

REVIEW ARTICLE

MECHANISMS OF DISEASE

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RENAL OSTEODYSTROPHY

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RENAL osteodystrophy, the term used to describe the skeletal complications of end-stage renal disease, is a multifactorial disorder of bone remodeling. The actions of some of the factors involved are well defined, and successful strategies have been designed to prevent them. For example, the identification of secondary hyperparathyroidism and $1\alpha,25$ -dihydroxycholecalciferol ($1\alpha,25$ -dihydroxyvitamin D_3) deficiency as major contributors to renal osteodystrophy has led to the development of treatment regimens that can maintain normal serum calcium and phosphate concentrations, reduce parathyroid hormone secretion, and correct a deficiency of $1\alpha,25$ -dihydroxycholecalciferol. These improvements in treatment have resulted in decreases in the frequency and severity of osteitis fibrosa, the most common type of renal osteodystrophy (Fig. 1).

During the 1970s and 1980s, it was discovered that an accumulation of aluminum from water used for dialysis and aluminum salts used as phosphate binders caused osteomalacia and an adynamic bone disease (Fig. 1). The identification of these disorders broadened the spectrum of renal osteodystrophy and led to changes in the composition of dialysis fluids and the substitution of calcium carbonate for aluminum salts. As a result, the frequency of aluminum-related bone disease is waning.¹ Other factors must be involved, however, since the prevention of osteitis fibrosa and aluminum intoxication may not result in normal bone histology.¹⁻⁶ Patients may have an adynamic bone disease¹⁻⁷ or a mild bone disease (early osteitis fibrosa).

In this review, we focus on new pathophysiologic concepts of renal osteodystrophy and relate them to the management of this disorder in patients with end-stage renal disease. The roles of various cytokines, such as interleukin-1, tumor necrosis factor α , interleukin-6, and interleukin-11, and their soluble receptors or circulating antagonists are considered. These substances are involved in bone remodeling, and their activity is in-

creased in patients with end-stage renal disease.⁸⁻¹¹ In the context of adynamic bone disease, inhibitors of bone remodeling and the possible deficiency of bone growth factors are considered. The causative role of beta₂-microglobulin deposition in the development of dialysis-related bone cysts and the osteoarthropathy syndrome has been elucidated elsewhere.¹²

NORMAL BONE REMODELING

Renal osteodystrophy must be considered in the context of bone remodeling, a multistep coupled process consisting of the resorption of bone and its replacement by new bone at discrete locations in the skeleton (Fig. 2). The bone-remodeling cycle begins with an initiating event, such as the stimulation of osteoblast precursors and marrow stromal cells. Osteoblasts are derived from pluripotent mesenchymal stem cells, which give rise to resident marrow stromal-cell progenitors that can proliferate and differentiate into fibroblasts, chondrocytes, adipocytes, or muscle cells, as well as osteoblasts.²² Parathyroid hormone or locally produced interleukin-1 or tumor necrosis factor α stimulates the release of soluble factors from stromal cells and osteoblasts that induce the proliferation and differentiation of osteoclast precursors and activate the function of osteoclasts (Fig. 2).^{14,23,24} The soluble factors thought to be involved in the development of osteoclasts include macrophage colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, interleukin-6, and interleukin-11.^{19,25,26} Parathyroid hormone, tumor necrosis factor α , and interleukin-1 stimulate the production of osteoclasts at different stages of cell differentiation, leading to synergism when the concentrations of cytokines and parathyroid hormone are both elevated, as in chronic renal failure.²⁷ In osteoblasts and bone lining cells that activate the resorptive process, parathyroid hormone, interleukin-1, or tumor necrosis factor α stimulates the secretion of collagenase²⁸ and tissue plasminogen activator²⁹ and inhibits the synthesis of collagen³⁰ and DNA³¹ (Fig. 3).

With the normal interactions among type I collagen, matrix proteins, and bone mineral disrupted, chemotactic factors are released locally, and osteoclasts are exposed to them. The leading candidates for this chemotactic role are the matrix proteins osteocalcin, osteopontin, and bone sialoprotein. Although all these factors interact with type I collagen,³² osteopontin and bone sialoprotein have the arginine-glycine-aspartic acid sequence for cell adhesion^{32,33} recognized by osteoclast integrins.³⁴ These two chemotactic factors may be the natural ligands for integrin $\alpha_v\beta_3$, which, when bound, directs chemotaxis and organizes the osteoclast for resorptive activity.^{35,36} The organized osteoclast features unique cell-matrix interactions in the region where the cell adheres to bone (osteoclast clear zone), which is not permeable to ions, and the insertion of

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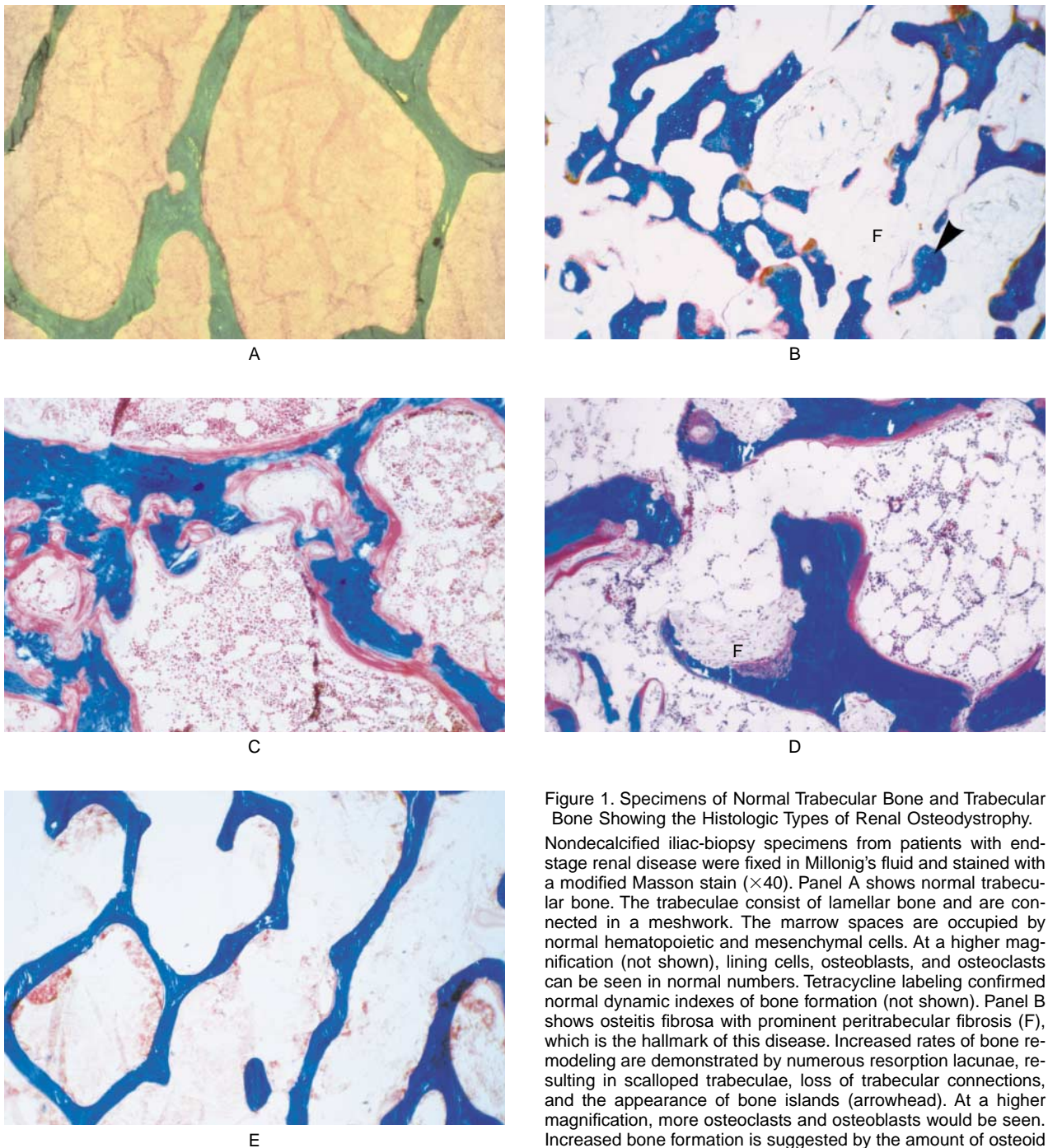


Figure 1. Specimens of Normal Trabecular Bone and Trabecular Bone Showing the Histologic Types of Renal Osteodystrophy.

Nondecalfied iliac-biopsy specimens from patients with end-stage renal disease were fixed in Millonig's fluid and stained with a modified Masson stain ($\times 40$). Panel A shows normal trabecular bone. The trabeculae consist of lamellar bone and are connected in a meshwork. The marrow spaces are occupied by normal hematopoietic and mesenchymal cells. At a higher magnification (not shown), lining cells, osteoblasts, and osteoclasts can be seen in normal numbers. Tetracycline labeling confirmed normal dynamic indexes of bone formation (not shown). Panel B shows osteitis fibrosa with prominent peritrabecular fibrosis (F), which is the hallmark of this disease. Increased rates of bone remodeling are demonstrated by numerous resorption lacunae, resulting in scalloped trabeculae, loss of trabecular connections, and the appearance of bone islands (arrowhead). At a higher magnification, more osteoclasts and osteoblasts would be seen. Increased bone formation is suggested by the amount of osteoid (red areas) and indexes of formation derived from tetracycline labeling (not shown). Panel C shows osteomalacia with increased unmineralized bone matrix (osteoid, red). Decreased rates of remodeling are suggested by the decreased activity and number of osteoclasts. Tetracycline labeling (not shown) demonstrated poorly organized and diminished mineralization fronts. The osteoid accumulates and is poorly resorbed. Panel D shows mixed disease, characterized by areas of fibrosis (F) and increased remodeling activity adjacent to areas of increased osteoid deposition, with poor mineralization and remodeling. Panel E shows adynamic bone disease, characterized by an absence of remodeling activity. The number of bone cells (osteoblasts and osteoclasts) is decreased, and there is minimal evidence of osteoid production.

vacuolar ATPases and cathepsins into a specialized area of plasma membrane (the ruffled border) that results in matrix degradation and mineral dissolution.^{37,38}

After remodeling has been activated, bone is resorbed by multinucleated osteoclasts. When a quantity of bone has been resorbed, increased local concentrations of calcium³⁹ or activation of latent factors in the bone matrix (e.g., transforming growth factor β)⁴⁰ leads to diminished osteoclast activity, separation of osteoclasts from the bone surface, and apoptosis (Fig. 2).

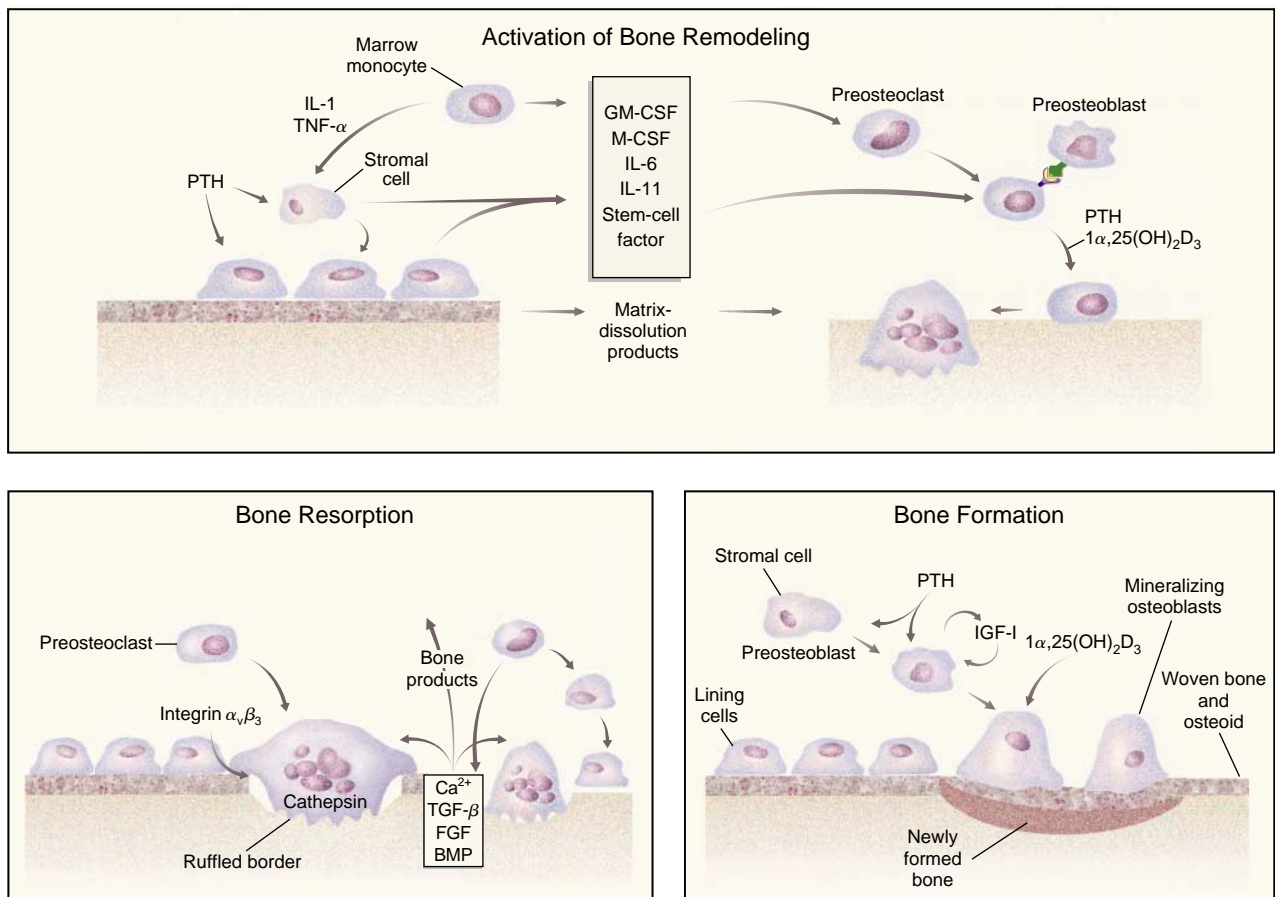


Figure 2. Bone Metabolism in Renal Osteodystrophy.

Factors such as parathyroid hormone (PTH), tumor necrosis factor α (TNF- α), and interleukin-1 (IL-1) activate the remodeling cycle (top panel) through actions on the layer of osteoblasts covering bone surfaces. Existing osteoclasts are attracted to the site and activated by matrix-dissolution products. In addition, stimulated osteoblasts and other cells in the bone microenvironment, such as marrow stromal cells, produce granulocyte-macrophage colony-stimulating factor (GM-CSF), macrophage colony-stimulating factor (M-CSF), interleukin-6 (IL-6), interleukin-11 (IL-11), and stem-cell factor, which stimulate the proliferation and differentiation of osteoclast precursor cells (preosteoclasts), leading to an enlargement of the osteoclast pool. Osteoclasts are derived from hematopoietic granulocyte-macrophage colony-forming units, and precursors fuse. The action of IL-6 depends on its circulating soluble receptor, which with IL-6 couples to the cell-membrane protein gp130, activating signal transduction.¹³ In addition, cells of the osteoblast lineage (preosteoblasts), stimulated by activators of bone resorption, participate in osteoclast differentiation through cell-to-cell communication. PTH and calcitriol ($1\alpha,25$ -dihydroxycholecalciferol [$1\alpha,25(\text{OH})_2\text{D}_3$]) are also important factors in the differentiation of committed preosteoclasts.¹⁴ Expression of IL-1, TNF- α , IL-6, and IL-11 and their soluble receptors is increased in end-stage renal disease, suggesting that they play a part in the activation of remodeling in renal osteodystrophy.^{8-11,15-20}

In the resorptive component of remodeling (bottom left panel), the multinucleated osteoclast is formed by the fusion of mononuclear precursors that differentiate from bone marrow granulocyte-macrophage colony-forming units. Recognition of bone matrix by the integrin $\alpha_v\beta_3$ stimulates cellular remodeling, resulting in the adherence of osteoclasts to the bone matrix and the formation of a specialized resorbing domain of the plasma membrane, the ruffled border. The products of bone resorption, calcium and transforming growth factor β (TGF- β), inhibit osteoclast function or serve as growth factors (TGF- β , basic and acidic fibroblast growth factor [FGF], and bone morphogenetic protein [BMP]) for osteoblasts, which move into the resorption lacunae and produce new bone.

In the bone-formation component of remodeling (bottom right panel), osteoblast precursors are derived from marrow stromal osteoprogenitor cells. The precursor pool is expanded by proliferative factors, and the pool differentiates to the bone, forming cuboidal osteoblasts responsible for matrix synthesis, mineralization, and remodeling. At the completion of bone formation, the differentiated osteoblast-lining cells form a syncytial-cell layer covering endosteal and periosteal bone surfaces that are not actively involved in remodeling. PTH stimulates osteoblastic proliferation at a discrete undetermined point in osteoblast ontogeny, in part by stimulating the production of insulin-like growth factor I (IGF-I). Calcitriol ($1\alpha,25(\text{OH})_2\text{D}_3$) also regulates osteoblast ontogeny, leading to the differentiation of the osteoblast, and organizes the regulation of matrix-protein production.²¹

Some of the same signals that decrease resorptive activity (transforming growth factor β and the heparin-bound growth factors — i.e., fibroblast growth factors) bring osteoblasts into the resorption lacunae and activate them.^{23,41} This process initiates bone formation

(Fig. 2), which includes proliferation and differentiation of osteoblast precursors, matrix (osteoid) synthesis, mineralization, and resorption of woven bone and its replacement with lamellar, nutrient-supplied bone. At the end of the remodeling cycle, the amount of bone

formed is slightly smaller than that which was resorbed. This difference increases with age, so that older patients with end-stage renal disease may have osteopenia that is independent of renal osteodystrophy.

Of the factors that increase bone formation, parathyroid hormone is the best known.⁴²⁻⁴⁴ Administration of parathyroid hormone induces bone formation, at least in part because of its ability to increase the pool of osteoblast precursors.⁴² Parathyroid hormone also increases the production of insulin-like growth factor I by osteoblasts *in vitro*⁴⁵ and *in vivo*.⁴⁶ The extent to which increased production of insulin-like growth factor I contributes to the expansion of the osteoblast pool is unclear, but the growth factor alone does not account for all the anabolic function of parathyroid hormone.⁴⁴ In osteitis fibrosa, the role of parathyroid hormone in bone formation is reflected by the increases in numbers of osteoblasts, alkaline phosphatase activity, and bone-matrix production.⁴⁵

PATHOPHYSIOLOGY

Renal osteodystrophy is classified as osteitis fibrosa, osteomalacia, or mixed, mild, or adynamic disease, according to the histologic features (Table 1).

Osteitis Fibrosa

The classic histologic form of renal osteodystrophy is osteitis fibrosa, which is caused by secondary hyperparathyroidism with contributions from locally derived cytokines and a deficiency of 1 α ,25-dihydroxycholecalciferol. A hallmark of osteitis fibrosa is marrow fibrosis, caused by the activation of marrow mesenchymal cells, which differentiate into fibroblast-like cells secreting the fibrous tissue occupying peritrabecular spaces. Another feature of this disorder is the increased frequency of bone remodeling, leading to increased resorption of bone. The increased resorption is caused by an increase in both the number and the activity of osteoclasts. Bone formation is also increased, as reflected by increased amounts of osteoid and nonlamellar bone, which are hallmarks of a high rate of bone turnover.⁴⁵

In osteitis fibrosa the focus of abnormal remodeling activity is often in the cortical osteons of long bones, leading to increased cortical porosity as a result of resorption and remodeling. In cortical osteons remodeling involves osteocytes and the osteocytic network that communicates with lining cells along the haversian ca-

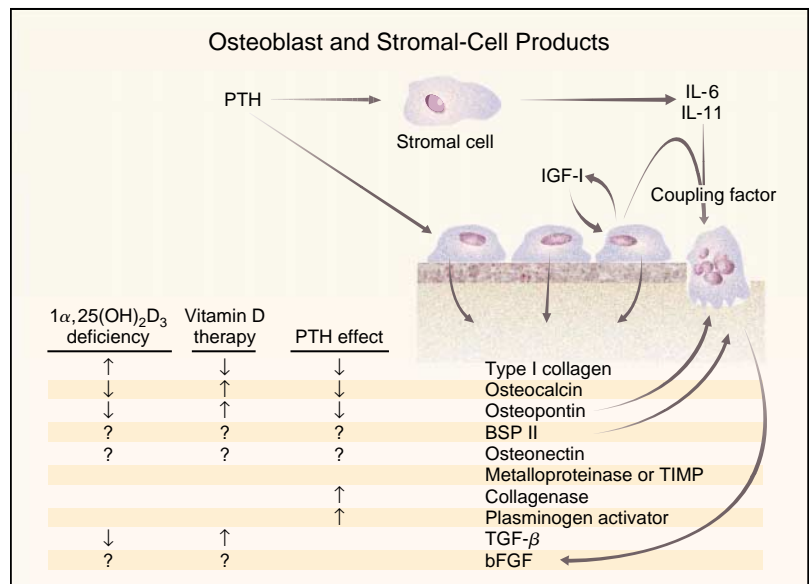


Figure 3. The Effects of Secondary Hyperparathyroidism, 1 α ,25-Dihydroxycholecalciferol (1 α ,25(OH)₂D₃) Deficiency, and Vitamin D Treatment on Cells of Osteoblast Lineage during Remodeling.

Cells of the mature osteoblast phenotype, such as bone lining cells, are stimulated by parathyroid hormone (PTH) to decrease the expression of proteins associated with bone formation (i.e., type I collagen and noncollagenous bone matrix proteins). In addition, PTH increases the expression of collagenase and plasminogen activator, whereas the tissue inhibitors of metalloproteinases are unaffected. As a result, matrix-dissolution products (osteopontin, bone sialoprotein, and collagen degradation fragments) are released that may serve as direct activators and chemoattractants of osteoclasts. In addition, PTH stimulates the secretion of interleukin-6 (IL-6) and interleukin-11 (IL-11) by cells of the osteoblast lineage that are not attached to the bone matrix, which may include the stromal-cell-osteoblast progenitor cells. Osteoblastic activity produces matrix deposition of latent transforming growth factor β (TGF- β), which, when activated during resorption, is a major factor producing local negative feedback for the resorption of osteoclasts and stimulation of the repair component of the remodeling cycle (i.e., bone formation). The stimulation of osteoblast growth factors by PTH also contributes to the later phases of bone formation. An example is PTH stimulation of the production of insulin-like growth factor I (IGF-I). BSP II denotes bone sialoprotein II, TIMP tissue inhibitor of metalloproteinase, and bFGF basic fibroblast growth factor.

nal. Osteocytes are important as sensors of mechanical strain and local damage, but their regulation by hormones and cytokines has not been studied extensively.⁴⁶ The effect of end-stage renal disease on osteocyte function is unknown. In long bones increased cortical resorption tends to reduce the bone mass, but in trabecular bone the accumulation of woven bone may leave the bone mass unchanged, despite a decrease in lamellar bone.⁴⁵ Osteitis fibrosa may be associated with osteopenia and fractures, but measurements of bone density do not correlate well with bone strength because of confounding variables, such as dystrophic mineralization and the accumulation of woven bone (mineralized, nonlamellar, immature bone), which is much weaker than its lamellar counterpart.

Another important factor in the pathophysiology of renal osteodystrophy is the deficiency of 1 α ,25-dihydroxycholecalciferol (Table 2). In end-stage renal disease, this deficiency results in decreased intestinal absorption of calcium and increased secretion of para-

Table 1. Histologic Classification of Renal Osteodystrophy.

DISORDER	DESCRIPTION	PATHOGENESIS	FREQUENCY (%)*
Osteitis fibrosa	Peritrabecular fibrosis, increased remodeling — resorption and formation	Secondary hyperparathyroidism, secondary role of cytokines and growth factors	50
Osteomalacia	Increased osteoid, defective mineralization	Aluminum deposition, plus unknown factors	7
Mixed disease	Features of both osteitis fibrosa and osteomalacia	Secondary hyperparathyroidism and aluminum deposition, plus unknown factors	13
Mild disease	Slightly increased remodeling	Early or treated secondary hyperparathyroidism	3
Adynamic renal bone disease	Hypocellular bone surfaces, no remodeling	Aluminum deposition, parathyroid hormone suppression, and other factors (deficiency of bone growth factors or increased suppressors of bone remodeling)	27

*The frequency at the start of therapy for end-stage renal disease is shown. Data are from Hutchison et al.⁷ Although the data are based on a small series, the distribution of disorders is similar to that generally seen in current clinical practice.

thyroid hormone.⁴⁷ $1\alpha,25$ -Dihydroxycholecalciferol is a critical differentiation factor in the skeleton for both osteoblasts²¹ and osteoclasts (Fig. 2).¹⁴ The effect of its deficiency on histologic characteristics of bone in patients with end-stage renal disease is difficult to assess; $1\alpha,25$ -dihydroxycholecalciferol is deficient in all forms of renal osteodystrophy, and relations between specific abnormalities and serum $1\alpha,25$ -dihydroxycholecalciferol concentrations have not been established. The important role of $1\alpha,25$ -dihydroxycholecalciferol in the organization and mineralization of bone matrix is demonstrated by its strong transcriptional up-regulation of

Table 2. Factors Contributing to Renal Osteodystrophy.

FACTOR	ROLE
Secondary hyperparathyroidism	Contributes to osteitis fibrosa
Hypocalcemia*	
$1\alpha,25$ -dihydroxycholecalciferol deficiency*	
Parathyroid gland abnormalities	
Chromosomal alterations ³⁹	Causes defective mineralization (osteomalacia)
Vitamin D-receptor deficiency ⁴⁰	
Metal intoxication	Causes defective mineralization (osteomalacia)
Aluminum	
Iron	
Cadmium	Secondary factors in osteitis fibrosa
Local factors — cytokines	
Interleukin-1, tumor necrosis factor	
Interleukin-6	
Interleukin-11	
Interleukin-4	
Endothelin	Potential factors in adynamic bone disease
Endothelium-derived relaxing factor	
Retained products	May have direct effects on parathyroid hormone secretion and $1\alpha,25$ -dihydroxycholecalciferol synthesis, in addition to causing hypocalcemia
Phosphate*	
Beta ₂ -microglobulin*	
Parathyroid hormone-related protein (C-terminal fragments)	
Growth factors	May contribute to adynamic bone disease
Deficient osteogenic protein-1	
Gonadal dysfunction†	May contribute to osteopenia

*Has a defined role in the pathogenesis of renal osteodystrophy.

†Gonadal dysfunction in end-stage renal disease is complex, characterized by a tendency toward low serum concentrations of gonadal steroids and gonadotropins and hyperprolactinemia.

the genes for osteocalcin and osteopontin (Fig. 3),²¹ which are secreted by differentiated osteoblasts at the time of mineralization. Reduced secretion of these matrix proteins by osteoblasts would be expected to affect matrix organization and mineralization. $1\alpha,25$ -Dihydroxycholecalciferol also inhibits cell proliferation by decreasing the expression of *c-myc* proto-oncogenes, which regulate the cell cycle. This effect is important to consider in treating patients with well-controlled serum parathyroid hormone concentrations, because the use of $1\alpha,25$ -dihydroxycholecalciferol may promote the development of adynamic bone disease.⁶ The clear-

est clinical role of $1\alpha,25$ -dihydroxycholecalciferol in renal osteodystrophy is its ability to prevent secondary hyperparathyroidism by correcting hypocalcemia and inhibiting parathyroid hormone gene transcription.⁴⁴ Besides hypocalcemia and a deficiency of $1\alpha,25$ -dihydroxycholecalciferol, chromosomal deletions⁴⁸ and decreased concentrations of vitamin D receptors in parathyroid tissue also cause secondary hyperparathyroidism in patients with end-stage renal disease¹⁵ (Table 2). Recent clinical trials of vitamin D sterols in the treatment of renal osteodystrophy provide evidence that alkaline phosphatase and parathyroid hormone escape the suppressive actions of alfacalcidol and calcitriol.³ These studies support the concept that factors other than hypocalcemia and $1\alpha,25$ -dihydroxycholecalciferol deficiency lead to secondary hyperparathyroidism.^{3,6}

Osteomalacia

Osteomalacia is a common component of bone disease in patients with end-stage renal disease, although its prevalence is decreasing.^{1,7} The disorder is characterized by low rates of bone turnover, a mineralization defect, and an accumulation of unmineralized osteoid (bone matrix). The type of osteomalacia associated with end-stage renal disease differs from that caused by vitamin D deficiency, and the role of $1\alpha,25$ -dihydroxycholecalciferol deficiency in osteomalacia associated with end-stage renal disease is unclear. The most common cause of osteomalacia is intoxication with aluminum and other heavy metals associated with the treatment of end-stage renal disease.¹⁶ Such intoxication causes defective mineralization and increased matrix synthesis by existing osteoblasts but long-term inhibition of osteoblast differentiation. Intoxication also affects osteoclasts and inhibits their function. The incidence of osteomalacia has decreased with the elimination of aluminum exposure in patients with end-stage renal disease. Exposure to iron, either alone or in combination with aluminum, may also cause osteomalacia. The incomplete disappearance of osteomalacia after the removal of aluminum indicates that other fac-

tors, such as 25-hydroxycholecalciferol deficiency,¹⁷ are involved in this potentially devastating form of osteodystrophy. The accumulation of unmineralized osteoid and the decrease in bone turnover despite resorptive activity result in a considerably weakened skeleton. Patients with osteomalacia often have skeletal deformities, bone pain, fractures, and marked musculoskeletal disability. This form of osteodystrophy is refractory to treatment with vitamin D sterols.¹⁸

Adynamic Bone Disease

The pathogenesis of adynamic renal bone disease is poorly understood. This disease is most common in patients with end-stage renal disease who do not have secondary hyperparathyroidism (e.g., after parathyroidectomy), who have been overtreated with calcium and vitamin D, or who have diabetes mellitus or aluminum intoxication. The association between continuous ambulatory peritoneal dialysis and adynamic renal bone disease may be related to the greater transfer of calcium from the dialysate to the patient and suppression of parathyroid hormone secretion that occurs with this form of dialysis as compared with hemodialysis.¹⁹ Hypersecretion of parathyroid hormone may thus be required to maintain normal rates of bone formation in patients with end-stage renal disease,^{3,4,20} and the need to maintain bone remodeling at a normal level may be an inherent stimulus for hyperparathyroidism in such patients. As discussed above, this concept is supported by recent clinical studies.^{3,6}

The presence of adynamic bone disease in patients with end-stage renal disease who have normal parathyroid function suggests that the production of one or more suppressors of bone formation is increased (Table 2) or that other promoters of bone formation (growth factors) are not produced; either mechanism could contribute to the need for increased parathyroid hormone secretion. Recent reports that therapy for end-stage renal disease activates the immune system suggest that there are numerous candidates for suppression factors (Table 2),^{49,50} including interleukin-11, which may inhibit osteoblastic bone formation,⁵¹ and interleukin-4.⁵² Interleukin-1 and tumor necrosis factor α are generally considered to be activators of the remodeling cycle, but evidence that their soluble receptors and antagonists are increased during dialysis^{53,54} indicates that we still know little about the overall production and action of these factors in patients with end-stage renal disease. A net suppressive effect is possible, if the soluble receptors or antagonists override the actions of tumor necrosis factor α or interleukin-1. There may also be other inhibitors of bone remodeling in patients with end-stage renal disease, including nitrous oxide⁵⁵ and fragments of parathyroid hormone-related protein.^{56,57}

In addition to the direct suppression of bone remodeling in end-stage renal disease, a deficiency of a factor involved in bone formation or growth may contribute to adynamic bone disease. Osteogenic protein-1 (also called bone morphogenic protein-7), a potent osteoblast

growth factor, is produced by normal renal tubular cells.^{58,59} A deficiency of this factor may lead to the need for more parathyroid hormone.

Another important factor contributing to osteopenia in patients with end-stage renal disease is hypogonadism⁶⁰ (Table 2). In both women and men with end-stage renal disease, serum concentrations of gonadal steroids tend to be low, as a result of a complex set of endocrine and nonendocrine factors. These factors include variable decreases in the secretion of follicle-stimulating hormone and luteinizing hormone and increased secretion of prolactin. As a result, anovulation, amenorrhea or oligomenorrhea, infertility, impotence, loss of libido, oligospermia, and gynecomastia can occur.

Although initial reports suggested that adynamic bone disease does not often cause symptoms,^{3,5} subsequent follow-up has shown that the disease is associated with an increased fracture rate, as compared with that in the general population, and an increased mortality rate, as compared with that among patients with other forms of osteodystrophy.⁶¹ Microfractures would be expected to cause bone pain in patients with osteopenia due to adynamic bone disease. Recent studies⁶² demonstrate that adynamic bone disease is associated with a decrease in the ability of the skeleton to take up calcium. The decrease in the number of remodeling sites in this disorder is equivalent to the decrease in the pool of exchangeable calcium and thus in skeletal calcium uptake, which is probably the basis for the higher incidence of hypercalcemia among patients with adynamic bone disease.

DIAGNOSIS

The recognition that renal osteodystrophy encompasses a spectrum of disorders may increase the importance of performing a bone biopsy in order to make an accurate diagnosis. Patients with adynamic bone disease tend to have normal or reduced bone density, only slightly elevated serum alkaline phosphatase concentrations, relatively normal serum parathyroid hormone concentrations, an absence of bone aluminum, and hypercalcemia. Parathyroid hormone measurements can be used to differentiate osteitis fibrosa or mixed disease from adynamic bone disease but are not sufficient to establish the type of osteodystrophy in an individual patient,^{4,6,7,63,64} especially if calcitriol has been administered. Standard clinical practice in treating patients with end-stage renal disease and renal osteodystrophy has evolved away from the performance of a diagnostic bone biopsy before the initiation of therapy, because of pain associated with the procedure and because the presence of osteitis fibrosa can be predicted on the basis of elevated serum concentrations of parathyroid hormone and alkaline phosphatase. In addition, serum aluminum concentrations, especially after the administration of deferoxamine, indicate the presence of aluminum-related bone disease.⁶⁴ However, a bone biopsy remains the best way to ascertain the type of renal osteodystrophy.⁶⁵ In addition, im-

improvements in biopsy techniques have reduced post-surgical pain.

With the advent of assays for intact parathyroid hormone in serum, it is possible to vary dialysate calcium concentrations and administer calcium salts and vitamin D preparations in order to keep serum parathyroid hormone concentrations within a desired range, but the ideal serum parathyroid hormone concentration in a patient with end-stage renal disease is not known. The disease is associated with a resistance to the action of parathyroid hormone,⁶⁶ which is thought to be due to down-regulation of parathyroid hormone receptors. The features of adynamic bone disease, however, suggest that other mechanisms contribute to a resistance to the action of parathyroid hormone and that higher serum parathyroid hormone concentrations may be required to overcome the inhibition of bone-remodeling factors or the deficiency of bone-forming factors in end-stage renal disease. Serum parathyroid hormone concentrations should probably be maintained at a level three to four times above the upper limit of normal, although in a recent study,⁶ children with higher serum parathyroid hormone concentrations who were receiving calcitriol therapy still had adynamic bone disease. Thus, calcitriol-induced suppression of osteoblast proliferation may increase the likelihood of adynamic bone disease even when serum parathyroid hormone concentrations are high, possibly because of the antiproliferative action of $1\alpha,25$ -dihydroxycholecalciferol.

CURRENT MANAGEMENT RECOMMENDATIONS

The mainstays of the prevention and treatment of renal osteodystrophy continue to be phosphate binders and supplemental calcium.⁶⁷

Control of Serum Phosphate

A low-phosphate diet is integral to the management of end-stage renal disease, because it is the best way to maintain a normal serum phosphate concentration. A phosphate binder, either calcium carbonate⁶⁸ or calcium acetate,⁶⁹ taken with each meal in proportion to the phosphate content of the meal, is usually also required; aluminum-containing phosphate binders should be avoided. Reducing dialysate magnesium concentrations and adding magnesium-containing binders to decrease the calcium salts may allow both the control of serum phosphate concentrations and higher doses of calcitriol⁷⁰ (and Delmez J: personal communication). Magnesium inhibits mineralization, however, and its use requires careful monitoring of serum magnesium concentrations.

Control of Serum Calcium

Calcium malabsorption is very common in end-stage renal disease because of deficient $1\alpha,25$ -dihydroxycholecalciferol. Serum calcium concentrations need to be maintained at the high end of the normal range in order to prevent or suppress oversecretion of parathyroid hormone.⁷¹ A dialysate calcium concentration of 7 mg per deciliter (1.75 mmol per liter) provides an influx of approximately 800 mg per treatment.⁷² The positive

calcium balance is greater in patients treated with continuous ambulatory peritoneal dialysis than in those treated with hemodialysis, providing more effective suppression of parathyroid hormone secretion.²¹ This effect, along with greater phosphate removal,¹⁹ is probably the basis for the higher prevalence of adynamic renal bone disease that is associated with continuous ambulatory peritoneal dialysis. When calcium salts are required to control hyperphosphatemia, the increased dialysate calcium concentration may cause hypercalcemia. The dialysate calcium concentration should be reduced to 5 mg per deciliter (1.25 mmol per liter), a level that will not affect the calcium balance and will allow for sufficient oral intake of calcium salts to maintain normal serum phosphate concentrations.⁷³ The timing of oral calcium intake is important; calcium taken between meals is more a calcium supplement than a phosphate binder.

Use of Vitamin D Analogues

Calcitriol and other vitamin D preparations (vitamin D, alfacalcidol, dihydrotachysterol, and calcifediol) have been widely used to treat secondary hyperparathyroidism, as well as to correct deficient endogenous production of $1\alpha,25$ -dihydroxycholecalciferol. These agents lessen bone pain, improve bone histologic characteristics, and suppress parathyroid hormone secretion by both raising serum calcium concentrations and inhibiting parathyroid hormone gene transcription.⁴⁷ Calcitriol is the most potent agent in suppressing parathyroid hormone secretion, but it and all other vitamin D preparations can cause hypercalcemia. None of these agents should be used in the presence of hyperphosphatemia, to avoid high concentrations of serum calcium-phosphorus products and extraskeletal calcification. Intermittent intravenous or oral administration of calcitriol is perhaps the most effective means of suppressing parathyroid hormone secretion.^{74,75} Since vitamin D preparations suppress parathyroid hormone secretion and decrease the proliferation of osteoblasts, these agents should not be given to patients with adynamic bone disease. The use of vitamin preparations associated with a lower incidence of hypercalcemia before the initiation of therapy for end-stage renal disease will contribute substantially to the prevention of osteodystrophy.³

CONCLUSIONS

The recognition that a range of disorders account for renal osteodystrophy occurs at a time when our understanding of the pathogenesis of the disease is improving. New information about the physiology of bone remodeling in relation to the actions of cytokines and growth factors will increase our understanding of the pathophysiology of renal osteodystrophy. The possible discovery of additional substances with important pathophysiologic roles in osteitis fibrosa and adynamic bone disease may lead to improved approaches to the prevention and treatment of renal osteodystrophy.

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