Clinical Reviews in Bone and Mineral Metabolism, vol. 5, no. 1, 11–19, 2007

1534-8644/07/5:11–19/$30.00 ISSN 1559-0119 (Online)

Pathophysiology of Renal Osteodystrophy

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Abstract

Renal osteodystrophy is a common complication of chronic Kidney disease, and abnormalities of bone metabolism are a reflection of broad-based disturbances in the control mechanisms for mineral metabolism. Secondary hyperparathyroidism is a major contributor to the high turnover form of renal osteodystrophy. Detailed investigations over the past several decades have uncovered many of the mechanisms involved in the initiation and maintenance of secondary hyperparathyroidism and it is these mechanisms that provide the basis for therapeutic intervention to control this complication of chronic kidney disease. An additional form of renal osteodystropy is characterized by abnormally low bone turnover, which also is multi-factorial in origin. Again, an understanding of the mechanisms involved in abnormal bone and mineral homeostasis provide the basis for therapy. It is only with a through understanding of the mechanisms involved in the initiation and maintenance of these complications that rational approaches to treatment may be instituted.

Key Words: renal osteodystrophy, hyperparathyroidism, adynamic bone, Phosphorus, vitamin D.

The abnormalities of the skeleton that can occur in association with chronic kidney disease are termed "renal osteodystrophy" and reflect a broad spectrum of skeletal abnormalities *(1–3)*. At one end of this spectrum are the effects of high levels of parathyroid hormone (PTH) on bone, which are associated with a high bone turnover. Other abnormalities can lead disturbances at the opposite end of the spectrum, and are characterized by an abnormally low bone turnover, known as adynamic bone. A second form of low bone turnover disease, osteomalacia, also occurs in some cases, although it is less prevalent in the United States in the present era. These abnormalities of bone may occur together such that there are features of impaired mineralization together with evidence of high bone turnover, and this mixed picture is known as mixed renal osteodystrophy. Although these broad categorizations of skeletal abnormalities encompass most of the abnormalities seen, the skeleton can also be affected by many other processes associated with advanced kidney disease, such as the accumulation of β-2 microglobulin. The skeletal picture can also be modified by other systemic abnormalities, including postmenopausal osteoporosis, or osteoporosis as a result from steroid or immunosuppressive therapy directed toward the underlying kidney disease. In addition, the metabolic acidosis that may occur in the presence of chronic kidney disease can also influence bone metabolism.

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Pathogenesis of High Turnover Renal Osteodystrophy

Hyperplasia of the parathyroid glands and high levels of PTH in blood have been known to occur early in the course of chronic kidney disease and progressively increase with the duration of the kidney disease *(4,5)*. It is now known that many factors

contribute to the overactivity of the parathyroid glands in this clinical setting. These abnormalities can be categorized into five broad groups, each of which may have several contributing factors as illustrated in Fig. 1. These are (1) phosphate retention, (2) low levels of calcitriol, (3) intrinsic abnormalities of the parathyroid gland, (4) hypocalcemia, and (5) skeletal resistance to the actions of parathyroid hormone. These abnormalities are often closely interrelated and one or more of these factors may be predominate during the course of kidney disease.

Phosphorus Retention

Phosphorus retention as a result of decreased kidney function has been proposed as an important factor in the pathogenesis of secondary hyperparathyroidism *(6–8)*. Substantial experimental and clinical observations over many years have given support to this process. Although it was originally proposed that phosphorus retention can stimulate parathyroid function by causing a decrease in the levels of ionized calcium, subsequent work has shown that hypocalcemia is not necessary for hyperparathyroidism to occur, and these observations have led the way to further evaluation of the potential effects of phosphorus on the parathyroid glands *(9)*. It is now known that phosphorus can directly affect the parathyroid gland to increase the rate of growth and increase the secretion of parathyroid hormone. Two groups of investigators have demonstrated in vitro that changes in extracellular phosphorus concentration resulted in increased PTH secretion, in spite of the absence of alterations in ionized calcium

Phosphorus Retention	↓ Renal Mass ↓ GFR
Low Calcitriol Levels	↑ Phosphorus ↓ Renal Mass ? acidosis ? other
Altered Parathyroid Cell Growth and Function	Hypocalcemia ↓ Calcitriol Calcitriol resistance ↑ Set-point ↓ VDR PTG Hyperplasia ↑ PTG Mass ↑ Ca Receptor ↑ Phosphorus △ PTH mRNA stability
Hypocalcemia	↑ Phosphorus ↓ Calcitriol Calcitriol Resistance Skeletal Resistance
Skeletal Resistance	↑ Phosphorus Desens. to PTH ↓ PTH -R ? ↓ Calcitriol ? Uremic toxins ? PTH inhibitors

Fig. 1. The pathogenesis of hyperparathyroidism: major factors involved (LEFT PANEL) and their contributing abnormalities (RIGHT PANEL).

in the medium *(10,11)*. These observations demonstrate clearly that phosphorus can directly increase PTH secretion, although the mechanism of this effect is not fully understood at the present time. It appears that the effect of phosphorus to increase PTH secretion is posttranscriptional and recent studies have indicated that phosphorus may have an important effect on stabilizing the messenger ribonucleic acid (RNA) for parathyroid hormone and decrease its degradation within the parathyroid gland, thereby setting the stage for increased PTH secretion *(12–14)*. The signaling mechanisms involved in this effect may be related to phosphate regulation of the production of arachadonic acid by parathyroid tissue *(15)*.

Phosphorus also affects the parathyroid gland by regulating its growth. Thus, it has been shown that changes in dietary phosphorus have an important effect on parathyroid cell proliferation. Using the technique of proliferating cell nuclear antigen (PCNA) staining of parathyroid tissue in rats in vivo, it has been shown that a high-phosphorus diet is associated with increased rates of parathyroid growth, whereas a low-phosphorus diet is associated with rates of cell division that are close to normal *(16)*. A low-phosphorus diet is extremely effective in preventing parathyroid growth. This process of phosphate-regulated parathyroid growth appears to be of extreme importance in the management of hyperparathyroidism, since studies in animals have shown that this effect of phosphorus in increasing parathyroid hyperplasia is extremely rapid and occurs within days of the induction of renal insufficiency *(17)*.

Additional studies have shown that a high-phosphorus diet results in an increase in the expression of transforming growth factor (TGF)-α, which is a growth factor for parathyroid cells *(17–20)*. The increase in TGF-α parallels the increase in PCNA expression. It appears that the effects of TGF-α are mediated through the epidermal growth factor (EGF) receptor, which on activation leads to activation of the mitogen activated protein (MAP) kinase pathway, resulting in the stimulation of cell proliferation. The effect of a low-phosphorus diet in preventing parathyroid growth appears to be associated with an increase in the cyclin-dependent kinase inhibitor, P21, which will prevent parathyroid cell division *(20)*.

Decreased Synthesis of Calcitriol

Since the kidney is the principal site for the production of calcitriol, it follows that a decrease in renal mass should lead to a decrease in the ability of the kidney to produce calcitriol *(21)*. Decreases in calcitriol will lead to increases in PTH secretion both directly and indirectly. The indirect effects are mediated by the important effect of calcitriol in regulating intestinal calcium absorption, which has been well described to gradually fall in patients with chronic kidney disease.

Decreases in calcitriol will also directly affect the parathyroid gland, as there is substantial evidence over the past fifteen years that calcitriol affects many processes within the parathyroid *(22–27)*. Thus, there is evidence that calcitriol can directly affect PTH gene transcription, the regulation of parathyroid vitamin D receptors, the regulation of parathyroid cell growth, the expression of the calcium-sensing receptor, and perhaps the regulation of the setpoint for calcium-regulated PTH secretion.

In recent years, an additional mechanism that could limit the production of calcitriol in the course of kidney disease has been emphasized by work that has delineated the pathways by which 25-hydroxyvitamin D is delivered to the 1-alpha-hydroxylase *(28)*. This process has been demonstrated to involve the uptake of the vitamin D-binding protein bound to 25-hydroxyvitamin D, following glomerular filtration, by megalin in the proximal tubule. This complex is then internalized and following the digestion of vitamin D-binding protein, the 25-hydroxyvitamin D can be delivered to the mitochondria for 1-hydroxylation. This pathway appears to be the rate-limiting step for the production of 1,25-vitamin D by the kidney tissue, and accordingly, with decreases in glomerular filtration rate (GFR) where the delivery of the precursor is impaired, this could limit the ability of the kidney to produce 1, 25-vitamin D.

Calcitriol has been shown in vitro to be a regulator of parathyroid cell growth. Thus, bovine parathyroid cells in culture, when stimulated to grow, have been demonstrated to have decreased rates of growth with calcitriol added to the medium *(29)*. Further studies have shown that the antiproliferative effects of calcitriol appear to be related to the up-regulation of the cyclin-dependent kinase inhibitor, P21. This appears to involve atranscriptional mechanism regulated by the vitamin D receptor *(20)*.

In addition to decreases in calcitriol production, there may also be resistance to the actions of calcitriol that occur in the uremic state *(30)*. Studies have shown that there appear to be substances in the uremic milieu that appear to interfere with the ability of the vitamin D receptor complex to bind to deoxyribonucleic acid (DNA), which, consequently, may result in resistance to the actions of calcitriol. Some work has suggested that this resistance may involve decreases in the binding partner for the vitamin D receptor, that is, RXR, which is an essential partner to form a functional heterodimer that interacts with vitamin D response elements *(31)*.

Altered Parathyroid Function

As discussed earlier, abnormal parathyroid growth is a common feature of chronic kidney disease, and it is now realized that the enlarged parathyroid glands removed from patients with severe hyperparathyroidism appear to have numerous nodules within the tissue. Studies by Fukuda and others have demonstrated that the staining for vitamin D receptor appears to be markedly decreased in these nodules *(32)*, and there is evidence to suggest that some of these nodules represent monoclonal expansions of parathyroid cells *(33)*. Subsequent studies by other investigators have shown that these nodules may also have a marked decrease in the expression of the calcium receptor *(34)*. Accordingly, since parathyroid hormone secretion is regulated by calcium receptors and by vitamin D receptors, these nodules, as a result of reduced expression of these regulator pathways, will secrete PTH at an increased rate and be poorly responsive to these normal regulatory pathways. An important question is whether the loss of vitamin D receptors or calcium receptors leads to the accelerated growth of the parathyroid cells, or whether the accelerated growth is a result of the loss of these receptors. This issue was investigated by Ritter et al., who showed that parathyroid cell proliferation appears to precede the loss of the calcium receptor from the parathyroid glands of rat with uremia *(35)*. However, there is also evidence that the calcium receptor may be involved in the regulation of parathyroid growth, thus, administration of a calcimimetic agent has been demonstrated to suppress and prevent the development of parathyroid hyperplasia in experimental animals *(36,37)*.

Hypocalcemia

Hypocalcemia is a powerful stimulus for PTH secretion, as well as for parathyroid growth, and although hypocalcemia may occur in patients with renal failure, it is not essential for the development of hyperparathyroidism *(9)*. The calcium receptor pathway is important in the regulation of PTH secretion, and accordingly, the decrease in calcium receptor expression discussed above is important for the regulation of PTH by calcium in this setting. Some studies have shown that the setpoint for calcium-regulated PTH secretion has shifted to the right in patients with severe hyperparathyroidism, although others have not confirmed these observations *(38–44)*. There is now evidence that several factors may regulate the set point for calcium-regulated PTH secretion, including not only the baseline serum calcium, but also, the size of the parathyroid glands, the rate of change in the serum calcium, and the polymorphisms of the calcium-sensing receptor gene. Thus, there are many factors that may explain the apparently conflicting results that have been obtained from clinical studies.

Skeletal Resistance to the Action of PTH

Forty years ago, it was demonstrated that patients with chronic kidney disease had a decreased calcemic response to PTH, thereby suggesting that the skeleton had become resistant to the actions of parathyroid hormone *(45)*. There appear to be several mechanisms involved in this decreased calcemic response to PTH. There is evidence that phosphorus retention can play a role in this regard using a model of experimental uremia in the rat *(46)*. These observations in vivo are supported by in vitro studies that show that elevated phosphorus concentrations can decrease calcium mobilization from bone.

Some investigators have suggested that decreased levels of calcitriol may also contribute to the reduced calcemic response to PTH *(47)*. Others have not been able to confirm this effect in other experimental settings *(48,49)*. Studies have suggested that there might be a down-regulation of PTH receptor in the target tissues in uremia and this could lead to an impaired response to PTH *(50,51)*. Recent observations have extended these studies by demonstrating that the expression of the PTH receptor mRNA appears to be reduced in the skeleton of patients with

chronic kidney disease *(52)*. Interestingly, the reduced levels of PTH receptor mRNA did not appear to change after parathyroidectomy, suggesting that other factors might be regulating PTH receptor mRNA.

In recent years, an additional mechanism that may contribute to skeletal resistance to the actions of PTH has been uncovered. Thus, it has been demonstrated that N-terminal truncated PTH fragments, such as PTH 7-84, can exist in the circulation and may have biological effects that have not been recognized before *(53,54)*. Administration of PTH 7-84 has been demonstrated to blunt the calcemic effect of PTH 1-84, and these and additional studies have suggested that there may be direct effects of PTH 7-84 on bone cells *(55–57)*. These observations are related to a large body of work, which suggests that there is a presence of receptors for the C-terminal region of PTH, and thus there may be a potential biological pathway by which C-terminal fragments of PTH accumulate in the circulation of patients with chronic kidney disease as a result of decreased GFR, and these fragments may contribute to blunting of the calcemic effects of PTH.

Pathogenesis of Low Bone Turnover Renal Osteodystrophy

The low bone turnover skeletal problems in patients with chronic kidney disease include adynamic bone, which is characterized by extremely low bone formation. An additional bone turnover type of skeletal abnormality is osteomalacia, which is also characterized by a low rate of bone formation, but there is marked evidence of defective bone mineralization. Osteomalacia occurring in the setting of chronic kidney disease has been most often related to the accumulation of aluminum in the era when aluminum-based phosphate binders were widely utilized, and water purification techniques were evolving, and this is not often seen in the United States at the present time *(58)*. The adynamic bone lesion, without aluminum accumulation, is common in patients with chronic kidney disease on dialysis, although cases have been described with chronic kidney disease before dialysis is required *(59,60)*. This type of skeletal abnormality appears to be especially prevalent in patients on peritoneal dialysis *(3,61)*. The pathogenesis of this nonaluminum-related adynamic bone disease is not well understood, but many factors have been implicated in its pathogenesis *(62)*. This is illustrated in Fig. 2.

There is one group of factors that seems to be associated with the relative hypoparathyroidism, which in turn will lead to decreased bone formation rate. There is a second group of factors that can directly affect bone formation rate, and many

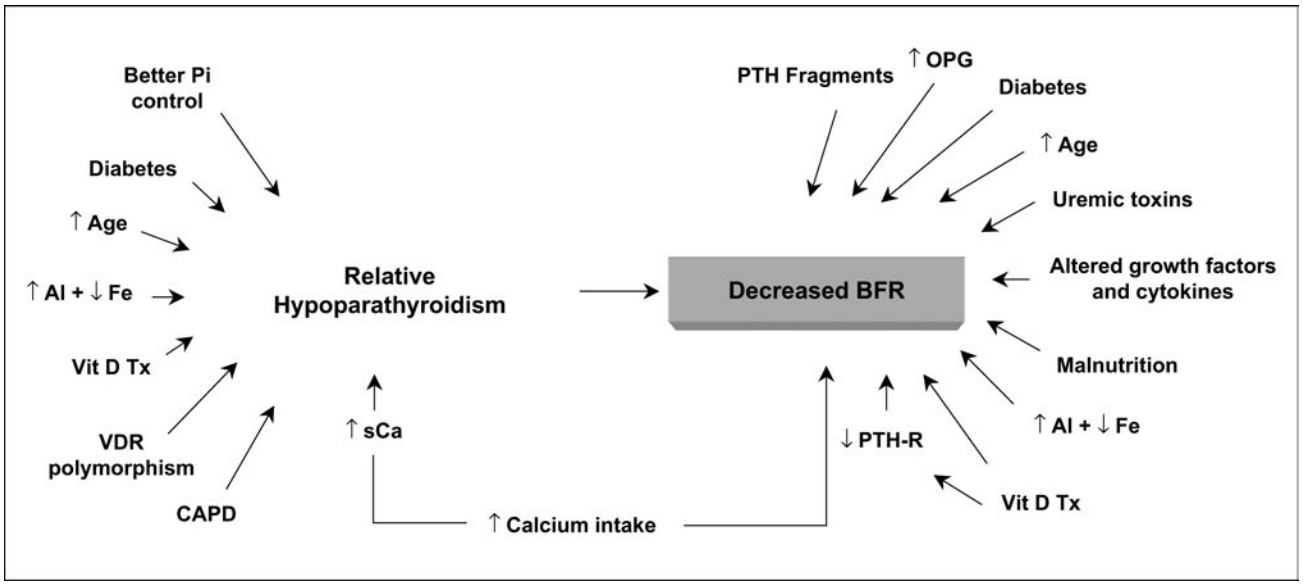

Fig. 2. The pathogenesis of adynamic bone in uremia.

abnormalities in uremia may contribute to this pathway. Some aspects of this pathogenetic scheme may relate to treatment of hyperparathyroidism, which, in general principle, is related to phosphate control, the administration of vitamin D sterols, and efforts to raise serum calcium to normal. All of these maneuvers may reduce parathyroid function to a degree that bone formation rate is reduced.

Other Factors that May Affect the Skeleton in Chronic Kidney Disease

Metabolic Acidosis

Metabolic acidosis is a common finding in chronic kidney disease and may have important effects on the skeleton *(63–65)*. Acidosis is associated with increased calcium efflux from bone, which occurs by a variety of mechanisms. One mechanism involves the buffering of hydrogen ions by bone, which results in the solubilization of bone mineral. Acidosis has also been shown to increase bone resorption, as well as to depress bone formation *(66–70)*. Acidosis may also have systemic effects that affect the skeleton, by altering the biological activity of PTH, as well as by altering the metabolism of vitamin D *(71)*. The mechanism by which metabolic acidosis appears to augment the action of PTH and osteoblast-like cells has been shown to be associated with an increase in the expression of PTH receptor mRNA in the presence of metabolic acidosis *(72)*. Acidosis-induced osteoclastic-mediated bone resorption appears to involve the increased expression of RANKL mRNA *(69)*. Clinical studies have shown that the treatment of metabolic acidosis in patients on hemodialysis appears to result in improved manifestations of hyperparathyroidism in bone *(73)*.

Corticosteroids

Corticosteroid-induced bone loss has been recognized for many years *(74)*. Corticosteroids decrease the rate of bone formation and result in rapid loss of bone during the first few months of treatment, followed by a more prolonged phase of steady bone loss. Corticosteroids have been shown to promote aptosis in both osteoblasts and osteocytes, and it is believed that this process contributes to the pathogenesis of glucocorticoid-induced osteopenia *(75–77)*.

Growth Factors

Increasing evidence suggests that the process of osteoblast development and differentiation is regulated by multiple systemic and local factors, including parathyroid hormone, insulin-like growth factor-1, (IGF-1) the bone morphogenetic proteins, fibroblast growth factor, TGF-β, and epidermal growth factor *(78–80)*. Many of the hormone systems are altered in the presence of kidney disease and can therefore possibly contribute to the pathogenesis of renal bone disease. Thus, abnormalities in the IGF-1 and IGF-binding protein systems have been described and can potentially contribute to altering the manifestations of renal bone disease *(81,82)*. The bone morphogenetic proteins may also influence the skeleton and it has been suggested that the basic metabolic panel-7 bone morphogenetic protein-7 (BMP-7) might be particularly involved in this process, as BMP-7 administration has been shown to modify high turnover renal osteodystrophy *(83)* and, under some circumstances, may actually alter the manifestations of adynamic bone *(84)*.

Cytokines

Alterations in cytokines may also affect the skeleton. There is substantial evidence that there is an increase in pro-inflammatory cytokines in uremia *(85–88)*. These cytokines may modulate the bone remodeling process by affecting the RANK/RANKL/OPG system that is essential for the normal metabolism of bone *(89)*. IL-6 levels have also been associated with bone disease in uremia, but its precise contribution remains unclear at the present time *(87,90)*. Circulating levels of OPG may also be increased in patients with advanced kidney disease and also have the capacity to influence bone turnover *(91,92)*. Further studies are necessary to analyze the precise contribution of these cytokines to the final manifestations of renal bone disease.

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