as Paget's disease of bone, fracture healing, osteogenesis imperfecta, and in primary or secondary hyperparathyroidism. In adults, woven bone is indicative of rapid, uncontrolled bone formation and high bone remodeling that is attributable to either local or systemic factors. It is of note that woven bone is inferior to lamellar bone in terms of mechanical properties.

Bone Cells

The Osteoclasts

Osteoclasts are large multinucleated cells located in resorption lacunae in the vicinity of

mineralized bone. Osteoclasts represent the main cells in the breakdown of bone matrix and bone mineral. They vary in size from 20 – 100 μm in diameter and usually display projections and lobes that give them an irregular appearance. Osteoclasts are highly mobile and go through cycles of resorption and rest. Thus, it is not surprising that these cells vary in histologic appearance, depending on the stage of the cycle at which they are observed. In normal skeleton, osteoclasts are somewhat larger than macrophages and may have from 2 – 5 nuclei. In pathologic states, osteoclasts are large, with up to 100 nuclei. The nuclei are found in the center of the cell. They are characteristically round or oval and usually contain 1 – 2 prominent nucleoli. Osteoclasts may appear mononucleated depending on the plane of the sections; however, serial sections may show other nuclei. These cells exhibit a characteristic pink staining with the modified Masson-Goldner trichrome stain due to abundance of mitochondria, lysosomes, and ribosomes in their cytoplasm. Their foamy appearance reflects the presence of numerous endocytic and lysosomal vacuoles. The ruffled border, the ultrastructural trademark of osteoclasts, consists of numerous foldings of the apical membrane and is occasionally identified at high magnification on thin histologic bone sections. However, in the majority of bone samples, the ruffled border is not recognizable.

The Osteoblast Lineage Cells

Osteoblasts are mononucleated cells responsible for production of bone matrix and are involved in its mineralization. Under light microscopy, mature osteoblasts in normal bone form a monolayer of cells in front of the bone formation site. They are cuboidal, polarized cells measuring between 15 – 25 μm in diameter. Their round nuclei are located at the basal pole of the cells (away from bone) and contain one or more nucleoli. The cytoplasm is strongly basophilic due to the large amount of endoplasmic reticulum and Golgi apparatus responsible for active production of type I collagen and other substances found in the bone matrix. Osteoblasts at a bone formation site give the appearance of an epithelium-like organization. They exhibit gap junctions that ensure their cohesion and provide cell-to-cell communication. During active bone formation, osteoblast cells are plump. Towards completion of the new bone packet, the osteoblast shape flattens, its cytoplasm loses its basophilic characteristics, and its nuclei become elongated. The majority of these resting osteoblasts become bone-lining cells observed above the quiescent surfaces.

Also, approximately 10% of osteoblasts turn into osteocytes, that is, they become embedded in the bone matrix before its mineralization and become stellar cellular complexes with a central nucleus and numerous long cellular processes. Gap junctions have also been described between the peripheral processes of osteocytes, osteoblasts, and bone lining cells from the same bone area. When matrix mineralizes, osteocytes are found in osteocytic lacunae, the border of which has been found to be calcified by osteocytes. Long cytoplasmic processes are seen in canaliculae. Newly embedded osteocytes conserve the cellular characteristics of osteoblasts, and the oldest ones in deeper bone area lose signs of protein synthesis and accumulate glycogen. The periosteocytic space between osteocytes and mineralized bone contains the bone extracellular fluid (1 – 1.5 L), and the bone-lining cell/osteocyte network plays an important role in the minute-to-minute Ca homeostasis as the osteocytes are rapidly exposed to changes in circulating factors. Due to their deep location in mineralized bone, osteocytes

are also considered sensors for fatigue damage and microfractures and thus may represent an important contributor to the regulation of bone remodeling and bone turnover.

Bone Marrow Cells

Besides bone cells, other cells are present in the bone microenvironment. There is ample evidence that bone marrow cells play a role in the local regulation of bone remodeling and bone turnover. Cells from the monocyte-macrophage and lymphoid lineages produce various substances such as cytokines and growth factors that directly or indirectly act on bone cell recruitment and activity [16]. Moreover, macrophages have the capability to produce calcitriol [17, 18]. Mast cells, which produce heparin, a proven stimulator of bone resorption, may also be involved in the local regulation of bone [19, 20].

On bone biopsy samples, it is common to observe that states of high bone turnover are often associated with various degrees of bone marrow cell hyperplasia, whereas low-turnover states of bone are accompanied by variable hypoplasia of hematopoietic cells [2].

Bone Modeling and Remodeling

During life, the skeleton is not static but undergoes numerous transformations. First, there is growth, also called bone modeling, when the overall shape and size of bones change. The 2 types of bone growth are longitudinal and appositional modeling. Longitudinal growth occurs by enchondral ossification, a process that takes place at the growth plate, when cartilage proliferates and progressively calcifies creating new trabeculae until the epiphyseal growth plate fuses. Appositional modeling, i.e. the growth of bone in width, proceeds by periosteal apposition of new bone and endosteal resorption of old bone.

After epiphyseal growth plates close, the adult skeleton continues to renew itself without noticeable changes in macroscopic shape. This is bone remodeling. The primary function of bone remodeling is to replace old bone with new bone. Old bone contains high mineral density and microfractures that decrease its mechanical properties. Approximately 3% of cortical bone and 25% of cancellous bone are renewed per year in the mature human skeleton [21]. Bone remodeling occurs in distinct locations on bone surfaces, the bone remodeling units (BRUs) [15]. BRUs require the involvement of a team of different cells, the bone multicellular units (BMUs). The remodeling of a “packet” or “quantum” of bone entails sequential events known as the remodeling cycle. This remodeling cycle includes activation, resorption, reversal, formation, and quiescence.

The signaling factors responsible for the initiation of the remodeling cycle are not well understood. Structural and/or biomechanical characteristics of old bone packets may play a role in this early phase, and signals may be relayed through the osteocyte-lining cell system to osteoblasts and bone marrow cells [15]. Numerous factors known to stimulate bone resorption are probably involved in the activation of bone remodeling that also requires interaction between hormones, cytokines, and growth factors and their receptors in bone cells and bone marrow cells. Activation of bone surface is accompanied by mobilization of mononucleated osteoclast precursors, retraction of the lining cell layer, and exposure of bone matrix chemotactic substances such as osteocalcin, osteopontin, transforming growth factor β (TGFβ), and type I collagen [22 – 29].

The progressive fusion of mononucleated osteoclast precursors results in a team of 1 – 4 mature, active, and multinucleated osteoclasts at each remodeling site. The team of osteoclasts then adheres to bone surface along a ring, i.e. the sealing zone, leaving an extracellular bone-resorbing compartment, and then bone resorption begins. Osteoclasts dissolve bone mineral through acidification of the subosteoclastic compartment. This process involves proton pumps and carbonic anhydrase. Bone matrix is hydrolyzed by proteolytic enzymes such as collagenase. Osteoclasts are motile cells and move along the erosion cavity. They are responsible for the rapid resorption (~ 7 days) of two-thirds of the final eroded cavity. Mononucleated cells resorb the other one-third at a slower rate (~ 36 days) [30]. These mononucleated resorbing cells consist of either unfused original osteoclast precursors or segmentated osteoclasts. The rapid osteoclastic resorption leaves behind a rather rough surface that is transformed by the mononuclear cells into a smooth bone surface. In cortical bone, the resorption process takes place along the long axis of bone, and osteoclasts are observed in the cutting cone with depths reaching 100 μm. In normal cancellous bone, osteoclasts erode bone parallel to the bone surface, forming a shallow cavity with a depth of 40 – 60 μm.

After resorption ceases, there is a transition period before bone formation occurs, i.e. the reversal phase. During this 1-to 2-week phase, a layer of material with particular optical characteristics is deposited at the bottom of the resorption lacunae. On histologic section this line is positive for acid phosphatase staining and presents with a different birefringence under polarized or phase contrast light microscopy. This line (surface) serves as a cement or glue between old and new bone to be apposed and is referred to as the reversal or cement line. Only mononucleated cells are seen in front of the resorption lacunae during this phase and probably are responsible for the deposition of cement line. The exact origin of these cells is not known. Concurrent with the reversal phase, other events take place that are responsible for the coupling between resorption and formation. In the adult skeleton, bone is formed only on a previously eroded surface. This implies that signals are emitted to promote osteoblast proliferation and to direct osteoblast precursors to a precise location on the bone surface. The complex mechanisms responsible for this coupling phenomenon are not fully understood. However, several local agents such as chemotactic substances, growth factors, and cytokines are probably involved in this event.

After differentiation, osteoblasts form a layer in front of the reversal lacunae and deposit matrix protein, i.e. osteoid. Mineralization of osteoid seam starts 5 – 15 days later when the osteoid seam is approximately 20 μm thick. Apposition of osteoid is rapid at first, then progressively slows down. The mineral apposition rate follows the same pattern. First, osteoid is mineralized at a rate of 1 – 2 μm/day and subsequently slows down but is still faster than matrix apposition at that time. When matrix apposition ceases, the remaining layers of osteoid are slowly mineralized. The first hydroxyapatite crystals are small and immature, and therefore Ca ions can chelate other substances present at high concentration in the bone microenvironment. These substances may include aluminum, fluoride, and others, in particular tetracycline hydrochloride. Under fluorescent light microscopy, deposits of tetracycline in new bone are spontaneously visible on unstained sections and appear as bright yellow bands. The technique of tetracycline double labeling (discussed later) uses this phenomenon to determine the rate of mineralization. However, when tetracycline is administered, it chelates reversibly to all ex-

posed bone surfaces, i.e. resorptive cavities and at the mineralization front. Therefore, it is necessary to perform a bone biopsy within a few days after the last administration of the antibiotic, usually 2 – 4 days. This ensures that the tetracycline chelated at the mineralization front is protected from leaching out by a thin layer of newly mineralized bone. During bone formation, osteoblasts are first cuboidal and very active, then they flatten and become lining cells when the osteoid seam is completely mineralized. Moreover, a certain fraction of osteoblasts is embedded in bone matrix and becomes osteocytes (see above). Also, some osteoblasts may locally undergo apoptosis [31]. The total duration of the bone formative phase in normal skeleton is approximately 3 months.

A phase of quiescence follows. During the beginning of this phase (3 – 6 months), the newly formed "young" bone packet will mature by increasing its mineral density. New bone is separated from bone marrow by the layer of lining cells and a thin collagenous membrane. In normal adult bone, the majority of bone surface is in a quiescent stage (80%).

Bone Balance and Bone Turnover

In normal young adults, coupling between the amount of bone resorbed by osteoclasts and the amount of bone formed by osteoblasts results in bone balance. Uncoupling between formation and resorption will result either in negative or positive bone balance at the remodeling site. In states of negative bone balance, the amount of bone resorbed is disproportionately higher than bone formed; conversely more bone is deposited than resorbed when bone balance is positive.

If bone remodeling represents the cellular-based events that occur at a specific site of the bone surface, bone turnover represents the rate at which the skeleton is renewed. This depends on the activation rate and the extent and distribution of the remodeling sites among the various bone envelopes. If bone turnover is high, the minute changes observed at the bone remodeling sites are amplified. For example, in case of negative bone balance, bone loss is greater in individuals with high bone turnover, and reduction of turnover will result in slower bone loss.

In bone biopsies, it is common to observe that states of high bone turnover are often associated with various degrees of bone marrow cell hyperplasia, whereas low-turnover states of bone are accompanied by variable hypoplasia of hematopoietic cells [2].

Role of Bone in Calcium and Phosphate Metabolism

Bone has an important role in mineral and acid-base homeostasis. Bone possesses 2 fundamental properties that greatly facilitate this function. First, there is the enormous capacity of the apatite crystals and the calcium phosphate salts to adsorb bone-seeking elements such as Ca, phosphorus (Pi), magnesium, aluminum, and zinc. Second, the large skeletal surface between the osteocyte-lining cells network and the extracellular fluid compartment facilitates ion exchange. Besides facilitating mineral movement in and out of bone, these highly complex anatomical arrangements contribute to the metabolic and electrical coupling of bone cells.

Bone is considered the largest primary Ca reservoir of the body, and it plays a major role in Ca homeostasis. The extracellular Ca concentration is determined by the rates of Ca entry into and loss from the extracellular fluid. Ca enters the extracellular space via 3 routes:

intestinal absorption, which is the major contributor to the available Ca pool, Ca release from bone and renal tubular reabsorption. Ca loss occurs by means of gastrointestinal digestive juices, bone uptake during mineralization and urinary loss.

There is a daily flux of approximately 110 nmoles of Ca into and from the bone [32]. Only 10% of this Ca is exchanged through remodeling surfaces [32]; the rest is transferred across the quiescent surfaces of bone and bone lining cells. The exact cellular mechanism(s) that influence Ca fluxes across this bone membrane are poorly understood. However, there is considerable evidence to suggest that parathyroid hormone and calcitriol, individually or synergistically, play an important role in governing Ca translocation across bone surfaces, independently of their role in bone remodeling [32].

The Role of Bone in Acid-base Homeostasis

It has long been recognized that bone mineral contributes to the buffering mechanisms in acute and chronic acidosis [33 – 35]. It appears that both low pH and low bicarbonate concentration independently influence Ca flux from bone [36]. Current evidence indicates that short-term acidosis mainly influences the physicochemical solution equilibria, while long-term acidosis affects Ca efflux via the activation of bone resorption mechanism [36].

Factors Affecting Bone Metabolism

It is increasingly apparent that bone cells are regulated by a complex interplay between systemic hormonal signals and local factors [37]. Bone cells are influenced by systemic factors and various circulating blood cells, particularly leukocytes that reach bone via capillary circulation. Bone cells are also in close proximity to local cells such as endothelial cells, chondrocytes and stromal (hematopoietic) cells that are capable of responding to circulating substances as well as secreting their own growth-regulating factors. It is only for simplification and practicality that one can categorically separate circulating factors from local factors.

Circulating Factors

Parathyroid Hormone (PTH)

PTH, an 84 amino acid polypeptide, is synthesized in a precursor form, pre-pro-PTH of 115 amino acids. Post-translational cleavages yield a 90 amino acid polypeptide (pro-PTH) and then the active 1-84 PTH, which is stored within intracellular secretory granules [38]. In the absence of a stimulus for PTH release, partial or complete intracellular degradation of the hormone to smaller polypeptide fragments or to its constituent amino acids may occur [39]. For example, a significant proportion of the immunoassayable hormone is secreted in the COOH-terminal fragment form during hypercalcemia [40]. The half-life of intact 1-84 PTH is short (< 10 minutes) due to effective enzymatic cleavage in the liver

(Kupffer cells) and the kidney (tubular cells) [41 – 43]. An important initial cleavage is around position 35, yielding to the bioactive 1-34 NH2-terminal and the bioinactive COOH-terminal, which has a longer half-life (1 – 2 hours) and is excreted by the kidney. Therefore, the kidney plays an important role in PTH metabolism, both by glomerular clearance of C-terminal fragments and by tubular degradation of intact PTH.

Intracellular cAMP is an important modulator of PTH secretion. Factors that increase cAMP accumulation (β-adrenergic catecholamines, dopamine, secretin, prostaglandin E2, glucagon, vasoactive intestinal peptide and histamine) all stimulate PTH secretion. Conversely, agents that inhibit cAMP accumulation in parathyroid cells such as Ca, α-adrenergic catecholamines, and prostaglandin F2α, also inhibit PTH secretion [44, 45]. Extracellular ionized calcium concentration [Ca^{2+}] is the principal regulator of PTH release. Many studies have documented a steep inverse sigmoidal relationship between the extracellular [Ca^{2+}] and PTH secretion [46], in which a minimal reduction of 0.1 – 0.2 mg/dL of [Ca^{2+}] represents a significant stimulus to PTH release [47]. A parathyroid calcium-sensing receptor was long suspected [46]. However, it was not until recently that such a receptor was isolated and characterized [48]. The Ca receptor is linked to several intracellular second messenger systems by guanine nucleotide regulatory (G) protein [46]. Some of the intracellular effects of the Ca receptor agonists include the inhibition of cAMP accumulation, the accumulation of inositol triphosphate (IP3), with the resultant increase in intracellular Ca concentration, and the inhibition of protein kinase C [46]. Exactly how these intracellular events lead to the inhibition of PTH secretion is uncertain. Recently, Okazaki et al. described a negative calcium-responsive element located upstream of the PTH gene and regulated by extracellular Ca concentration [49].

Accumulated evidence suggests that PTH secretion follows a circadian rhythm, with peak levels in the late evening hours [50, 51]. Furthermore, broad pulsatile secretion patterns were observed to occur approximately each hour [50, 52]. It has also been recognized that the rate and direction of the changes in Ca concentrations, in addition to the absolute extracellular Ca concentration, are important in modulating PTH secretion. For example, at any given low Ca concentration, the PTH level would be higher if measured during induction of hypocalcemia than if measured during the recovery of a hypocalcemic state. This phenomenon is termed hysteresis [53, 54].

In vitro studies show that magnesium appears to parallel the effect of Ca on PTH release, although with reduced efficacy [55, 56]. However, in vivo studies show that chronic severe hypomagnesemia impairs PTH secretion and reduces its end-organ effects [57 – 59]. Hyperphosphatemia is associated with increased circulating levels of PTH in renal failure. This effect is, in part, secondary to the associated hypocalcemia that accompanies elevated Pi levels [60]. However, a recent preliminary study by Silver et al. demonstrated a direct effect of Pi on the secretion of PTH messenger RNA (mRNA) in vitro [61].

Parathyroid cells possess vitamin D receptors and are capable of localizing injected radioactive 1,25-[H3]-dihydroxyvitamin D [62]. It is now apparent that 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) has multiple direct effects on parathyroid glands that include: inhibition of PTH synthesis and secretion [63, 64], reduction in parathyroid cell proliferation [65], and possibly facilitation of cell death by apoptosis [66]. Conversely, PTH exhibits a positive effect on 1-α hydroxylase, a tightly regulated enzyme in the production pathway

of $1,25(OH)_2D$ [67]. These observations explain the elevated circulating levels of $1,25(OH)_2D$ found in patients with primary hyperparathyroidism [68]. The interactions between PTH and $1,25(OH)_2D$ form the basis of a feedback loop that has an important role in the pathogenesis of secondary hyperparathyroidism in patients with renal failure.

The major role of PTH is to tightly regulate extracellular Ca concentration and keep it within narrow limits. This function is achieved by exerting important direct actions on bone and kidney and indirect effects on the intestine. Receptors for PTH have been recently cloned and characterized in opossum kidney, rat osteoblasts, and human kidney cells [69 – 71]. Parathyroid hormone interacts with these specific membrane-bound receptors to initiate a cascade of intracellular events that involve protein G activation with resultant cAMP generation, phosphatidylinositol and Ca transport activation [72].

Effects of PTH on Bone

PTH maintains extracellular Ca concentration by facilitating Ca fluxes from and to the skeleton. Osteoblasts and cells of osteoblastic lineage (the lining cells and osteocytes) are the only cell type in bone found to possess PTH receptors [73 – 76]. It appears that Ca movements from bone proceed in at least 2 phases. First, there is a rapid mobilization from the lining cells and osteocytes as evidenced by the prompt structural response of these cells to injected PTH [77] as well as the rapid release of radiolabeled Ca from bone surfaces following PTH administration [78]. Secondly, there is a slow (hours) response that is dependent on mineral release by osteoclasts during bone resorption [78]. One of the most recognized effects of PTH on bone is the enhancement of osteoclast activity and numbers [79]. This effect is, in fact, dependent on osteoblast activation since, in vitro, osteoblasts are required for PTH control of bone resorption [74, 80] and osteoblasts release factor(s) that stimulate bone osteoclastic resorption [81, 82]. However, most recently Langub et al. (submitted) were able to show PTH/PTHrP receptors in osteoclasts of bone biopsies from normal human individuals and patients with renal failure.

In vivo, PTH increases not only osteoclastic resorption but also osteoblastic anabolic activity. In vitro, however, PTH inhibits osteoblast activity [83]. This apparent discrepancy can be related to differences in dosages or to the intermittent and pulsatile secretion of PTH in vivo, as opposed to the continuous effect in vitro [83, 84]. Under physiological conditions, these synchronized anabolic and resorptive actions of PTH contribute to the maintenance of skeletal balance, which can be markedly disturbed in hyperparathyroidism.

Effects of PTH on the Kidney

In order to maintain Ca homeostasis, PTH enhances fractional absorption of Ca in the thick ascending loop of Henle and in the distal tubule [85, 86]. PTH also enhances phosphate secretion by inhibiting phosphate reabsorption in the proximal as well as the distal tubules [87 – 90]. During hypocalcemia, this phosphaturic effect of PTH facilitates the disposal of the large phosphate load that is invariably coupled to Ca mobilization from bone.

Another important renal action of PTH is its influence on the production of $1,25(OH)_2D$, the active metabolite of vitamin D. As discussed above, PTH directly activates 25(OH)D-1α-hydroxylase found in proximal tubular cells leading to an increase in $1,25(OH)_2D$ production [67]. Finally, PTH also inhibits proximal bicarbonate reabsorption [88]. This effect is usually minor at physi-

ological concentrations of the hormone or is overridden by other homeostatic mechanisms. However, it is not unusual to see systemic acidosis in hyperparathyroidism secondary to urinary bicarbonate losses [44].

Other Effects of PTH

PTH administration leads to an increase in intestinal Ca absorption, an effect related to the increase in vitamin D production. In the liver, PTH undergoes degradation and enhances gluconeogenesis. Recently, Tian et al. observed the presence of PTH receptor mRNA in many tissues other than the kidney [90], including the liver, heart, brain, testis, spleen, lung and skeletal muscle. The role of PTH in these organs is not yet entirely clear. Langub et al. (submitted) demonstrated PTH/PTHrP receptor message in human osteoblasts, ostecytes, and osteoclasts.

Vitamin D

Vitamin D molecules are fat-soluble steroids known to have a protective effect against rickets [91]. It is only in recent years that modern molecular techniques have uncovered remarkable findings that have substantially augmented the role of these hormones. It is now recognized that the most biologically active vitamin D metabolite, calcitriol ($1,25(OH)_2D_3$) binds to a cytoplasmic vitamin D receptor (VDR). The vitamin D-VDR complex subsequently binds to nuclear DNA and alters a variety of transcriptional genes [92]. VDR have been found not only in the conventional target organs for vitamin D such as the intestine, the kidney and bone; but also in a number of diverse tissues: parathyroid glands, pituitary gland, ovaries, skin, hair follicles, stomach, pancreas, thymus, breast, peripheral leukocytes, cardiac and skeletal muscles, and tumor cell lines, among others [92 – 98]. The physiological and clinical implications of these newly discovered functions of vitamin D are exciting and hold tremendous potential.

In humans, there are 2 major sources for vitamin D. One is through the conversion of 7-dehydrocholesterol to cholecalciferol (vitamin D_3) by the effect of sunlight on the skin. The other is through the intestinal absorption of both vitamin D_3 from animal sources and ergocalciferol (vitamin D_2) synthetically produced by ultraviolet irradiation of plants or fungal ergosterol. Since sun exposure can vary widely and few food products contain vitamin D, many countries throughout the world now employ dietary vitamin D supplementation. Once vitamin D (D refers to D_2 and D_3) reaches the circulation from the skin or via the lymphatic thoracic duct, it binds to an α2-protein, vitamin D-binding protein (DBP), which transports the vitamin primarily to the liver and body fat pools [99]. Adipose tissue and the large proportion of the unbound DBP (> 95% of its binding capacity) provide a large pool for vitamin D that protects against excess vitamin D intake or skin production [100, 101]. In the liver, vitamin D is hydroxylized, by the enzyme 25-hydroxylase, to 25-hydroxyvitamin D (25-(OH)D). This is the most abundant form of vitamin D [102, 103]. It is 2 – 5 times more active than vitamin D itself [104]. The normal plasma concentration of 25-(OH)D is 10 – 40 ng/mL and its half-life is estimated to be approximately 15 days. In contrast, parent vitamin D has a normal plasma level of 1 – 2 ng/mL and its half-life approaches 30 days.

To exert its full range of biological activities, 25-(OH)D requires further metabolism in the kidney [105] by 25-(OH)D-1α-hydroxylase, a tightly regulated enzyme located mainly in the proximal tubules. This enzyme

converts 25-(OH)D to 1,25-$(OH)_2$D [106, 107] which is approximately 10 times more potent than its parent vitamin D [104]. Normal plasma concentration of calcitriol is 15 – 60 pg/mL and its half-life is only 5 hours [44]. 1α-hydroxylase enzyme is regulated by a variety of factors that maintain a highly controlled calcitriol production. Hypocalcemia, with the resultant increase in PTH plasma levels, enhances calcitriol production [108, 109] in order to correct the Ca deficit. In vitro, low Pi is a direct stimulus to 1α-hydroxylase [110], and in humans hypophosphatemia stimulates calcitriol production [111]. Vitamin D monitors its own production. In states of vitamin D deficiency, there is a marked increase in 1α-hydroxylase activity [112] while in states of calcitriol excess 1α-hydroxylase is inhibited [93]. When Ca demands are increased, for example during pregnancy, lactation, or skeletal growth, there is an enhancement of calcitriol production probably through the direct or indirect effect of estrogen, prolactin, or growth hormone [105, 113]. It is known that the kidney is the main source of 25(OH)D-1α-hydroxylation. However, other organs such as the placenta or granulomatous tissues may contribute to 1,25-$(OH)_2$D production [105]. Furthermore, 1,25-$(OH)_2$D is synthesized and utilized locally at the bone cellular level [114 – 116].

In the kidney, 25-(OH)D can also be metabolized by 24-hydroxylase, which results in 24,25-$(OH)_2$D, an inactive metabolite [117]. This metabolite is the most abundant dihydroxyvitamin D in the serum (100 times the concentration of calcitriol) [44]. Its production is activated by calcitriol [117, 118]. Therefore, excess calcitriol leads to inhibition of 1α-hydroxylase in order to reduce calcitriol production and to prevent hypercalcemia; and activation of 24-hydroxylase in order to enhance 25-(OH)D conversion to an inactive metabolite.

Actions of Vitamin D

An important function of vitamin D is to enhance Ca and Pi absorption in the gut [93, 119]. The exact mechanism by which vitamin D increases Ca absorption is not yet well known. It could involve the production of several intestinal proteins that may serve as Ca carriers across the plasma membrane, through the cytoplasm of intestinal cells, and across the basolateral membrane [93, 105]. In mammals, vitamin D enhances the production of a calcium-binding protein (CaBP), calbindin D9k, which contains 2 domains that bind Ca with high affinity [44]. There is a close association between the appearance of this protein and the induction of Ca absorption [93], which indicates its possible role as a Ca carrier. Calbindin D9k may also play a role as an intracellular Ca buffer [120]. Vitamin D also stimulates phosphate absorption [93]. No carrier for phosphate is identified, and the exact mechanism by which vitamin D enhances phosphate transport is yet to be clarified [93].

Effects of Vitamin D on Bone

It is well known that vitamin D deficiency leads to rickets or osteomalacia [93]. Therefore, the role of vitamin D in bone mineralization has been suspected. Evidence from rat studies suggests that vitamin D indirectly affects mineralization through maintaining normal serum Ca and Pi levels [93, 121]. However, we have demonstrated in dogs, which have skeletons more akin to humans, that vitamin D is required, in addition to normal Ca and Pi concentrations, for adequate mineralization [122]. In vitro, vitamin D has a direct resorptive effect on bone [123]. It also stimulates Ca mobilization from the bone fluid compartment to the extracellular space [93]. In vivo, however, the direct resorptive effect of vitamin D is shown only in hypocalcemic conditions or states of vitamin D deficiency.

There is also significant evidence to suggest that the effect of PTH on bone is facilitated by vitamin D [124, 125].

Renal Effects of Vitamin D

The exact role of vitamin D in renal handling of Ca and Pi remains unclear. In part this is due to its interaction with other hormones, particularly PTH, that might lead to synergistic or antagonistic effects [126]. Vitamin D increases tubular phosphate reabsorption, an effect that can be attributed to PTH suppression [127]. The effect of vitamin D on renal Ca handling is also suggestive of a tubular Ca reabsorptive effect [128]. As indicated above, 1,25-$(OH)_2D$ inhibits renal 1α-hydroxylase and activates 24-hydroxylase [106, 107, 117].

Other Effects of Vitamin D

Recently, diverse effects of vitamin D have been described. As discussed above, vitamin D directly inhibits PTH production, PTH secretion, and parathyroid cell proliferation [63 – 65]. Vitamin D also inhibits the proliferation of cultured melanoma cells, fibroblasts, and keratinocytes [129 – 131]. There is evidence to suggest that vitamin D enhances cell differentiation and inhibits cell growth [95, 132, 133]. Finally, by affecting lymphocytes, vitamin D may play a role as an immunoregulatory hormone [134, 135]. These effects of vitamin D are the result of its role in regulating a large number of genes upwards or downwards.

Calcitonin

Calcitonin, a 32-amino acid peptide, is secreted by the parafollicular cells of the thyroid gland. Its main action is to inhibit osteoclast resorption activity via a cyclic AMP (cAMP)-mediated mechanism [136]. The antiresorptive effect is quite rapid and evident at the physiological concentration of the hormone [136]. The calcitonin hypocalcemic effect is probably related to its antiresorptive activity [44] and usually is not evident unless a state of high bone turnover is present [137]. In other words, calcitonin does not induce hypocalcemia in normal subjects [138]. Many factors affect calcitonin secretion, the most important of which is hypercalcemia [139]. Other factors include gastrin, cholecystokinin, and probably estrogen and calcitriol [137]. Calcitonin gene-related peptide (CGRP) is another peptide encoded by the calcitonin gene. Like calcitonin, this hormone has similar action on osteoclasts, but it might also have a PTH-like effect on osteoblasts [137]. The physiological role of this peptide in bone remodeling may be related more to its local abundance at the bone level rather than as a circulating hormone [137].

Other Circulating Factors

Other hormonal factors such as thyroid hormone, estrogen, testosterone, and glucocorticoid have an impact on bone metabolism [140]. Also, vitamins A, C, and K all play a role in maintaining normal bone metabolism. Hypovitaminosis A may lead to inhibition of bone resorption and enhancement of bone formation [141]. Vitamin C is required for the hydroxylation of proline and lysine, an essential step in the synthesis of bone matrix collagen [142]. Finally, vitamin K is required for the synthesis of many proteins including osteocalcin, a protein that may play a role in bone mineralization [143] and Ca homeostasis [144].

Local Factors

It is increasingly apparent that the highly coordinated process of bone remodeling depends on the production of local substances [37]. PTH stimulates osteoblasts to produce local coupling factors involved in the activation of osteoclasts [81]. It is also possible that the timing of the end of resorption and the initiation of bone formation in the remodeling cycle are controlled by local signals. A number of growth factors are involved in the local control of bone remodeling. These factors are synthesized by skeletal cells or by cells from adjacent tissues (cartilage, marrow cells) [145]. In vitro, insulin-like growth factors (IGF-I and IGF-II) were shown to stimulate bone cell proliferation and collagen synthesis. In vivo, transforming growth factor β (TGFβ) was shown to enhance bone formation [146, 147]. TGFβ also stimulates bone resorption, probably by enhancing prostaglandin production [148]. Interleukin-1 (IL-1) and tumor necrosis factor (TNF) are stimulators of bone resorption [149, 150]. Recently, it was shown that IL-6 and IL-11 production can be regulated by PTH [151 – 153]. This adds further evidence of the importance of the interplay between systemic and local factors.

Pathogenesis of Renal Osteodystrophy

With the progressive loss of excretory kidney function, abnormalities in divalent ions and secondary hyperparathyroidism typically develop early on.

Factors Implicated in the Development of Secondary Hyperparathyroidism

In advanced renal failure a variety of factors have been identified as direct stimulators of PTH secretion. They include hypocalcemia, low circulating calcitriol (the active vitamin D metabolite), and, more recently, hyperphosphatemia. However, most patients with mild chronic renal failure exhibit increased serum PTH levels without alterations in serum levels of Ca, Pi, and calcitriol.

Early Renal Failure

The early sequence of events is still not fully elucidated. However, the early stages of renal failure are marked by some signs of end-organ resistance to vitamin D, such as mild decrease in intestinal Ca absorption and altered calciuric response to oral (PO) supplementation of calcitriol. Calcitriol exerts its action by binding to VDR, which interact with specific sequences of nuclear DNA, the vitamin D response elements (VDRE) that control genomic synthesis of many proteins, including PTH. In early renal failure, the binding of the hormone-VDR complex to VDRE has been found to be reduced, which could lead to less suppressive effects of physiologic blood levels of calcitriol on PTH synthesis, and therefore PTH overproduction [154]. The exact mechanisms implicated in the impaired binding of hormone-VDR complex to VDRE are not fully elucidated. In experimental rats, alterations in the VDR heterodimer partner, retinoid X receptor (RXR), have been observed; however, this has not been proven in humans. Other alterations in accessory nuclear factors, abnormal phosphorylation, and conformation of VDR or chemical alteration

of the DNA binding domain may be involved in the impaired VDR response to calcitriol.

Advanced Renal Failure

With more advanced nephron loss, phosphate load of the remaining functioning nephrons progressively increases. This results in inhibition of C_1-α-hydroxylase, the enzyme responsible for the conversion of 25-hydroxy vitamin D to its active metabolite, 1,25-dihydroxy vitamin D (calcitriol). Calcitriol deficiency in turn further decreases intestinal Ca absorption, resulting in hypocalcemia. Calcitriol deficiency in advanced renal failure is associated with a decreased number of VDRs, in particular in parathyroid glands. Since calcitriol has been shown to suppress the expression of pre-pro-PTH mRNA, lower circulating calcitriol levels together with a low number of VDR in patients with ESRD result in stimulation of both PTH synthesis and secretion. Low blood Ca^{2+} levels rapidly stimulate PTH secretion, whereas high Ca concentrations suppress it. The relationship between Ca^{2+} and PTH follows a sigmoidal pattern. The action of Ca on parathyroid gland cells is associated with modulation of intracellular cyclic AMP. The short-term stimulation induced by low Ca is due to release of stored preformed hormone and an increase in the number of cells that secrete PTH. More prolonged hypocalcemia induces changes in intracellular PTH degradation with reutilization of degraded hormone and mobilization of secondary storage pool. Within days or weeks of the onset of hypocalcemia, pre-pro-PTH mRNA expression is stimulated. This effect is exerted through a recently described negative calcium-response element located in the upstream flanking region of the PTH gene. Ca exerts its effects on parathyroid gland cells through a recently isolated G-protein-coupled calcium-sensing receptor located on the cell membrane. The expression of the Ca receptor has been shown to be suppressed by calcitriol deficiency and stimulated by calcitriol administration, suggesting an additional regulatory mechanism of the active vitamin D metabolite on PTH production. The decreased number of calcium-sensing receptors with low circulating calcitriol may, at least in part, explain the relative insensitivity of parathyroid gland cells to Ca in patients on dialysis (higher set point).

When GFR reaches levels of < 25% of normal, serum Pi levels rise. At this level of reduced renal function, the ability of the remaining nephrons to increase phosphate excretion is exhausted. Increased serum Pi levels further decrease serum Ca through physicochemical binding and suppress the C-1α-hydroxylase activity, resulting in further lowering of circulating levels of calcitriol. Moreover, a direct stimulatory effect of Pi on parathyroid gland cells, independent of Ca and calcitriol, has been recently observed in ESRD patients. The mechanism of the direct action of Pi on PTH secretion is not fully elucidated.

All the mechanisms described above result in increased production of PTH and increased parathyroid gland mass. The size of the parathyroid glands progressively increases with time in dialyzed patients and parallels serum PTH levels. This increase in size is mainly due to cellular diffuse hyperplasia. Patients may also develop monoclonal cell growth resulting in the formation of tumor-like nodules that have less or no VDR and calcium-sensing receptors and that promote parathyroid gland resistance to calcitriol and Ca.

Factors Affecting PTH Production and Its Effects on Bone

Other systemic factors such as α-adrenergic agonists, dopamine, prostaglandin E, secretin, and phosphodiesterase inhibitors that alter the cyclic AMP content of parathyroid cells may increase PTH secretion. Recently, the inflammatory cytokine IL-8 has been found to stimulate PTH secretion. The effect of magnesium in regulating PTH secretion is similar to that of Ca but not as potent. Moreover, there is reduced peripheral degradation of PTH in uremia, and numerous PTH fragments circulate, thus prolonging the effects of PTH on target organs.

Accumulation of aluminum in bone and other organs such as the parathyroid glands may occur in patients on dialysis or before initiation of dialysis. Aluminum accumulation in the parathyroid glands results in decreased secretion of parathyroid hormone and suppression of bone turnover. In addition, aluminum inhibits renal and intestinal C1-α hydroxylase activity and may thus further contribute to reduced levels of calcitriol. Possible sources of aluminum include high concentrations in water used for dialysis, prescription of aluminum-containing phosphate binders, and aluminum in drinking water, infant formula, and other liquids or solid food.

Bone is an important buffer for excess acid production in patients with ESRD. Metabolic acidosis has been shown to stimulate bone resorption and to suppress bone formation, resulting in negative bone balance.

Patients with ESRD are in a hypogonadal state, and some of them are treated with glucocorticoids, which have an impact on bone metabolism. Patients on chronic dialysis present with retention of β_2-microglobulin and alterations in cytokines, growth factors, PTH, and VDR that may be involved in the regulation of bone remodeling, thus affecting the histologic pattern of renal osteodystrophy.

Histological Spectrum of ROD

Renal osteodystrophy is not a uniform bone disease. Depending upon the relative contribution of the different pathogenic factors, patients with ESRD will present different histological patterns.

Predominant Hyperparathyroid Bone Disease

Excess parathyroid hormone results in a marked increase in bone turnover. There is an abundance of osteoclasts, osteoblasts, and osteocytes (Figure 1). Disturbed osteoblastic activity results in a disorderly production of collagen, which is deposited not only toward the trabecular surface but also into the marrow cavity, causing peritrabecular and marrow fibrosis. The nonmineralized component of bone, i.e. osteoid, is increased, and the normal 3-dimensional architecture of osteoid is frequently lost. Osteoid seams no longer exhibit their usual birefringence under polarized light. Instead, a disorderly arrangement of woven osteoid and woven bone with a typical criss-cross pattern under polarized light is seen. The mineral apposition rate and number of actively mineralizing sites are increased, as documented under fluorescent light after administration of time-spaced tetracycline markers.

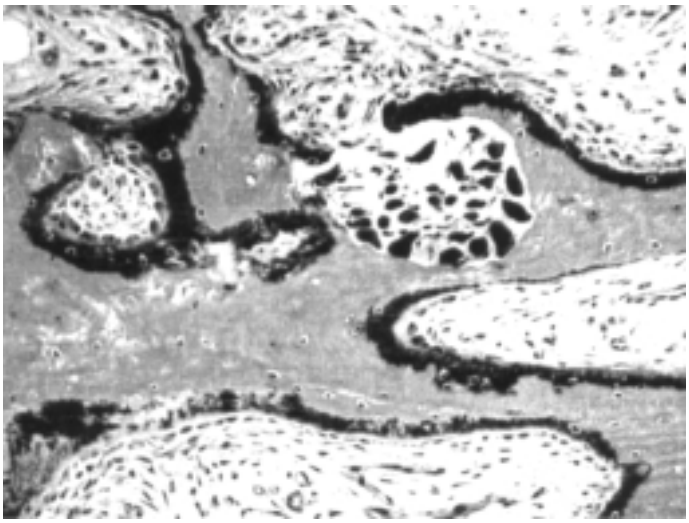

Figure 1. Predominant hyperparathyroid bone disease. High fraction of trabecular surface covered by osteoid seams; high number of osteoblasts and osteoclasts; deep resorption lacuna; marrow fibrosis; undecalcified; 3-µm-thick section of human iliac bone. Modified Masson-Goldner stain. Original magnification × 125.

Low-turnover Bone Disease

Low-turnover uremic osteodystrophy represents the other end of the spectrum of renal osteodystrophy. The histologic hallmark of this group is a profound decrease in bone turnover, i.e. a low number of active remodeling sites resulting in suppressed bone formation and bone resorption. The majority of the trabecular bone is covered by lining cells, and there are few osteoclasts and osteoblasts. Bone structure is predominantly lamellar. The extent of mineralizing surfaces is markedly reduced. Usually only a few thin single labels of tetracycline are observed. Two histologic subgroups within this type of renal osteodystrophy can be identified, depending on the sequence of events leading to a decline in the number and/or activity of the osteoblasts: low-turnover osteomalacia and adynamic bone disease.

Low-turnover osteomalacia is characterized by an accumulation of unmineralized matrix in which a diminution in mineralization precedes or is more pronounced than the inhibition of collagen deposition. Unmineralized bone represents a sizable fraction of trabecular bone volume. The increased lamellar osteoid volume is due to the presence of wide osteoid seams that cover a large portion of the trabecular surface (Figure 2). The occasional presence of woven bone buried within the trabecules indicates past high bone turnover. When osteoclasts are present, they are usually seen within trabecular bone, or at the small fraction of trabecular surface left without osteoid coating.

With adynamic uremic bone disease, the reduction in mineralization is coupled with a concomitant and parallel decrease in bone formation. It is characterized by few osteoid seams and few bone cells (Figure 3).

Mixed Uremic Osteodystrophy

Mixed uremic osteodystrophy is caused primarily by hyperparathyroidism and defective mineralization with or without increased bone

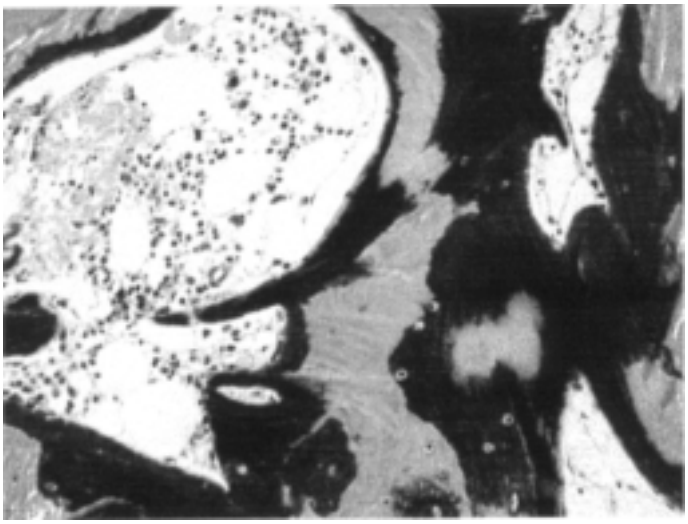

Figure 2. Low-turnover osteomalacia. Dramatically increased fraction of trabecular surface exhibiting osteoid seams; osteoid seam thickness increased; undecalcified; 3-µm-thick section of human iliac bone. Modified Masson-Goldner stain. Original magnification × 125.

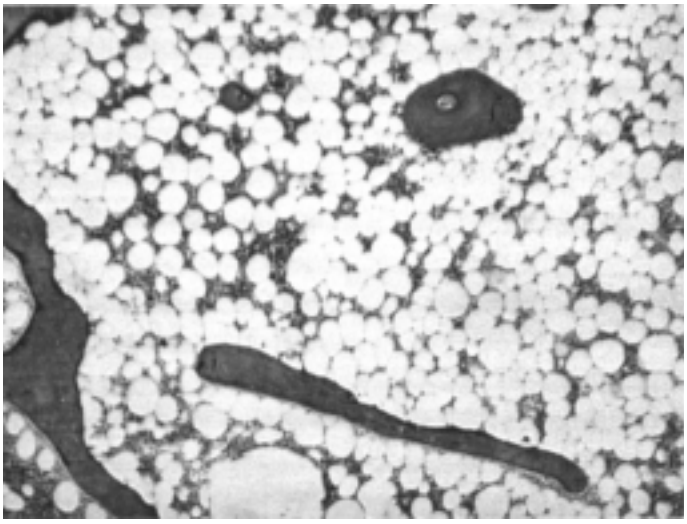

Figure 3. Adynamic bone disease. No accumulation of osteoid; absence of active resorption; undecalcified; 3 µm thick section of human iliac bone (modified Masson-Goldner stain; x 31).

formation. These features may coexist in varying degrees in different patients. Increased numbers of heterogeneous remodeling sites can be seen (Figure 4). The number of osteoclasts is usually increased. Because active foci with numerous cells, woven osteoid seams, and peritrabecular fibrosis coexist with adjacent lamellar sites with a more reduced activity, greater production of lamellar or woven osteoid causes the accumulation of osteoid with normal or increased thickness of osteoid seams. While active mineralizing surfaces increase in woven bone with higher mineralization rate and diffuse labeling, mineralization surfaces may be reduced in lamellar bone with a decreased mineral apposition rate.

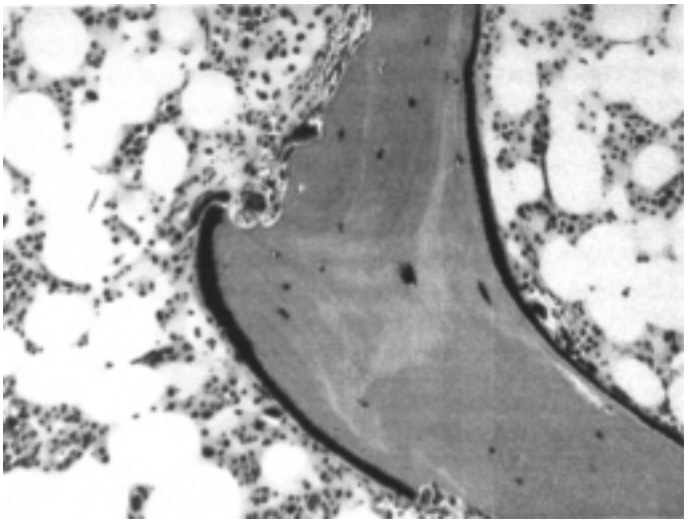

Figure 4. Mixed uremic osteodystrophy. Resorption lacunae with osteoclasts and peritrabecular fibrosis; increase in osteoid volume and surface; undecalcifed; 3-µm-thick section of human iliac bone. Modified Masson-Goldner stain. Original magnification × 200.

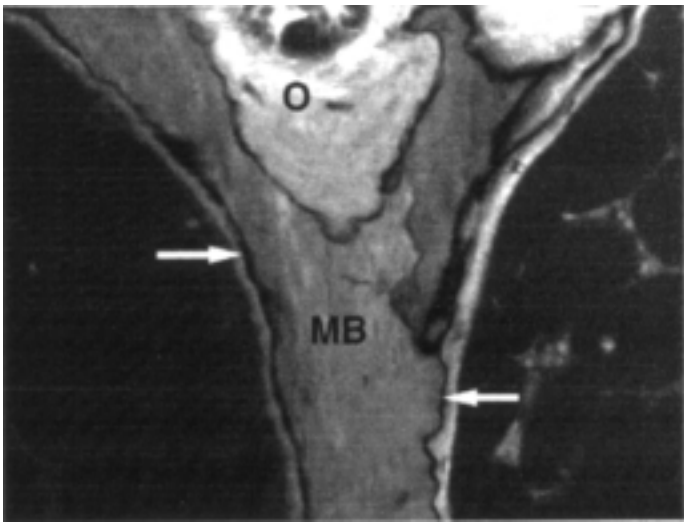

Figure 5. Aluminum deposits in bone (white arrows). Stainable bone aluminum at the osteoid (O)-mineralized bone (MB) interface, i.e. the mineralization front;. Undecalcified, 3 µm thick section of human iliac bone (aurin-tricarboxylic acid stain; × 200).

Associated Features

Bone Aluminum Accumulation

Aluminum accumulates in bone at the mineralization front (Figure 5), at the cement lines, or diffusely. The extent of stainable aluminum at the mineralization front correlates best with histologic abnormalities in mineralization. Aluminum deposition is most severe in cases of low-turnover osteomalacia. However, it can be observed in all histologic forms of renal osteodystrophy. In patients who develop increased aluminum burden, bone mineralization and bone turnover progressively decrease. These abnormalities are reversed with removal of the aluminum.

Osteoporosis and Osteosclerosis

With progressive loss of renal function, there is an increase in cancellous bone volume accompanied by a loss in cortical bone. In patients on chronic dialysis, there might be loss or gain in bone volume depending on bone balance. In case of negative bone balance, bone loss occurs in cortical and cancellous bone and is more rapid when bone turnover is high. When the bone balance is positive, osteosclerosis may be observed when osteoblasts are active in forming new bone exceeding bone resorption. When bone turnover is low, however, positive bone balance is often associated with hypercalcemia and possibly extraosseous calcifications.

β_2-Microglobulin-related Bone Disease

β_2-microglobulin (β_2-MG) amyloidosis represents osteoarthropathy and not a direct abnormality of bone remodeling in uremia. However, it is appropriate to consider it as an associated feature of ROD for 2 reasons: its clinical presentation can mimic other forms of ROD, and growing evidence suggests a direct or indirect effect of β2-microglobulin on bone metabolism.

β_2-MG is a polypeptide with a molecular weight of 11,800 daltons found on the surface of nucleated cells as part of the human leukocyte antigen (HLA) class I antigen complex [155 – 157]. Its concentration invariably increases in patients with renal failure since the kidney plays a major role in its catabolism [156, 158, 159]. Furthermore, β_2-MG production is influenced by various cytokines [160 – 162], many of which are increased in patients with ESRD [163]. The mechanism(s) that lead to the formation of β_2-MG amyloid fibrils and their predilection to be deposited in periarticular tissues are currently under study [164 – 166]. The type of HD membranes may affect β_2-MG concentrations [167]; however, β_2-MG amyloidosis is not limited to HD patients. It has been observed in continuous ambulatory peritoneal dialysis (CAPD) and CRF patients [168, 169].

In rats, Canalis et al. have identified a bone-derived growth factor as β_2-MG [170]. It is suspected that β_2-MG enhances bone growth by modulating other known growth factors such as insulin-like growth factor I [145, 171]. Similarly, β_2-MG may facilitate bone resorption by increasing the production of tumor necrosis factor or interleukin-1 [172 – 174]. Therefore, it is possible that the increased levels of β_2-MG in ESRD patients may interfere with normal bone metabolism and contribute to the spectrum of renal osteodystrophy independently from the clinical syndrome of β_2-MG amyloidosis.

Clinical Manifestations of ROD

Patients with mild to moderate renal insufficiency are rarely symptomatic. Symptoms appear in patients with advanced renal failure. However, clinical manifestations are preceded by an abnormal biochemical profile that should alert the physician and prompt steps to prevent more severe complications. When symptoms occur, they are usually insidious, subtle, nonspecific, and slowly progressive. Patients with ESRD are prone to develop a variety of symptoms related to alterations in bone and mineral metabolism.

Bone Pain, Fractures, and Skeletal Deformities

Bone pain is usually vague, ill defined, and deep-seated. It may be diffuse or localized in the lower back, hips, knees, or legs. Weight bearing and changes in position commonly aggravate it. Bone pain may progress slowly to the degree that patients are completely incapacitated. Bone pain in patients with ESRD usually does not exhibit physical signs; however, local tenderness may be apparent with pressure. Occasionally, pain can occur suddenly at one joint of the lower extremities mimicking acute arthritis or periarthritis not relieved by heat or massage. A sharp chest pain may indicate rib fracture. Spontaneous fractures or fractures after minimal trauma may also occur in vertebrae (crush fractures) and in tubular bones.

Bone pain and bone fractures can be observed in all patients with ESRD, independently of the underlying histologic bone disease, especially when osteoporosis is present. However, low-turnover osteomalacia and aluminum-related bone disease are associated with the most severe bone pain and the highest incidence of fractures and incapacity.

Skeletal deformities can be observed in children and adults. Most children with ESRD present with growth retardation and may develop bone deformities due to vitamin D deficiency (rickets) or secondary hyperparathyroidism. In rickets, there is bowing of the long bones, especially tibiae and femora, with typical genu valgum, which becomes more severe with adolescence. Long-standing secondary hyperparathyroidism in children may be responsible for slipped epiphysis due to impaired transformation of growth cartilage into regular metaphyseal spongiosa. This complication most commonly affects the hips, becomes obvious in preadolescence, and causes limping but is usually painless. When radius and ulna are involved, ulnar deviation of the hands and local swelling may occur. In adults, skeletal deformities can be observed in cases of severe osteomalacia or osteoporosis and include lumbar scoliosis, thoracic kyphosis, and recurrent rib fractures.

Myopathy

Proximal muscle weakness is fairly common in dialysis patients, particularly in those with aluminum toxicity, severe hyperparathyroidism, or osteomalacia. Its onset is usually gradual and mainly affects the lower extremities. Proximal myopathy is manifested by difficulty in rising out of a chair or climbing stairs. Patients may have a characteristic waddling gait.

Pruritus

Itching affects 40 – 90% of patients with ESRD. Pruritus can occur before institution of dialysis and can disappear after regular dialytic therapy. However, symptoms more often begin about 6 months after the start of dialysis and persist thereafter. Pruritus may be localized and mild or generalized and severe, preventing sleep and interfering with the patients normal activities.

The mechanisms underlying pruritus in ESRD patients are poorly understood. Several possible factors have been implicated (alone or in combination) such as secondary hyperparathyroidism, hypercalcemia, increased calcium-phosphorus (Ca-Pi) product, but also dry skin (xenosis), intradermic microprecipitation of divalent ions, peripheral neuropathy, allergic reactions, hypersensitivity, histamine, proliferation of skin mast cells, hypervitaminosis A, iron deficiency, and abnormal fatty acid metabolism.

Soft Tissue Calcifications, Tumoral Calcinosis, and Calciphylaxis

Asymptomatic vascular calcifications are common in patients with ESRD. Soft tissue calcifications may occur in the eyes presenting as band keratopathy in the sclerae or inducing an inflammatory response known as the "red eye syndrome" in the conjunctiva. These types of calcifications are usually associated with hyperparathyroidism or increased Ca-Pi product. Ca deposits are also found in the lungs, leading to restrictive lung disease. Deposits in the myocardium might cause arrhythmias, annular calcifications, or myocardial dysfunction. Most soft tissue calcifications are attributed to secondary hyperparathyroidism or to the increased Ca-Pi product associated with it. However, they have also been described in patients with adynamic bone disease. This could be explained by increased Ca and/or phosphate release from bone in patients with severe hyperparathyroidism and inability to maintain normal mineral accretion in patients with adynamic bone disease.

Tumoral calcinosis is a form of soft tissue calcification that usually involves the periarticular tissues. Ca deposits may grow to enormous sizes and interfere with the function of adjacent joints and organs. While this type of calcification is usually associated with high Ca-Pi product, its exact pathogenesis is poorly understood. It may also be associated with certain ill-defined intrinsic factors. Similar to soft tissue calcifications, it is observed with severe hyperparathyroidism and low-turnover bone disease.

The syndrome of calciphylaxis is characterized by vascular calcifications of the tunica media. These induce painful violaceous skin lesions that progress to ischemic necrosis. This syndrome is associated with serious complications and often death. Calciphylaxis has been associated with high serum Ca-Pi product and severe secondary hyperparathyroidism. However, it can also be seen in patients with normal or mildly elevated serum Pi or PTH levels. The pathogenesis of calciphylaxis is probably multifactorial because hyperparathyroidism, high Ca-Pi product, steroid therapy, vitamin D therapy, iron overload, aluminum toxicity, and protein C deficiency have all been implicated.

Dialysis Dementia

Clinically, dialysis dementia represents progressive neurological abnormalities that include dysarthria, dysphagia, amnesia, apraxia, mutism, myoclonic jerks, facial grimacing, seizures, and ultimately severe dementia and death. This condition is usually associated with severe aluminum accumulation.

Diagnosis

The only unequivocal tool for the exact diagnosis of renal osteodystrophy is bone biopsy for mineralized bone histology after tetracycline double labeling and aluminum staining. It determines, on the same bone sample, the precise level of bone formation, mineralization, bone resorption, bone turnover, and the extent of bone aluminum deposition, if present. The results serve as a basis for appropriate use of tailored therapeutic regimens.

In the absence of bone biopsy, the physician needs to estimate the level of bone turnover, presence of osteomalacia, and the possibility of bone aluminum toxicity. Abnormalities in serum Ca, Pi, and alkaline phosphatase levels indicate severe renal osteodystrophy but are

useless when used alone to indicate bone turnover or osteomalacia. Hypercalcemia may be observed in severe hyperparathyroidism or adynamic bone disease, especially with vitamin D therapy. Hyperphosphatemia indicates noncompliance with phosphate binders and/or severe hyperparathyroidism because of increased release of Pi from bone. High serum levels of alkaline phosphatase are usually seen in both osteomalacia and predominant hyperparathyroidism.

Skeletal X-ray abnormalities are seen when the disease is advanced [175]. They include erosive cortical defects in the skull ("pepper pot skull"), acroosteolysis of the clavicula, and erosion of the terminal finger phalanges. A rugger jersey appearance of the spine, a ground glass appearance of the skull, ribs, pelvis, and metaphysis of tubular bones reflect advanced cancellous changes. In severe hyperparathyroid bone disease, pseudocysts or brown tumors may be observed. However, signs of increased bone resorption may be seen on x-rays reflecting past resorbing activity, which may have been succeeded by accumulation of osteoid. Since osteoid is radiolucent, the superimposed osteomalacia will be missed by X-ray examination. Looser zones that are straight bands of radiolucency abutting onto the cortex and running perpendicular to the long axis of bone are of relatively low sensitivity and low specificity for the diagnosis of osteomalacia.

Serum PTH levels are better indicators of bone turnover, especially when measured with the immunoradiometric assay that detects only the intact hormone. However, a careful assessment of the predictive value of serum PTH levels for bone turnover shows that all patients with serum PTH levels within or below the normal range (< 65 pg/mL) have low bone turnover, and that values of serum PTH levels > 450 pg/mL are 100% and 95.5% specific for high bone turnover in patients on HD and PD, respectively [176]. For the majority of dialyzed patients, i.e. those with serum PTH levels between 65 and 450 pg/mL, bone turnover cannot be predicted accurately [176]. In addition to serum PTH values, certain risk factors for low bone turnover have been isolated such as PD, diabetes (DM), advanced age, high Ca content in dialysate, high doses of phosphate binders, aggressive vitamin D therapy, or previous parathyroidectomy. However, in individual patients, discrepancies between risk factors, PTH levels, and bone turnover are frequent, and this calls for bone biopsy.

Aluminum accumulation may be seen at any level of bone turnover or serum PTH levels. Although correlations exist between random serum aluminum levels and the extent of stainable aluminum in bone, no threshold value allows a clear-cut distinction between patients with and patients without aluminum-related bone disease. Deferoxamine (DFO) infusion test is advocated to improve the sensitivity of random serum aluminum levels. An increase in serum aluminum levels > 200 µg/L 48 hours after a standardized infusion constitutes a positive result. This test does improve the sensitivity of predicting aluminum-related bone disease, but specificity is greatly reduced. Both a positive DFO test and a PTH level < 200 pg/mL will make the diagnosis of aluminum-related bone disease with almost absolute certainty. However, the sensitivity is again greatly reduced and many patients will have false negative results.

Management of Dialysis Patients with ROD

Therapeutic intervention should begin before the patient develops far-advanced bone disease, that is, not later than at the time of

institution of dialysis. Secondary hyperparathyroidism can be prevented by avoiding deviations of serum Pi and Ca levels from normal. However, one cannot be dogmatic in the management of patients with ROD, and therapeutic approaches must be tailored to meet each patients individual needs.

Control of Serum Phosphorus

Hyperphosphatemia plays a major role in the induction and maintenance of secondary hyperparathyroidism. It also contributes significantly to the development of soft tissue calcifications. Therefore, controlling serum Pi in dialysis patients is of great importance and probably constitutes the greatest challenge in the management of ROD.

Role of Dialysis

Due to the compartmentalization and slow efflux of Pi from intracellular space, all dialytic methods are inefficient in Pi removal. It is estimated that, on the average, only 3 g of Pi/week can be removed by dialysis. Therefore, in patients with ESRD one must rely on strict dietary Pi restriction and the use of phosphate binders in order to achieve appropriate phosphate control. However, it has been shown recently that nocturnal dialysis 6 times a week was efficient in controlling Pi levels and prompted a reduction in intake of phosphate binders [177]

Dietary Phosphorus Restriction

Phosphate is present in most protein-containing food products. Therefore, severe Pi restriction cannot be implemented if adequate protein intake is to be maintained. With the current recommendations of dietary protein intake in dialysis patients of 1 g/kg/day [178], it is estimated that patients will receive a minimum of 1 g Pi/day. Therefore, phosphate binders have to be used frequently in order to prevent Pi retention in anuric patients.

Phosphate Binders

Phosphate binders are most effective when given with meals and in proportion to the size of the meal [179]. Patients with persistent hyperphosphatemia should have detailed dietary counseling to insure compliance with the diet and prescription of phosphate binders.

Ca salts are currently the most widely used phosphate binders. Calcium acetate appears to be more efficient in binding Pi than calcium bicarbonate [180, 181]. Therefore, lower doses of elemental Ca can be used with calcium acetate to achieve a similar degree of Pi control [182, 183]. However, in short-term studies, these findings did not translate to fewer incidences of hypercalcemia in patients treated with calcium acetate [182, 183]. Calcium citrate bears the risk of increasing aluminum absorption [184] and thus should be avoided.

Aluminum-containing phosphate binders are now rarely used by most nephrologists. Studies indicate that the aluminum in these products is absorbed and can accumulate in dialysis patients [185 – 187]. However, aluminum-containing phosphate binders may still be used, temporarily and rarely, only in patients with severe and uncontrollable hyperphosphatemia since in these patients high doses of Ca salts may precipitate soft tissue calcifications. Once Pi levels are reduced, aluminum products should be gradually replaced by Ca salts.

In some patients, high doses of Ca salts may lead to hypercalcemia without optimal Pi control. In these instances, one must again ascertain dietary compliance and that patients are taking the phosphate binders with meals. Lowering dialysate Ca concentration helps control hypercalcemia and allows the use of

higher doses of Ca salts [188 – 190]. However, one must be sure that patients are compliant with their Ca prescriptions since low calcium dialysate without adequate Ca intake may lead to negative Ca balance [179, 191]. If this strategy fails to control hypercalcemia and correct hyperphosphatemia, judicious use of low doses of aluminum-containing phosphate binders with careful monitoring of serum aluminum might be justified. However, we feel that the continuous use of even low doses of aluminum products will invariably lead to an increase in plasma aluminum levels and result in aluminum accumulation. Some investigators suggest the use of magnesium-containing phosphate binders in conjunction with low dialysate magnesium and careful monitoring of serum magnesium levels [192, 193]. Although in one study, patients showed no adverse effect of magnesium-containing products on bone [194], magnesium is a known inhibitor of bone mineralization. Therefore, long-term effects of magnesium-containing phosphate binders on bone microstructure need further study before their routine use in dialysis patients can be recommended.

There are currently efforts to develop non-calcium and nonaluminum-containing phosphate binders. RenaGel has been recently approved by the Food and Drug Administration (FDA). Long-term effects on control of phosphate and bone histology, however, are not yet available.

In some patients, persistent hyperphosphatemia could be the result of severe hyperparathyroidism with enhanced bone resorption leading to Pi mobilization from bone. These patients need careful control of the underlying secondary hyperparathyroidism and may require parathyroidectomy.

In treating patients with hyperphosphatemia, it is important to avoid hypophosphatemia. Pi serum levels should be maintained at 4.5 – 5.5 mg/dL. The cause of hypophosphatemia in dialysis patients, when present, should be investigated and treated appropriately.

Maintenance of Serum Calcium

Intestinal Ca absorption is reduced in patients with advanced renal failure [195]. Ca supplementation in these patients can restore positive Ca balance and alleviate secondary hyperparathyroidism [118]. Thus, Ca salts in dialysis patients have dual functions: to bind Pi and to provide Ca supplementation. When Ca supplementation is needed, Ca salts should be given between meals to enhance its absorption. Serum Ca levels should be maintained in the mid to upper range of normal to ensure parathyroid gland suppression. The use of high doses of Ca salts in patients with advanced renal failure can lead to hypercalcemia since these patients are unable to compensate for high Ca administration by increasing urinary Ca excretion. In dialysis patients, serum Ca levels can be influenced by manipulating dialysate Ca concentration. This approach may facilitate the use of Ca salts as phosphate binders. However, if the balance between Ca removal during dialysis and oral administration of Ca salts is poorly maintained, the patient risks either transient increases in parathyroid gland activity or extraosseous calcifications [196].

If hypercalcemia persists despite the reduction of oral Ca intake, one must rule out the presence of severe hyperparathyroidism (high bone turnover), aluminum bone accumulation or adynamic bone disease (low bone turnover). It is also important to rule out causes other than the underlying form of ROD such as malignancy, paraproteinemia, immobilization, granulomatous diseases, and other known etiologies of hypercalcemia.

Vitamin D Therapy in Dialysis Patients

Calcitriol

The use of calcitriol to control secondary hyperparathyroidism in dialysis patients is an established practice. However, its use is not without complications and limitations. There are also numerous questions regarding to the optimal time and route of administration.

Many studies have described a beneficial effect of daily oral $1,25(OH)_2D$ on biochemical, radiological and histological signs of hyperparathyroid bone disease [197, 198]. However, hypercalcemia is a rather common side effect of this therapy, requiring temporary cessation of the drug. Slatopolsky et al. found that intravenous (IV) administration of $1,25(OH)_2D$ suppresses PTH levels with decreased incidence of hypercalcemia [199]. Oral intermittent therapy (2 – 3 times/week) has also been shown to be effective in controlling hyperparathyroidism [200 – 204] indicating that intermittent high peak levels of calcitriol in addition to the route of administration are important for PTH suppression.

We observed that the incidence of hypercalcemia was higher in patients receiving PO than IV pulse therapy [205]. On the other hand, hyperphosphatemia and increased Ca-Pi product were the major limiting factors in the efficacy of IV therapy [205]. To minimize these side effects, some investigators advocate the use of low-dose IV calcitriol as a safe and effective therapy in controlling secondary hyperparathyroidism in HD patients [206, 207]. In our experience the therapeutic window of pulse calcitriol therapy is limited, and high doses are frequently needed in order to achieve significant reduction in PTH serum levels [205]. In CAPD patients, both subcutaneous (SC) and intraperitoneal (IP) administration of calcitriol have been described as effective in controlling hyperparathyroidism [208, 209]. However, their advantage over oral administration is not established [210].

The optimal serum PTH levels in dialysis patients have not yet been established. Customarily, nephrologists try to maintain intact PTH levels at 1.5 – 2 times the upper range of normal. It was recently suggested that uremic patients require 2.5 × normal intact PTH to maintain normal bone turnover [211]. We observed that serum levels of intact PTH between 65 – 450 pg/mL are a poor predictor of the underlying bone turnover. Only with levels > 450 pg/mL can one predict with certainty the presence of high bone turnover [212]. Therefore, serum PTH levels should not be aggressively suppressed with PO or IV calcitriol unless evidence of high bone turnover is substantiated by bone biopsies. The role of bone markers, i.e. osteocalcin, alkaline phosphatase, and hydroxyproline in guiding calcitriol therapy needs further study. Similarly, further studies are needed to assess the efficacy and safety of long-term IV vs. pulse PO calcitriol therapy. Currently, there are no controlled studies to evaluate who should get daily or pulse PO therapy for supplementation of a missing hormone vs. suppression of parathyroid gland overactivation.

Other Vitamin D Metabolites

The optimum vitamin D metabolite for maintenance therapy should maintain the cellular differentiating effect of vitamin D with only mild antiproliferative effects. In addition, this metabolite should have a limited effect on intestinal Ca absorption and serum Ca. This metabolite would obtain a balance between the satisfactory suppression of parathyroid gland and adequate bone turnover without hypercalcemia.

Several endogenous and synthetic vitamin D metabolites are available and hold promise for the treatment of secondary hyperparathyroidism [213]. 1α-hydroxyvitamin D (alfa-

calcidol) has been shown to be effective in suppressing PTH in dialysis patients [214, 215] but probably has no advantage over calcitriol. The effect of 24,25$(OH)_2$D alone on secondary hyperparathyroidism is controversial [216]. However, a recent report advocates its use in combination with calcitriol [217]. This combination may effectively reduce bone resorption without affecting bone formation. 22-oxa-1,25$(OH)_2$D (OCT) has gained recent attention as a potent suppressor of PTH secretion with relatively less effect on intestinal Ca absorption [218, 219]. In nephrectomized dogs, OCT was efficient in preventing the increase in serum PTH levels. However, some episodes of hypercalcemia were observed [220]. Interestingly, however, OCT did not suppress bone turnover and thus appears unlikely to induce adynamic bone disease [220]. 19-Nor-1-alpha-25-dihydroxyvitamin D_2 (Zemplar) has been recently introduced as a less hypercalcemic vitamin D analog for control of secondary hyperparathyroidism [221]. However, its effects on bone are not known at this time.

Parathyroidectomy

Surgical parathyroidectomy is currently reserved for patients with overt hyperparathyroidism (symptomatic or progressive) who do not respond to vitamin D therapy or who develop side effects from such therapy. Indications for parathyroidectomy include:

- Patients with persistent hypercalcemia despite adjustments in dialysate Ca concentration. These patients must demonstrate histological evidence of severe hyperparathyroidism without aluminum accumulation prior to being subjected to surgical parathyroidectomy.
- Patients with persistent hyperphosphatemia and high Ca-Pi product despite aggressive dietary counseling and compliance with prescriptions. Prior to parathyroidectomy, these patients must also have histological evidence of severe accelerated bone resorption that would explain the presence of persistent hyperphosphatemia.
- Patients with progressive and symptomatic soft tissue calcifications, including the syndrome of calciphylaxis. Again, these patients must have biochemical and histological evidence of hyperparathyroidism with high bone turnover at the time of parathyroidectomy.
- Patients with severe progressive and symptomatic hyperparathyroidism when rapid reduction in PTH is required and vitamin D pulse therapy has failed. These patients usually have significant increase in their parathyroid gland size.
- Patients with refractory pruritus. Prior to parathyroidectomy, these patients must have evidence of severe hyperparathyroidism and have failed all other remedies for itching.

There are 3 surgical approaches to parathyroidectomy: subtotal parathyroidectomy, total parathyroidectomy with parathyroid autotransplantation, and total parathyroidectomy. Each approach has its own merits and complications [222]. Subtotal parathyroidectomy risks the possibility of inadequate reduction in parathyroid gland mass or the recurrence of hyperparathyroidism in the remaining tissue. Both of these possibilities require re-exploration of the neck, which can be technically difficult due to the formation of scar tissue. Total parathyroidectomy with parathyroid autotransplantation in the forearm allows an easy access to the residual parathyroid tissue, should this be necessary. However, there have been reports of migration of the transplanted gland cells into the venous circu-

lation and the muscles of the forearm [223 – 225]. Furthermore, the aggressive use of vitamin D in the prevention or treatment of hypocalcemia post-parathyroidectomy may interfere with the successful autotransplantation of the parathyroid tissue. This may lead to severe postoperative hypoparathyroidism. Finally, total parathyroidectomy has been advocated to reduce the risk of recurrence [226]. Surprisingly, postsurgical symptoms of hypoparathyroidism were mild or absent. However, further studies are needed to evaluate this procedure carefully.

A recent randomized study evaluating subtotal parathyroidectomy and total parathyroidectomy with autotransplantation showed that the latter was superior in regard to normalization of serum Ca and alkaline phosphatase, improvements in clinical and radiographical abnormalities, and recurrence rate of hyperparathyroidism [227]. However, another study revealed a very high recurrence rate after total parathyroidectomy with autotransplantation [228]. It is clear that prospective randomized trials comparing all these surgical procedures are needed before recognizing the best approach.

Recently, percutaneous ethanol injection under ultrasound guidance was described as an alternative to surgical parathyroidectomy [229 – 232]. Patients may require multiple injections at weekly intervals for better results. The main complication of this procedure is transient [230] or permanent [233] paralysis of the recurrent laryngeal nerve. It is also possible that fibrosis of the surrounding tissues induced by alcohol may render subsequent surgical parathyroidectomy technically difficult. Therefore, current knowledge of this innovative procedure indicates that this treatment should be reserved only for patients unfit for surgery.

Patients undergoing parathyroidectomy require careful follow-up and meticulous management. Postoperative hypocalcemia should be anticipated and treated with PO and IV calcium. The use of calcitriol may minimize the need for large doses of Ca salts; however, it may interfere with the successful uptake of the transplanted gland. A reasonable approach would be the use of IV calcitriol administered at the end of each dialysis treatment for 2 – 3 treatments prior to parathyroidectomy [222] followed by the lowest dose of PO calcitriol needed. Preferably, the PO use of calcitriol post-parathyroidectomy with autotransplant should be delayed for a few days. Another potential complication of parathyroidectomy is the propensity of patients to accumulate aluminum [234 – 237]. Therefore, we strongly suggest that patients undergo a bone biopsy prior to parathyroidectomy to rule out with certainty the presence of aluminum accumulation in bone.

Aluminum Removal

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. Aluminum is 80% protein bound; therefore, only 20% of total aluminum is ultrafilterable. The elimination of aluminum from bone through normal turnover and by completely withdrawing aluminum sources is very slow and may take years. However, aluminum removal is greatly enhanced by the use of a chelator agent. A highly specific and completely safe chelator of aluminum does not exist. Deferoxamine (DFO) is presently the best chelator of aluminum. DFO increases the complex-bound fraction of aluminum and facilitates its removal through dialysis. DFO is relatively safe, but rare ocular complications such as cataracts, altered color vision, night blindness, or scotoma have been

reported [238]. Episodes of hypotension due to a histamine-mediated vasodilatory effect of the drug can occur during DFO therapy. Hypotension can be precipitated by rapid infusion (> 15 mg/kg/hour) and the use of low-calcium dialysate. It is usually easily reversible; however, in some cases angina has been reported. Nausea, vomiting, and neuromuscular excitability are usually transient. The association between DFO therapy and infections has been the subject of controversy. DFO is thought to act as siderophore and therefore may promote bacterial and fungal infections [239, 240]. Although numerous case reports of bacteremia and mucormycosis occurring with DFO therapy have been published, a large survey did not confirm that DFO increases the risk of bacteremia in dialysis patients [241]. The possible relationship between DFO therapy and mucormycosis, though rare, represents a very serious complications that deserves careful further investigation. Therefore, unequivocal documentation of aluminum overload is required before long-term DFO therapy is begun.

After DFO infusion, increases in serum aluminum levels are observed indicating the translocation of aluminum from bone and other organs into the blood. Peak levels decrease with time and reach baseline values after 3 – 12 months depending on the extent of initial aluminum overload [242]). Therapy should be discontinued when no increases in serum aluminum levels are seen 48 hours after infusion, and particularly when zero dialysance is observed. Failure to withhold therapy at this stage may lead to the chelation of other trace metals [243] and subject patients to the unnecessary risks of DFO side effects.

The optimal dose of DFO is not clearly established. Currently, based on the non-linear dose-chelation curves, most nephrologists are using lower doses than before. An appropriate dose range appears to be 5 – 20 mg/kg, 1 – 3 times/week infused slowly over 2 hours. Infusion of DFO at the end of dialysis is potentially more efficient since it allows the chelator to act longer. However, this bears the risk of inducing long-standing high serum levels of aluminum that could be redistributed to the brain causing acute encephalopathy. In CAPD patients, intramuscular (IM) or overnight IP DFO therapy has been advocated as an effective method [244, 245]. However, our experience indicates that IV administration during the last 2 hours of HD is preferable in patients with severe aluminum intoxication (> 90% of trabecular surface). The added expense and logistical problems of using special cartridges with microencapsulated carbon [246, 247] or DFO coating limit their application to severe aluminum toxicity when time is of the essence.

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