CHAPTER

77 Mineral and Bone Disorder in Chronic Kidney Disease

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Historically, renal osteodystrophy (ROD) was a term used to describe the metabolic bone disease caused by abnormalities in mineral homeostasis resulting from kidney failure.[1] In recent years, the recognition of a complex endocrine regulation of mineral and bone metabolism, the prominent extra skeletal manifestations of chronic kidney disease (CKD), and the association between abnormalities in mineral metabolism and increased morbidity and mortality in patients with kidney failure led to formulation of a new term—chronic kidney disease–mineral and bone disorder (CKD-MBD) (Table 77.1)[1]—which describes a broader clinical syndrome, including metabolic/endocrine abnormalities, parathyroid gland dysfunction, bone disease, and unique CKD-associated cardiovascular risk factors as well as other adverse clinical outcomes, such as fractures and vascular and soft tissue calcifications (Fig. 77.1). In this chapter we review separate components of CKD-MBD, clinical manifestations, and general principles of CKD-MBD treatment.

Four organ systems, including the gut (absorption of calcium [Ca] and inorganic phosphate [Pi]), kidneys (reabsorption and excretion of Ca, Pi, and calcitriol synthesis), bones (interchange of Ca and Pi with extracellular pool, and FGF23 secretion), and parathyroid gland (parathyroid hormone [PTH] secretion) are involved in regulating mineral homeostasis[2] and each play a role in the pathogenesis of CKD-MBD (Fig. 77.2).

BIOCHEMICAL ABNORMALITIES IN CKD-MBD

Calcium

There are three Ca pools in our body. The majority of Ca (99%) is found in bone. The remaining Ca is either intracellular (mostly protein bound), and extracellular (45% protein bound and 55% free calcium). PTH is a key regulator of serum calcium levels. The extracellular Ca concentration is tightly regulated by changes in PTH through sensing of calcium by the calcium-sensing receptor (CaSR)[3] and through actions of PTH on bone and kidney. In turn, Ca controls PTH secretion, synthesis, and degradation as well as parathyroid cell hypertrophy and hyperplasia.[4,5] PTH directly regulates the excretion of Ca by the kidney and also influences the exchange between bone and extracellular pools. PTH stimulates gut calcium absorption indirectly through the stimulation of $1,25(OH)_2D_3$ production by the kidney, which in turn activates calcium absorption through vitamin D receptor (VDR)-dependent mechanisms. Decrements in $1,25(OH)_2$ D_3 levels occur prior to elevations of PTH during the progressive loss of glomerular filtration rate (GFR). The increments in PTH maintain serum calcium concentrations in the normal range until late in the course of CKD (Fig. 77.3A,B).[6]

Phosphorus

Pi is required for cellular function and skeletal mineralization and excess phosphate is associated with soft tissue and vascular calcifications. Serum Pi level is less tightly regulated than Ca, but is maintained in normal range through a complex interplay between intestinal absorption, exchange with intracellular and bone storage pools, and renal tubular reabsorption. Pi is abundant in the diet, and intestinal absorption of Pi is stimulated by $1,25(OH)_2D$. The kidney is a major regulator of Pi homeostasis, where increases or decreases in its Pi reabsorptive capacity under the control of various hormones determine serum Pi levels. The crucial regulated step in Pi homeostasis is the transport of Pi across the renal proximal tubule via the type II sodium-dependent phosphate (Na/Pi) cotransporter 2a (NPT2a) and 2c (NPT2c). PTH and FGF23 are the two principal hormones that regulate NPT2 translocation to the proximal tubular brush border membrane. PTH inhibits renal phosphate reabsorption due to reductions in membrane expression of NPT2. FGF23, a bone-derived hormone originally identified as the causative factor in inherited and acquired hypophosphatemic disorders also inhibits proximal tubular phosphate transport through mechanisms that remain to be defined. Increments in FGF23 appear to precede elevations of PTH in CKD, but both work in concert to prevent elevations in serum Pi by increasing renal phosphate excretion.[6–14] Like Ca, serum Pi levels remain in the normal range until late in the course of

77.1 Classification of Chronic Kidney Disease: Mineral and Bone Disorder

CKD-MBD is either one or combination of the following:

- Abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism, as measured by laboratory values
- Abnormalities in bone turnover, mineralization, volume, linear growth, or strength, as measured mainly by bone histology
- Vascular or other soft tissue calcifications

CKD-MBD, chronic kidney disease–mineral and bone disorder; PTH, parathyroid hormone.
Adopted from KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl. 2009;(113):S1–130.

CKD, typically when glomerular filtration rate (GFR) is <30 to 40 mL/min/m^2.[6,8,11,15]

Vitamin D

Decrements in both 25(OH)D and $1,25(OH)_2D$ occur early in the course of CKD-MBD. Low levels of vitamin D are associated with increased mortality in CKD and treatment with vitamin D analogues are believed to have a survival benefit.[16] The mechanism for decreased circulating 25(OH)D levels in CKD are not well understood, but may result from poor nutritional status caused by chronic illness. Patients with CKD, however, may also be refractory to nutritional vitamin D supplementation, suggesting other mechanisms for decreased 25(OH)D levels.

$1,25(OH)_2D_3$, the active form of vitamin D, is synthesized from 25 (OH)D by 1α-hydroxylase- cytochrome P450, family 27, subfamily B, polypeptide 1(CYP27B1) located in the kidney proximal tubule. CYP27B1 is stimulated by PTH and inhibited by FGF23. Both 25(OH)D and $1,25(OH)_2D$ are catabolized by 25-hydroxyvitamin $D_3$24-hydroxylase (CYP24), which is also present in the proximal tubule. CYP24 is stimulated by FGF23 and inhibited by PTH. Decrements in $1,25(OH)_2D$ occur early in CKD. Diminished $1,25(OH)_2D$ levels are seen with early GFR decline to less than 60 to 70 mL/min/m^2 and are inversely related to elevation in FGF23.[8] The reductions in $1,25(OH)_2D$ in CKD were thought to be the result of reduced production of this hormone caused by the diseased kidney, but more recently it has been recognized that the suppression of $1,25(OH)_2D$ production is a regulated process due to the effects of FGF23 on CYP27B1-mediated production and/or CYP24–mediated degradation of $1,25(OH)_2D$.[17–19] Reduced GFR can additionally contribute to $1,25(OH)_2D$ deficiency via decrease in renal uptake of 25-hydroxyvitamin D by proximal tubular cells for its activation to $1,25(OH)_2D$ through decrease in amount of filtered 25-hydroxyvitamin D bound to vitamin D-binding protein available for uptake. Moreover, CKD leads to a decrease in kidney megalin content that is essential for the internalization of 25-hydroxyvitamin D into proximal tubular cells.[20]

The principal functions of $1,25(OH)_2D$ are to promote active intestinal absorption of Ca and Pi, suppress PTH gene transcription in the parathyroid gland, stimulate bone formation and resorption in bone, as well as regulate the innate immune response in other tissues. Alterations in $1,25(OH)_2D$ directly suppresses PTH gene expression through a genomic action[21] via VDR on parathyroid cells. $1,25(OH)_2D$ also indirectly regulates parathyroid gland function through elevations in serum calcium and stimulation of CaSR. Mouse genetic studies suggest that CaSR is dominant to VDR in regulation of parathyroid gland function, because calcium exerts PTH and VDR regulation in absence of any vitamin D source,[22] whereas ablation of VDR in the parathyroid gland results in hyperparathyroidism that can be rescued by raising serum calcium levels.[23,24] Several additional factors lead to impaired action of $1,25(OH)_2D$ on parathyroid gland in uremia, such as diminished activation of VDR with reduced $1,25(OH)_2D$ levels in CKD, and decrease in parathyroid VDR content, especially when nodular parathyroid hyperplasia is present.

FGF23

Elevations in circulating FGF23 levels are one of the earliest abnormalities in CKD-MBD and are strongly associated with increased all-cause mortality.[25,26] Elevations of FGF23

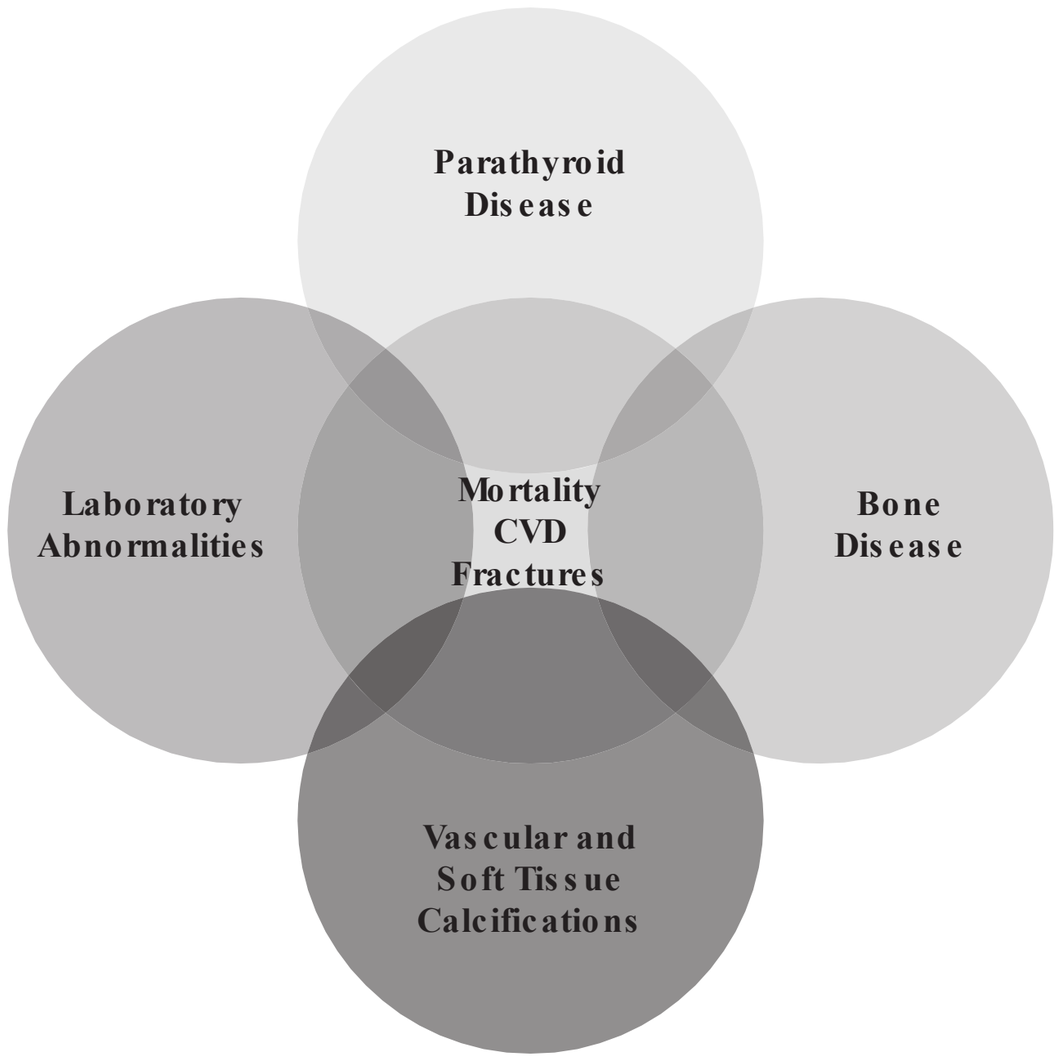

FIGURE 77.1 Spectrum of pathology in chronic kidney disease–mineral and bone disorder. (Modified from KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl.* 2009;(113):S1–130.)

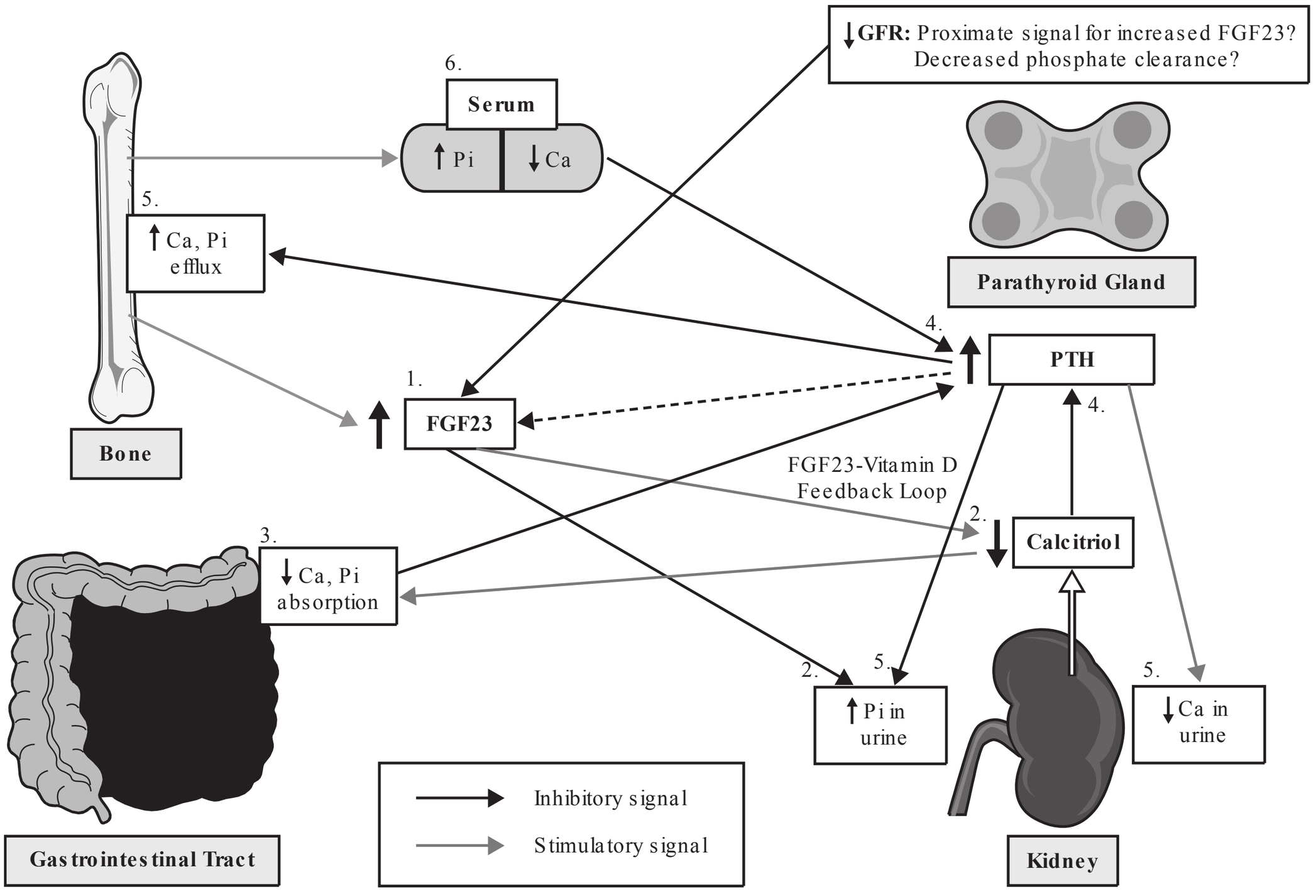

FIGURE 77.2 The schematic representation of chronic kidney disease–mineral and bone disorder pathogenesis. *Ca,* calcium; *Pi,* phosphorus. 1, Increase in FGF23; 2, suppression of calcitriol and increased urinary phosphate; 3, decreased gastrointestinal calcium and phosphorus absorption; 4, increased parathyroid hormone; 5, increased bone resorption/calcium and phosphorus bone efflux; increased phosphorus and decreased calcium in urine; 6, maintenance of serum phosphorus and calcium in normal range until stage V chronic kidney disease.

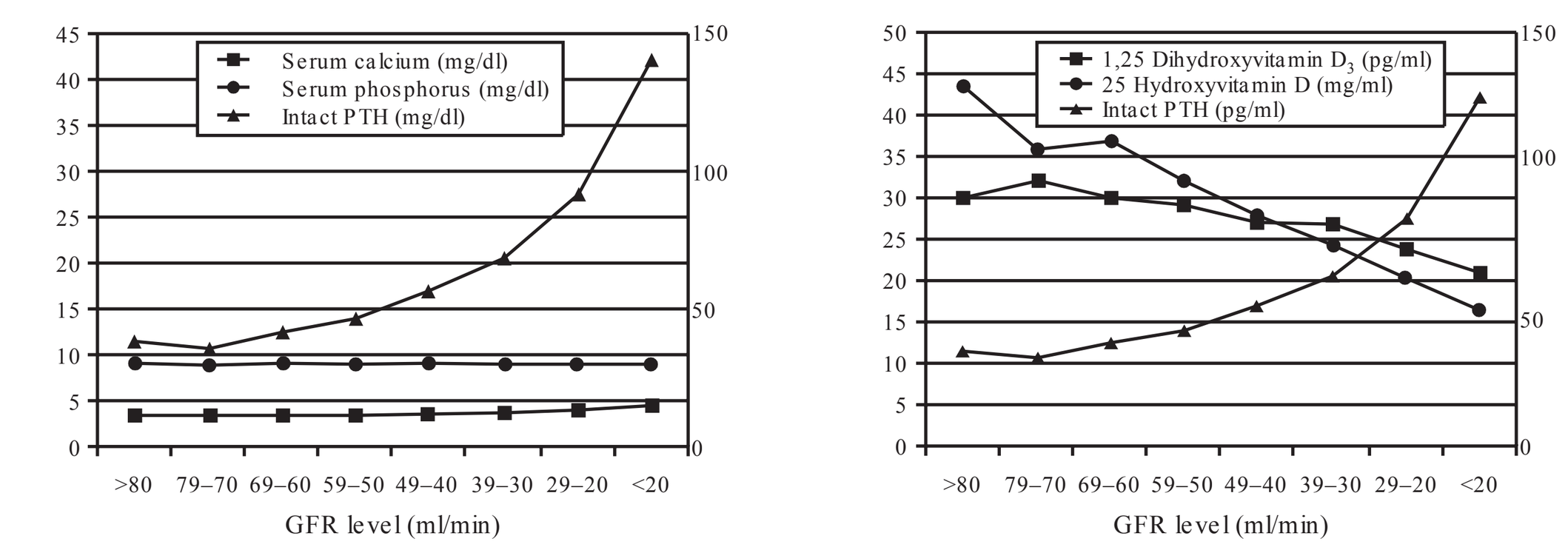

FIGURE 77.3 Relationship between glomerular filtration rate (GFR) and parathyroid hormone (PTH), calcium, phosphorus, and calcitriol levels in patients with chronic kidney disease. **A:** Median values of serum calcium, phosphorus, and intact PTH by GFR levels. **B:** Median values of 1,25-dihydroxyvitamin D, 25-hydroxyvitamin D, and intact PTH by GFR levels. (Adopted from Levin A, Bakris GL, Molitch M, et al. Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: results of the study to evaluate early kidney disease. *Kidney Int.* 2007;71(1):31–38.)

inversely correlate with GFR.[8,27–29] Patients with end-stage renal disease (ESRD) have markedly elevated levels of FGF23 that parallels with degree of hyperphosphatemia[30] and secondary hyperparathyroidism (SHPT).[31]

FGF23 is a 32-kDa protein with an N-terminal region containing the FGF-homology domain and a novel 71-amino acid C terminus[32,33] that interacts with FGF receptor (FGFR) in the presence of the members of Klotho family of proteins.[34,35] In vitro studies indicate that Klotho is an essential cofactor for FGF23 to activate FGFR.[34,36,37] Circulating FGF23 is mainly produced and secreted by osteoblasts and osteocytes in bone.[38] The target organs for FGF23 are defined by the coexpression of the membrane form of Klotho and FGFR.[37,39] Klotho is expressed in high levels in parathyroid gland, kidney, and several other organs; however, the kidney is the principal physiologically defined target for FGF23, where it inhibits phosphate reabsorption and $1,25(OH)_2D$ synthesis. The parathyroid gland is also a target for FGF23 action, but it is not clear if FGF23 stimulates or inhibits PTH secretion. Elevated levels of FGF23 in human disease and mouse models are associated with hyperparathyroidism (HPT),[40,41] likely due to the effect of FGF23 to suppress $1,25(OH)_2D$ leading to the secondary development of HPT. In contrast, in vitro studies demonstrated that FGF23 activates extracellular regulated kinases 1/2 - Egr-1 pathway leading to inhibition of PTH mRNA expression and PTH secretion from parathyroid cells.[42,43] Additionally, FGF23 suppresses parathyroid cell proliferation and increases CaSR and VDR expression in normal parathyroid gland.[44] In individuals with normal kidney function, FGF23 exerts negative feedback on the parathyroid gland; however, the fact that in CKD patients PTH remains high despite elevated FGF23 suggests the presence of resistance to FGF23 action. This possibility was reinforced by a finding of a reduced Klotho and FGFR expression in surgically removed parathyroid glands from uremic patients.[42]

The mechanism of increased FGF23 in CKD is poorly understood. The increase in serum FGF23 is not explained by reduced FGF23 clearance; and the proximate stimulus in early CKD that leads to increments in FGF23 are not clear. Nevertheless, FGF23 production is likely increased to counteract Pi retention due to reduced nephron mass by promoting urinary Pi excretion.[45] Elevations in FGF23 precede increments in PTH in CKD[46] and animal studies show that blockade of FGF23 by neutralizing antibodies lead to normalization of $1,25(OH)_2D$ and PTH levels in models of CKD.[47] On the other hand, there is also strong evidence supporting the ability of PTH to stimulate FGF23 expression in bone in patients with CKD. In this regard, parathyroidectomy reduces FGF23 in humans with ESRD and animal models of kidney failure.[48,49] Recent studies also demonstrate the ability of PTH to directly stimulate FGF23 expression in osteoblast cultures and overexpression of a constitutively active PTH stimulates FGF23 expression in bone of transgenic mice. Regardless, the discovery and elucidation of FGF23 functions as phosphaturic[50,51] and $1,25(OH)_2D$ counter-regulatory hormone[8,10,51] provided new insight for the understanding of SHPT. Primary decrease in Pi excretion due to loss of functioning renal mass when GFR falls below ~70 mL/min/m^2 somehow leads to increase in FGF23 secretion from bone, which in turn inhibits renal Pi reabsorption and suppresses production of $1,25(OH)_2D$.[52] Reduction in $1,25(OH)_2D$, leads to increase in PTH production.[12] Both PTH and elevated FGF23 work in concert to increase Pi excretion and to maintain normal serum Pi. Further loss of renal function and elevations of PTH further stimulate FGF23 in an abnormal positive feed forward loop.

Parathyroid Hormone

As noted previously, elevations in PTH occur early in the course of CKD, just after increments in FGF23 and decrements in $1,25(OH)_2D$ and before demonstrable alterations in serum calcium and phosphate levels.

PTH actions are mediated through PTH receptor (PTH1R) in the kidney—which inhibits renal Pi reabsorption, increases renal tubular calcium excretion, and increases $1,25(OH)_2D$ production—and in osteoblasts in bone, which stimulates bone formation and osteoclastic bone resorption.[53] Chronic elevation of PTH in SHPT leads to increased bone remodeling which plays a crucial role in mineral homeostasis by providing access to the stores in bones' Ca and Pi. PTH orchestrates a coordinated process of increased bone resorption by osteoclasts followed by new bone formation by osteoblasts. PTH stimulates osteoclast formation indirectly by binding to its receptor (PTH1R) on osteoblastic cells. This in turn triggers production of receptor activator of NFkB ligand (RANKL) and suppresses the RANKL decoy receptor osteoprotegerin (OPG), thereby stimulating maturation of osteocytes by RANKL.[54] PTH also increases osteoblast number and activity, possibly through release of growth factors from bone matrix during its resorption, although the mechanism is not entirely understood.[55] However, the net result of these changes by continuous PTH stimulation in SHPT is the loss of cortical bone and increased bone fragility. Additionally, PTH was implicated in reduced red cell production by causing marked bone marrow fibrosis.[56] Interestingly, PTH can exert anabolic or catabolic action on the bone depending on whether it acts on the bone in continuous or pulsatile fashion. Intermittent administration of PTH inhibits osteoblast apoptosis and increases osteoblast number, whereas chronic administration of PTH increases mostly osteoclast number.[57] The PTH1R is also found in nonclassical PTH target tissues such as breast, skin, heart, blood vessels, liver, and other tissues.

PTH is secreted as linear protein consisting of 84 amino acids also called intact PTH (iPTH). Interaction of the 1–34 amino acid N-terminal portion of PTH is required for activation of PTH1R. In addition to full length PTH, other PTH fragment are produced from 1–84 PTH in parathyroid gland and the liver, such as bioactive N-terminal fragment (1–34), as well as various C-terminal fragments that are found in blood.

There is increase in half-life of circulating PTH and especially C-terminal fragments observed in serum of patients with uremia, possibly due to reduced clearance as the kidney is one of the principal sites for the degradation of PTH and its fragments. Patients with advanced CKD also exhibit abnormal ratio in serum between circulating 1–84 PTH and its fragments as compared with healthy controls.[58] Conventional two-site immunoassays for intact (1–84) PTH can register long N-truncated C terminal PTH fragments that lack full N terminal region (1–34) necessary for PTH1R activation. These long N-truncated C terminal fragments accumulate disproportionally to 1–84 PTH in kidney failure and may constitute up to 50% or more to total PTH immunoreactivity, as compared to 15% to 20% in normal subjects. Some of these fragments have been identified as 7–84 PTH and studies in animal models demonstrated that 7–84 PTH can antagonize effects of 1–84 PTH on increased bone turnover and serum Ca levels.[59] It has been documented that patients with CKD have impaired serum Ca response to PTH and higher PTH levels are required to maintain eucalcemia. Several possible explanations of bone PTH resistance include presence of inhibitors, such as 7–84 PTH and elevated osteoprotegerin, as well as downregulation of PTH1R mRNA in animal models and patients with CKD.[60,61]

As noted previously, CaSR is the major regulator of PTH secretion and production as well as parathyroid gland hyperplasia. VDR plays an important modulating role on PTH gene transcription. Hyperphosphatemia may stimulate PTH secretion independently from low Ca or $1,25(OH)_2D$[62, 63] through poorly defined posttranslational mechanisms.[21,64,65]

Clinical Significance of Abnormal Biochemistries in Chronic Kidney Disease

The growing body of evidence links disordered values of all CKD-MBD laboratory markers and all-cause and cardiovascular mortality in patients with CKD. In the international study of ESRD patients, lowest mortality was observed for Ca at 8.6 to 10.0 mg per dL, corrected to albumin Ca of 7.6 to 9.5 mg per dL, phosphorus at 3.6 to 5.0 mg/dL, and PTH between 101 and 300 pg per mL, with the highest mortality for Ca or corrected to albumin Ca levels greater than 10.0 mg per dL, Pi levels greater than 7.0 mg per dL, and PTH levels greater than 600 pg per mL.[66] However, recent meta-analysis challenged the association between levels of Ca and PTH and all-cause or cardiovascular mortality, whereas still strongly supporting the association between rising levels of Pi and these outcomes.[67] There is also an evidence of possible nonlinear U-shape or J-shape association between levels of Ca, Pi, PTH, and mortality with both very low and high levels predicting poor outcomes.[68,69] FGF23 has also been strongly linked in several large observational studies to all-cause mortality in CKD patients both with earlier stages not requiring renal replacement therapy (RRT) as well as hemodialysis.[25,26,70] Additionally, higher FGF23 levels are associated with the faster progression of CKD to need of RRT.[70–72] The strong adverse association between disordered markers of CKD-MBD and mortality and risk of ESRD progression necessitates the need of clinical control studies aiming to improve these outcomes in CKD patients.

BONE ABNORMALITIES

Bone is central to the pathogenesis of CKD-MBD because it is: (1) a reservoir for calcium and phosphate; (2) a target for PTH, which activates PTH receptors located in osteoblasts to increase osteoblast-mediated bone resorption and to stimulate osteoclast mediated bone resorption through the release of Rank ligand; (3) a target for 1,25(OH)2D, which binds to VDR:RXR complexes to activate gene transcription in both osteoblasts and osteoclasts; and (4) the principal source of the phosphaturic and VDR hormone FGF23, which is made by osteoblasts and osteocytes.

Renal osteodystrophy (ROD) is a general term to describe the variety of skeletal histologic abnormalities that result from the changes in hormones and calcium/phosphate homeostasis in CKD.[73] The classification of ROD is based on quantitative bone histomorphometric analysis of bone biopsy that measures bone turnover (i.e., bone formation rates and resorption), mineralization of extracellular matrix, and trabecular bone volume and cortical porosity) (Tables 77.2 and 77.3). Based on the degree of bone remodeling and mineralization abnormalities, bone biopsy diagnoses typically include osteitis fibrosa cystica (characterized by excessive PTH-mediated increases in bone formation and resorption accompanied by peritrabecular fibrosis, woven osteoid, and increased cortical porosity), osteomalacia (characterized by excess unmineralized osteoid and prolonged mineralization lag time), and adynamic bone (characterized by severely diminished bone formation and resorption). Milder forms of these abnormalities can occur and combinations of abnormal bone turnover and mineralization can occur (referred to as mixed uremic osteodystrophy). Additionally, cortical osteopenia due to excess PTH and osteoporosis due to loss of trabecular bone volume can be found in CKD and lead to increased fracture risks. Other systemic abnormalities leading to skeletal abnormalities such as β_2–microglobulin amyloidosis and acidosis induced demineralization can also occur in patients with CKD.

The majority of epidemiologic data on ROD were obtained from cross-sectional analysis of bone biopsies in predialysis patients or patients on RRT; therefore, accurate data on patients with earlier stages of CKD are uncertain. The reported prevalence of ROD in CKD stage 4 and 5 ranges from 62% to 100%[5]; however, given the importance of bone remodeling as a target for PTH and 1,25(OH)2D in the maintenance of calcium metabolism, virtually all patients in the late stages of CKD would be expected to have high turnover ROD, either osteitis fibrosa (OF) or mixed uremic osteodystrophy (MUO).[74]

77.2 Classification of Bone Disease in Chronic Kidney Disease Patients

Renal Osteodystrophy
High-turnover bone disease (represented by increased bone formation rate, increased osteoblastic/osteoclastic activity and number, reduced osteoid volume, and high peritrabecular fibrosis surface area) ■ Osteitis fibrosa (associated with severe hyperparathyroidism) ■ Mild disease (associated with mild to moderate hyperparathyroidism)
Low-turnover bone disease (low bone formation rate is characterized as being equal to or below the lower value observed in normal individuals) ■ Osteomalacia (defined as markedly increased osteoid volume and thickness with decreased fibrosis and defective bone mineralization) ■ Adynamic bone disease (characterized by paucity of bone cells with severely reduced osteoid seams and absence of fibrosis)
Mixed uremic osteodystrophy (includes findings of increased osteoid volume and fibrosis surfaces and may present with different degrees of bone formation rate that vary from high to normal and low)
Osteopenia and Osteoporosis
Other Causes of Bone Pathology in CKD
■ Acidosis ■ β_2–microglobulin amyloidosis

CKD, chronic kidney disease.
Adopted from Sprague SM. The role of the bone biopsy in the diagnosis of renal osteodystrophy. Semin Dial. 2000;13(3):152–155.

77.3 TMV Classification System for Renal Osteodystrophy

Turnover	Mineralization	Volume
Low	Normal	Low
Normal	Abnormal	Normal
High		High

TMV, bone turnover, mineralization, and volume.
Adopted from Moe S, Drueke T, Cunningham J, et al. Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2006;69(11):1945–1953.

Although data are incomplete, the epidemiology of ROD appears to have changed in the last three decades, with a decline of OF and a higher prevalence of low bone remodeling states of uncertain clinical significance and etiology. Types of ROD also vary depending whether or not the patient already started RRT and on modality of RRT, with low turnover bone remodeling being the most common lesion in predialysis patients (27%–48%) and patients on peritoneal dialysis (48%–62%), whereas OF (32%–37%) and low turnover bone remodeling (32%–36%) occur with similar frequency in hemodialysis patients. Mixed disease represents about 10% to 13% of cases of ROD, and low turnover osteomalacia is present in 3% to 8% of patients. We lack diagnostic tools to accurately assess bone remodeling and mineralization, other than bone biopsy, making it difficult to determine the type and magnitude of bone abnormalities in an individual patient with CKD.

When GFR declines below 60 mL/min/m^2,[75] excess PTH and decrements in $1,25(OH)_2D$ are the major factors leading to abnormalities of high bone remodeling and abnormal mineralization in CKD that characterize OF and MUO. The pathogenesis of PTH and $1,25(OH)_2D$ alterations in CKD were discussed earlier in this chapter.

Low turnover bone disease is at the opposite end of the bone remodeling spectrum and is characterized by a diminished bone formation rate, a paucity of bone cells, an absence of fibrosis, and an abnormal bone mineralization. Adynamic bone disease (ABD) and osteomalacia are variants of low turnover bone disease in CKD. A reduction in the osteoid accumulation and number of bone remodeling sites are predominant features of ABD, which represent a primary defect in osteoblast-mediated bone formation or osteoclast-mediated bone resorption, whereas increased relative osteoid defines the presence of osteomalacia, which is a primary defect in the mineralization of extracellular matrix.

The cause of low turnover bone disease in CKD is poorly understood and it is likely to be a multifactorial condition. First reports of low turnover bone disease were osteomalacic lesions associated with aluminum toxicity; however, it was quickly recognized that low turnover bone disease can occur without aluminum accumulation in the bone. Presently, the emphasis on pathogenesis of ABD in CKD is placed on oversuppression of circulating PTH levels and concomitant skeletal resistance to PTH actions due to downregulation of PTH1R. Exposure to high Ca through the use of Ca-containing phosphate binders and dialysate with high Ca is a risk factor for ABD. Metabolic acidosis and uremia-induced oxidative stress are additional CKD-related risk factors that can induce low turnover bone disease via suppression of active vitamin D and collagen synthesis and reduction of osteoblast life span, respectively.[76] An advanced age, presence of diabetes,

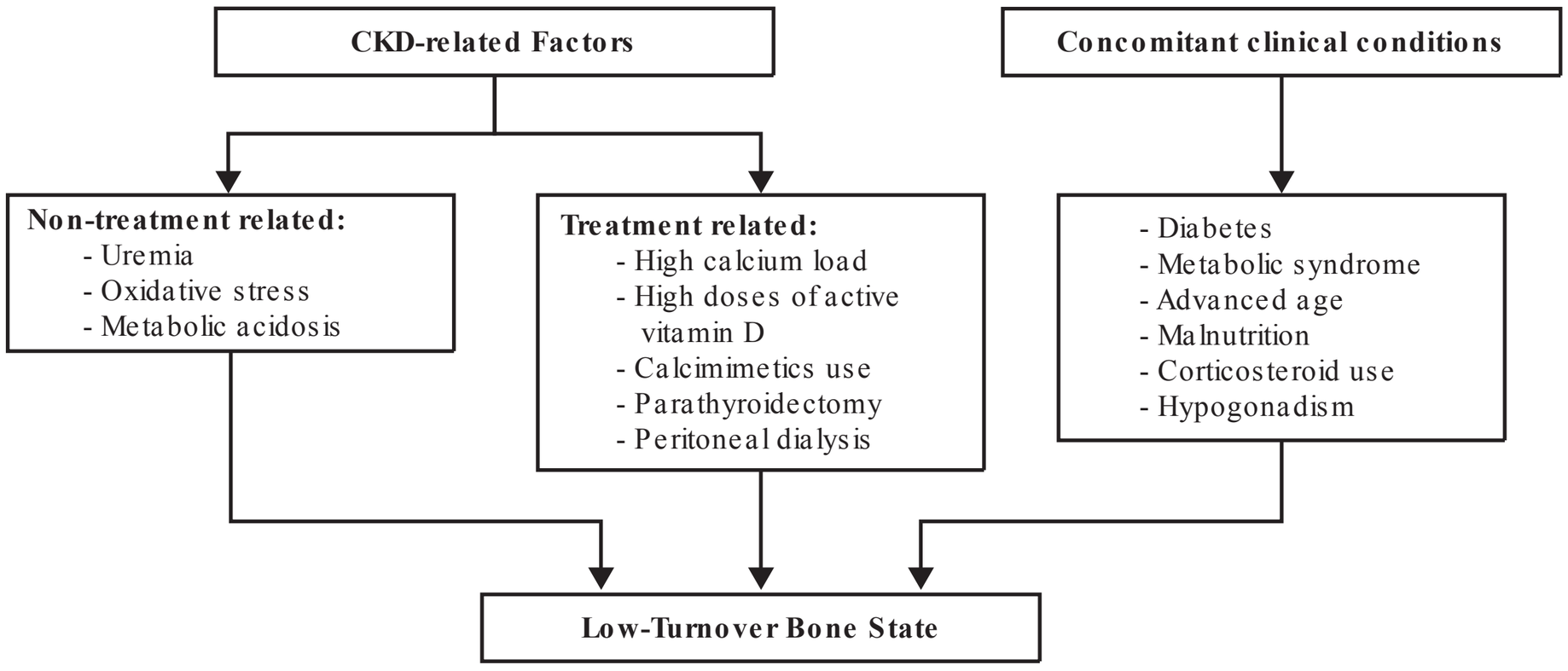

FIGURE 77.4 Low-turnover bone state risk factors.

hypogonadism, and a treatment with corticosteroids are also important clinical conditions associated with low turnover bone disease.[77] There is growing evidence linking ABD to the malnutrition-inflammation complex syndrome. Higher rates of ABD are reported in peritoneal dialysis patients with low albumin levels.[78] Additionally, several proinflammatory cytokines such as interleukin-1β and interleukin-6 were shown to inhibit PTH secretion in vitro.[79,80] Therefore, the development of ABD is influenced by patient characteristics, as well as treatment options for CKD-MBD (Fig. 77.4).

PTH is the most widely used surrogate marker of bone turnover (Table 77.4). Although relatively low to normal iPTH levels (<50–100 pg per mL) in ESRD patients are associated with biopsy proven ABD, higher iPTH levels (>300 pg per mL) can be also be seen in patients with biopsy-proven ABD,[81] especially in African Americans.[82,83] There are several proposed explanations of this variability of iPTH levels and ABD. First, iPTH assays and their ability to discriminate between whole PTH and its fragments differ across the studies. Some PTH fragments, such as 7–84PTH, can be actually inhibitory on bone formation and these fragments tend to accumulate in ESRD; therefore, higher PTH may not be equivalent of presence of high biointact PTH. Additionally, treatment modalities

77.4 Factors Regulating Parathyroid Hormone Secretion

Factor	Mechanism
Decreased PTH secretion	
Calcium	Direct activation of CaSR leading to posttranslational decrease in PTH secretion
Calcitriol	Direct inhibition of preproPTH gene transcription via VDR
	Indirect inhibition via increase in CaSR in parathyroid gland
FGF23	Direct inhibition of PTH mRNA expression
Increased PTH secretion	
High phosphorus	Posttranslational increase in PTH via stabilization of PTH mRNA
Low calcium	Indirectly via increase in unbound to calcium calreticulin that inhibits calcitriol action on PTH secretion
	Direct decrease in activation of CaSR
FGF23	Indirect increase in PTH secretion through decrease in calcitriol synthesis

PTH, parathyroid hormone; CaSR, calcium-sensing receptor; VDR, vitamin D receptor.

may influence bone formation rate independently from PTH levels. Lastly, PTH is not a bone-derived marker and therefore may never be a fully accurate indicator of bone turnover. At present, it is unknown what levels of PTH are associated with ABD in patients with less severe CKD not yet on renal replacement therapy. Bone-specific alkaline phosphatase (BSAP) may be an additional useful marker of ABD. Low levels of BSAP predict ABD and BSAP correlates with bone turnover in ESRD patients treated with hemodialysis.[82]

Fracture Risks in Chronic Kidney Disease

Patients with ESRD have fourfold increased risk of fractures; and the highest risk (10- to 100-fold increase) of fractures is observed in ESRD patients below age 65 as compared with age-matched individuals from the general population.[84] The risk of fractures is also augmented in early CKD.[85,86] Vertebral and hip fractures are shown to independently increase all-cause mortality in CKD patients.[87,88] The fracture risk in patients with low turnover bone disease remains controversial as no biopsy-proven studies are available investigating the association between adynamic bone disease and fractures in CKD patients. Because ABD is linked to PTH oversuppression, several studies demonstrated the association between relatively low to normal PTH levels and the risk of vertebral and hip fractures.[89,90] However, in a case-control study, dialysis patients who underwent parathyroidectomy were found to have 32% lower risk for hip fractures, and 31% lower risk for any fractures as compared with matched controls.[91]

Bone Disease and Vascular Calcifications

Vascular calcifications, and especially arterial calcifications, are very common in patients with CKD and correlate with cardiovascular complications.[92] The prevalence of vascular calcifications is the highest among patients with ESRD[93,94]; however, patients with CKD stages 2 to 4 are also found to have increased vascular calcifications on imaging studies as compared with the general population.[95] There are two types of arterial calcifications with different clinical consequences: one affects intimal layer of arteries and is associated with atherosclerotic plaque, and the second type involves medial wall or arteries (Mönckeberg sclerosis). The atherosclerotic plaques are usually patchy in distribution and lead to chronic and acute end-organ ischemia from vessel lumen obstruction from the plaque itself or acute thrombosis following plaque rupture, respectively. On the other hand, medial arterial calcifications are more diffuse and increase vessel stiffness and reduce vascular compliance. As the result of the latter, blood pressure rises with the development of left ventricular hypertrophy that compromises myocardial perfusion during diastole and is associated with high mortality rates in patients with ESRD.[96,97] The mechanism of vascular calcification is not completely understood and is likely multifactorial, involving factors promoting transformation of vascular smooth muscle cell into "bone-like" cells, elevation of calcium and phosphorus due to altered bone and mineral metabolism, low levels of circulating and locally produced inhibitors, impaired renal excretion, and current therapies such as the use of calcium-containing phosphate binders and active vitamin D.[98] There is well documented association between increased vascular[99,100] and soft tissue calcifications[101] and the biopsy-proven ABD in ESRD patients. ABD is characterized by a reduced bone ability to incorporate extracellular calcium and, therefore, diminished ability to buffer calcium load leading to more frequent hypercalcemia.[102,103] Cardiovascular mortality is shown to be increased in dialysis patients with higher burden of vascular calcifications and some observational studies also revealed increased mortality in patients with relatively low to normal PTH supporting ABD as a strong risk factor for cardiovascular death.[104] Interestingly, parathyroidectomy in ESRD patients was shown to improve long term survival by 15% in observational study; although postoperative PTH levels were not provided.[105]

PARATHYROID GLAND ABNORMALITIES

Parathyroid cells are generally quiescent and rarely divide under normal physiologic conditions. In addition to increased PTH secretion, stimulation of parathyroid gland (PTG) during the course of CKD leads initially to diffuse polyclonal proliferation (hyperplasia) followed by monoclonal nodular hyperplasia, which can be diffuse or have a predominant nodule.[106] Factors associated with PTG hyperplasia are listed in Table 77.5. Low Ca is involved in activation of parathyroid gland growth. In animal models, a diet low in Ca was shown to increase parathyroid cell proliferation 10-fold,[107] and in rats with kidney failure, the administration of a calcimimetic compound that binds to CaSR attenuated the parathyroid cell proliferation.[108] In addition to low serum Ca, high serum Pi is the major factor leading to parathyroid cell proliferation[107] and low Pi diet reduces parathyroid cell proliferation and PTH mRNA levels. In severe hyperparathyroidism, there is also a reduction in the number of CaSR, effectively shifting the calcium-PTH set point toward greater PTH secretion for any given serum Ca concentration and a loss of inhibitory Ca role on PTG growth.[109,110] Decrease in CaSR and VDR expression is observed during parathyroid proliferation and is especially pronounced in nodular hyperplasia.[44,58,111,112] Density of VDR was reported to be negatively correlated with both the weight and proliferative activity of the glands.[113] Administration of calcitriol and calcimimetics was shown to result in decrease of parathyroid cell proliferation and was associated with elevation of CaSR and VDR.[114,115] Moreover, low serum Ca may interfere with $1,25(OH)_2D$ action by inducing resistance to vitamin D via reduction of VDR[116] and upregulation of calreticulin.

77.5 Factors Regulating Parathyroid Gland Proliferation

Factor	Mechanism
Inhibitors of polyclonal PTG proliferation	
$1,25(OH)_2D$	Decreased c-myc expression that modulates cell cycle progression via VDR
	Activation of p21 gene expression that inhibits cell cycle
	Downregulation of EGFR signaling
	Indirect effect via upregulation of CaSR
Calcium	Direct effect via activation of CaSR
Stimulator of polyclonal PTG proliferation	
High phosphorus	Inhibits p21 gene expression and promotes cell cycle
Stimulators of monoclonal transformation	
Decreased CaSR gene expression	Decreased activation of CaSR
Decreased VDR gene expression	Decreased activation of VDR
Increased expression of EGFR	Decreased VDR gene expression

$1,25(OH)_2D$, active vitamin D; VDR, vitamin D receptor; EGFR, epidermal growth factor receptor; CaSR, calcium-sensing receptor, PTG, parathyroid gland.

Calreticulin is a calcium-binding intracellular protein, and when is unbound can inhibit $1,25(OH)_2D$ action on PTH gene transcription.[117] Enhanced expression of two receptors for potent growth promoters such as transforming growth factor alpha (TGFα) and epidermal growth factor (EGF) was also described to contribute to PTG hyperplasia in patients with CKD.[118,119] In nodular hyperplasia, activation of EGFR by TGFα was shown to be associated with 80% reduction of VDR mRNA levels leading to $1,25(OH)_2D$ resistance.[118] It is uncertain, at present, if impaired apoptosis contributes to PTG hyperplasia.

The reversibility of PTG hyperplasia is a subject of debate.[120,121] Size of PTG as determined by ultrasound has been shown to be a sensitive indicator of therapeutic responsiveness to pharmacologic treatment of SHPT. Histologic studies demonstrated that PTG heavier than 0.5 to 1.0 g were composed in the majority of cases of nodular hyperplasia[122] and were refractory to therapy with calcitriol or its analogs.[123,124]

CLINICAL MANIFESTATIONS OF CKD-MBD

Patients with SHPT frequently remain asymptomatic even with advanced disease and presence of biochemical and imagining abnormalities. In general, signs and symptoms are nonspecific (Table 77.6) and related to osteitis fibrosa or electrolyte changes such as hypercalcemia and/or hyperphosphatemia. The severity of symptoms also varies from moderate bone or joint pains and bone deformities and fractures to life threatening calciphylaxis and cardiovascular disease as a result of calcium deposition in vasculature and other organs. Fracture risk, vascular calcifications, and mortality associated with CKD-MBD were discussed earlier in this chapter.

DIAGNOSIS OF CKD-MBD

Diagnostic tests for CKD-MBD are divided into biochemical, imaging, and bone biopsy and will be briefly discussed in the following sections.

Serum Markers of CKD-MBD

Parathyroid Hormone

The biochemical diagnosis of SHPT relies on finding of elevated serum iPTH. The most commonly used assays for PTH determination represent second generation two-site immunometric assays that recognize full length intact 1–84 PTH; however, this assay also cross reacts with large PTH fragments, such as 7–84 PTH which antagonizes PTH action on elevation of serum Ca levels and osteoblasts.[59]

77.6 Signs and Symptoms of Secondary Hyperparathyroidism

Skeletal	Extraskeletal
Osteoporosis	Vascular calcification leading to cardiovascular disease
Bone fractures	Calciphylaxis (calcific uremic arteriopathy)
Bone and joint pain	Pruritus
Bone deformities	Anemia
Growth retardation in children	Red eye syndrome

1–84 PTH usually represents only 50% to 60% of whole PTH determined by these assays. There has been developed a new third generation assay that measures only the full length 1–84 PTH (biointact PTH) and not amino-terminally truncated fragments.[125] Additionally, the measurement of a ratio of 1–84 PTH to large C-terminal fragments has been proposed[126] for evaluation of high turnover bone disease; however, the usefulness of these new methods remains to be elucidated.

Calcium and Phosphate

Ca and Pi usually remain normal until GFR reaches below 30 to 40 mL/min/m^2 and then Ca tends to fall while Pi rises.[6] Nonetheless, hypercalcemia can also be observed in setting of large doses of vitamin D administration, especially while using calcium-containing phosphate binders, or with the development of severe hyperparathyroid bone disease. Pi is almost uniformly high in untreated patients with ESRD; however, normal and even low Pi may be present with concomitant malnutrition.

Vitamin D Metabolites

25-hydroxyvitamin D deficiency is common in CKD patients.[6,127] 25-Hydroxyvitamin D is shown to correlate with PTH levels and the rate of bone turnover[128] and is considered as the best index of vitamin D status in CKD patients because of its long half-life (about 3 weeks) and ability to access both endogenous and exogenous sources of vitamin D. Additionally, levels of 25-hydroxyvitamin D positively correlate with serum $1,25(OH)_2D$ in CKD patients but not in healthy individuals,[129,130] suggesting that $1,25(OH)_2D$ production is more dependent on substrate availability in CKD. $1,25(OH)_2D$ is not routinely measured in patients with CKD because its levels do not differentiate between different histologic variants of renal osteodystrophy nor predict any other clinical outcomes.

Markers of Bone Formation and Resorption

Bone formation markers such as total alkaline phosphatase (TALP) and bone-specific alkaline phosphatase (BSALP) are useful markers of bone turnover in CKD. Importantly, metabolism of TALP and BSALP is not impaired by the presence of reduced GFR and higher levels of BSALP correlate with high rates of bone turnover and PTH.[131,132] Usefulness of BSALP in the predicting of high and low turnover bone disease is further increased if BSALP is combined with simultaneous measurements of iPTH.[133,134] Osteocalcin (OC) and tartrate-resistant acid phosphatase (TRACP) are two markers of bone resorption that also have been shown in small studies to correlate with histomorphometric parameters of bone turnover.[132] OC accumulates with CKD and its low levels are sensitive in predicting low turnover bone disease,[135] whereas TRACP levels are not affected by CKD and high levels predict osteoclastic activity and high turnover bone disease.[136] Nevertheless, the role of OC and TRACP is still under investigation.

FGF23

Elevated FGF23 predicts all-cause mortality and faster evelopment of ESRD as discussed previously. Therefore, FGF23 level may be a useful prognostic marker; however, its determination is available only in experimental research.

Imagining Studies

X-rays

Although routine radiography is not used in diagnosis of ROD, plane X-rays can help in differential workup by revealing several skeletal abnormalities of CKD-MBD.[137,138] Subperiosteal bone resorption is a feature of advanced SPHPT and in adults most commonly affects the phalangeal tufts, the radial aspect of the proximal and middle phalanges of the fingers, the metatarsals, the rib margins, the lamina dura, and the medial margins of the proximal humerus, femur, and tibia. Subchondral resorption can occur at several sites, including the sternoclavicular and acromioclavicular joints, the symphysis pubis, the sacroiliac joints, and the diskovertebral joints. Additionally, an erosive type arthropathy is reported with secondary hyperparathyroidism. Brown tumors are a manifestation of advanced SHPT and are seen rarely with modern therapy of CKD-MBD. Brown tumors radiographically can look similar to lytic lesions and can occur essentially in any bone. Plain X-ray also detects extra-osseous calcifications developing with SHPT such as vascular calcifications, calcified pulmonary nodules, chondrocalcinosis, and calcifications of various organs (breast, heart, liver, and kidney).

Computer Tomography

Computed tomography (CT) is not routinely used for diagnosis of ROD, as CT scan is not sensitive in detecting changes related to SHPT. However, several CT techniques have been successfully applied for the diagnosis of vascular calcifications.[139]

Bone Biopsy

Bone biopsy with quantitative histomorphometric analysis is a gold standard in diagnosis of renal osteodystrophy. Yet, bone biopsy is not routinely performed because of its invasive nature and the ability of iPTH to predict type of bone disease in CKD patients due to reasonably reliable correlation between levels of iPTH and bone histology. Nevertheless, bone biopsy remains an important tool in differentiation of low and normal bone turnover disease, or when aluminum-related bone disease is suspected. General indications for bone biopsy are listed in Table 77.7. We will conclude this chapter by discussing general therapeutic approaches for the treatment of CKD-MBD.

TREATMENT OF CKD-MBD

General Strategy Overview

Treatment strategies differ for the various stages of CKD. The abnormalities in mineral metabolism begin from stages 2 to 4 of CKD; therefore, the prevention and treatment of CKD-MBD should be started early in the course of kidney disease before elevations in serum phosphate or reductions in serum calcium. At present serum PTH and FGF23 levels are not routinely measured in patients with mild degrees of renal dysfunction. Serum 25(OH)D levels are commonly measured in the general population and efforts to normalize 25(OH)D levels in CKD seem to be a reasonable therapeutic goal as low levels of 25(OH)D are known to cause secondary HPT even in patients with normal kidney function.[140] Treatment with phosphate binders in early CKD is theoretically attractive when there is evidence for increased fractional excretion of phosphate, but at present the use of phosphate binders in CKD patients with normal serum phosphate levels is not approved and their effects have not been studied in clinical trials. Once secondary hyperparathyroidism has developed, as evidenced by elevated serum PTH levels, treatment with calcium supplementation and use of active vitamin D sterols can be considered. Calcimimetics are not approved for use in early stages of CKD stages 3 to 5 and their use in this setting suppresses PTH but increases serum phosphate levels. In contrast, active vitamin D analogues suppress PTH in CKD stages 3 and 4 without increasing serum phosphate levels, possibly due to their effect to also stimulate FGF23. The asymptomatic nature of CKD-MBD contributes to the challenge of treating this disorder. In CKD stage 5D, combinations of treatments are needed to reduce serum phosphate levels while suppressing PTH concentrations that include the use of calcium and noncalcium phosphate binders (for phosphate control) and the use of active vitamin D analogues and calcimimetics (alone or in combination) to suppress circulating PTH levels and to prevent the progression of parathyroid gland diseases, while optimizing bone health. Different treatment strategies include: (1) use of increasing doses of active vitamin D analogues and increasing does of phosphate binders versus (2) use of increasing doses of cinacalcet, fixed physiologic replacement doses of active vitamin D analogues, and phosphate binders to suppress PTH and treat hyperphosphatemia.

77.7 Indications for Bone Biopsy in Patients with Chronic Kidney Disease

Discrepancy between biochemical parameters leading to no conclusion
Fracture or unexplained bone pain
Severe progressing vascular calcifications
Unexplained hypercalcemia
Suspicion of aluminum intoxication
If considering treating a patient for fractures

Treatment Target Guidelines

There are several clinical practice guidelines such as Kidney Disease Outcomes Quality Initiative (KDOQI),[141] Kidney Disease: Improving Global Outcomes (KDIGO),[1] and Japanese Society of Dialysis Therapy (JSDT)[142] that developed recommendations for the target levels of serum Ca, Pi, and PTH at different stages of CKD (Table 77.8). All these guidelines regarded CKD-MBD as systemic disorder and uniformly agreed on the paramount importance of maintaining Ca and Pi homeostasis as close to normal as possible irrespective of degree of renal impairment in order to avoid the development of vascular calcifications. However, KDOQI, KDIGO, and JSTA have different target ranges for PTH. KDOQI PTH targets between 150 and 300 pg per mL is based on the estimated levels of PTH to maintain normal bone remodeling, with the higher than normal range reflecting the resistance to PTH actions and assessment of circulating inactive PTH fragments in dialysis patients.[143] The emphasis of changes in PTH and higher (i.e., <600 pg per mL) threshold PTH concentrations in the KDIGO recommendations reflects the variability in existing PTH assays in measuring bioactive PTH and the recognitions that high PTH values are associated with increased mortality. In contrast, for the patients with ESRD JSTA advocates PTH concentrations closer to the normal range for the general population, which emphasizes the prevention of progressive parathyroid gland hyperplasia.[144]

77.8 Target Levels for Calcium, Phosphorus, and Parathyroid Hormone

	KDOQI	KDIGO	JSDT
Calcium			
CKD stage 3–5	Normal range	Normal range	N/A
CKD stage 5D	Normal range	Normal range: 8.4–10 mg/dL	Preferably 8.4–9.5 mg/dL
Phosphorus			
CKD stage 3–4	2.7–4.6 mg/dL	Normal range	N/A
CKD stage 5	3.5–5.5 mg/dL	Normal range	N/A
CKD stage 5D	3.5–5.5 mg/dL	Toward normal range	3.5–6 mg/dL
Intact PTH			
CKD stage 3	35–70 pg/mL	Optimal level is unknown	N/A
CKD stage 4	70–110 pg/mL	Optimal level is unknown	N/A
CKD stage 5	200–300 pg/mL	Optimal level is unknown	N/A
CKD stage 5D	200–300 pg/mL	2–9 times above upper limit of normal	60–180 pg/mL

KDOQI, Kidney Disease Outcomes Quality Initiative; KDIGO, Kidney Disease: Improving Global Outcomes; JSDT, Japanese Society of Dialysis Therapy; PTH, parathyroid hormone; CKD stage 3: glomerular filtration rate (GFR) 30–59 mL/min/m^2; CKD stage 4, GFR 15–29 mLmin/m^2; CKD stage 5, GFR ≤15 mL/min/m^2 but not on dialysis; CKD stage 5D, GFR ≤15 mL/min/m^2 on dialysis.

Specific Treatments

Maintenance of Neutral Phosphorus Balance

The maintenance of normal Pi level is the goal. The rationale to maintain normal Pi level in CKD comes from human observational studies linking Pi levels above the normal range with the increased mortality, presence of soft tissue and vascular calcifications, and from the experimental data strongly supporting the role of Pi in the development of SHPT, calcitriol deficiency, and extraskeletal calcifications. Recommended level of Pi depends on stage of CKD with the goal to maintain normal serum Pi in mild to moderate CKD (stages 3 to 4) or 2.7 to 4.6 mg per dL, and toward normal levels for ESRD, 3.5 to 5.5 mg per dL.[141] Adequate Pi level can be achieved by the restriction of amount of Pi absorbed in gastrointestinal (GI) tract by limiting dietary Pi intake and the use of Pi binders. Dietary Pi absorption is dependent on active vitamin D; therefore limiting dose of vitamin D analogs administered for the control of elevated PTH may also reduce the amount of absorbed Pi in the intestine. In patients with ESRD, hemodialysis and peritoneal dialysis also contribute to normal Pi balance by elimination of Pi from the body.

Diet. Pi retention due to reduced nephron mass from CKD plays a critical role in the development of CKD-MBD. Therefore, it is logical to implement primary prevention of CKD-MBD by introducing moderate Pi restriction by means of mild protein restriction from earliest stages of CKD, even before any abnormalities in Pi level or PTH are detected.[141] KDOQI[141] specifically recognized the limitations of the above conclusion as it is based on: (1) studies that primarily restricted protein intake and therefore, only indirectly restricted Pi intake; (2) it is possible to restrict protein intake without restricting Pi intake; (3) most of the reports provided analysis for "prescribed diet" rather than "consumed diet"; and (4) in many studies, the patients had concomitant therapy with vitamin D and/or phosphate binders making interpretation of the results difficult. In order to accomplish the Pi restriction, it is critical to gain the knowledge on the best but yet minimally invasive and less costly way to educate patients on low Pi diet. It is essentially unknown what intervention is needed for patients to reduce their Pi intake. Additionally, it is unknown if low Pi diet could actually achieve its goal of reducing CKD-MBD. The data about beneficial effects of low Pi diet on improving parameters of CKD-MBD are scarce and controversial at present, with some studies showing no benefit in PTH or FGF23,[145] whereas others showing improvement in PTH levels.[146,147]

Dietary Pi consumption parallels intake of protein and it is not uncommon to observe normal and even low levels of Pi in uremic patients who have inadequate protein intake. It is important to avoid malnutrition while minimizing Pi intake and this potentially could be achieved by choosing protein from plant sources. Pi in meats is stored in organic form which is easily hydrolyzed and absorbed in gastrointestinal tract. Three fourths of Pi in plant proteins is in inorganic form and humans lack the enzyme phytase that is necessary

77.9 Classification of Phosphate Binders: Advantages and Disadvantages

Drug	Advantages	Disadvantages
Calcium-containing	Effective, inexpensive	May cause hypercalcemia and/or promote vascular calcifications
Sevelamer	Effective, may reduce GI side effects (nausea, vomiting, vascular calcifications, diarrhea, bloating, abdominal pain) due to less hypercalcemia	Expensive, higher pill burden as compared with Ca-based binders
Lanthanum	Effective, less hypercalcemia	Expensive, long-term safety unknown, various GI side effects
Magnesium-containing	Effective, inexpensive	GI side effects (diarrhea), rare respiratory depression
Aluminium-containing[a]	Effective, inexpensive	Encephalopathy, anemia, osteomalacia

[a]Aluminum-based binder use should be limited to 4 weeks.[1]
GI, gastrointestinal; Ca, calcium.

for its hydrolysis and subsequent absorption. Therefore, bioavailability of Pi from plant sources is significantly less than from animal origin.

Phosphate Binders. With the progression of CKD, dietary Pi restriction alone is not sufficient to maintain normal Pi levels. Therefore, specific treatment is usually needed in the form of oral Pi binders aimed to prevent systemic Pi absorption from the gut. Nevertheless, the use of Pi binders should always be combined with dietary Pi restriction in order to reduce pill burden from Pi binders and their potential side effects. Many compounds have been found to be effective Pi binders such as aluminum, magnesium, iron, calcium, and lanthanum salts, and nonabsorbable polymers. Their efficacy and side effects vary widely and are summarized in Table 77.9. Calcium-containing phosphorus binders and sevelamer have become most commonly used contemporary Pi binders. Ca-containing binders are cheap, effective, and well tolerated by patients. Their popularity has been decreasing in recent years due to accumulating evidence that Ca binders may contribute to progression of vascular calcifications and low turnover bone disease in patients with CKD, and therefore, higher CV mortality as compared with sevelamer-containing binders, although no data from randomized controlled trials exists to support this theory. Most common side effects of Ca-containing Pi-binders is hypercalcemia and KDOQI recommends limiting daily Ca intake to 2,000 mg of elemental Ca including Ca from Ca-based agents.[141] Nonabsorbabale polymer sevelamer, which acts as an anion-exchange resin, has many potential advantages over Ca-based binders as its use is not associated with Ca load and also can lower LDL cholesterol; therefore, having potential advantageous effect on cardiovascular disease. However, there is a controversy as to whether sevelamer use is associated with reduced risk of vascular calcifications, and there is no data to support its superior role in reducing cardiovascular mortality on CKD patients. Additionally, it is expensive and requires significantly higher pill count to achieve adequate Pi control as compared with Ca-based binders. Lanthanum is a newest and highly potent Pi binder. It is expensive and its long-term safety is still unknown.

Removal of Phosphate with Hemodialysis and Peritoneal Dialysis. Once a patient with CKD reaches ESRD, RRT in a form of hemodialysis (HD) or peritoneal dialysis (PD) becomes an additional means of Pi elimination. HD is more efficient in removing Pi with a single 4-hour HD session eliminating about 800 mg of Pi. About 300 mg of Pi is removed during daily PD but weekly removal of Pi is comparable in both modalities, as PD is a daily treatment, as opposed to thrice weekly conventional HD. It is important to recognize that neither conventional HD nor PD can substitute for normal kidneys for the elimination of all absorbed dietary Pi. Even with moderate Pi restriction to 800 mg per day, assuming that 40% to 80% of dietary Pi absorbed, up to 5,600 mg of Pi is gained per week in patients with ESRD, whereas only about 2,400 mg of Pi can be removed with RRT, leading to a positive Pi balance. Therefore, patients with ESRD must continue to follow dietary Pi restriction and use Pi binders on daily basis. The limitation of Pi removal with hemodialysis is due to majority of body Pi being distributed intracellularly. When dialysis is started, the plasma concentration

of Pi falls rapidly during first 60 to 90 minutes.[148] After this initial phase, the removal of Pi is limited by Pi transfer from intracellular to intravascular space which is rate-limited step in Pi clearance. Different approaches tested, such as use of low and high flux dialyzer membranes,[149,150] delayed correction of metabolic acidosis,[151] or lengthening the hemodialysis session were not found to increase Pi removal with hemodialysis. However, increasing frequency of HD sessions to six or seven times per week as with short daily HD or nocturnal HD can lead to improved Pi control with lesser dose of Pi binders and even discontinuation of Pi binders.[152,153]

Other Approaches for Reduction of Dietary Phosphate Absorption

Reduction of Dose of Active Vitamin D and Its Analogs. Because the administration of active vitamin D analogs increases GI Ca and Pi absorption, their use is associated with both hypercalcemia and hyperphosphatemia. Therefore, the prescription of lower doses of active vitamin D analogs and alternative strategies to suppress PTH may lead to lower Pi absorption by the GI tract, and lower serum Pi.

Niacin. Niacin is converted into niacinamide during its metabolism and reduces intestinal transport of Pi via inhibition of Na-Pi cotransporter 2b which is responsible for up to 50% of absorbed Pi. Both niacin and niacinamide are available pharmacologically. As oppose to niacin, niacinamide does not cause vasodilatation or flushing because it does not activate G-protein coupled receptors for niacin. However, niacinamide has no lipid-lowering properties of niacin. Niacinamide has been shown in small clinical trials to effectively reduce serum Pi levels in hemodialysis patients,[154,155] as well as peritoneal dialysis patients.[156] Niacin was also found to successfully lower Pi while additionally elevating high density lipoprotein cholesterol in a prospective observational study.[157]

Maintenance of Normal Calcium Level

Maintenance of Ca in normal range is the goal in CKD, and both hypocalcemia stimulating PTH release and hypercalcemia that can lead to vascular and soft tissue calcifications should be avoided. Ca intake in patients with CKD requires individualization to account for the use of Ca-based Pi binders, presence of vascular calcifications, and low turnover bone disease. It is recommended that most CKD patient consume no more than 2 g of elemental Ca per day to avoid hypercalcemia. However, patients after parathyroidectomy may be an exclusion from this rule and require substantial amounts of Ca to maintain eucalcemia. Because Ca absorption in GI tract is vitamin D dependent, CKD patients should be screened for vitamin D deficiency and treated to maintain 25-hydroxyvitamin D levels above 30 ng per mL.[141]

Administration of Vitamin D

There are three forms of vitamin D (Fig. 77.5): (1) provitamin D (or simply vitamin D) includes ergocalciferol of plant source (vitamin D_2) and cholecalciferol (vitamin D_3) which could be of animal source or produced from skin 7-dehydrocholesterol under exposure to ultraviolet B solar radiation; (2) 25-hydroxyvitamin D (25(OH)D), precursor of active form of vitamin D that is produced in the liver after vitamins D_2

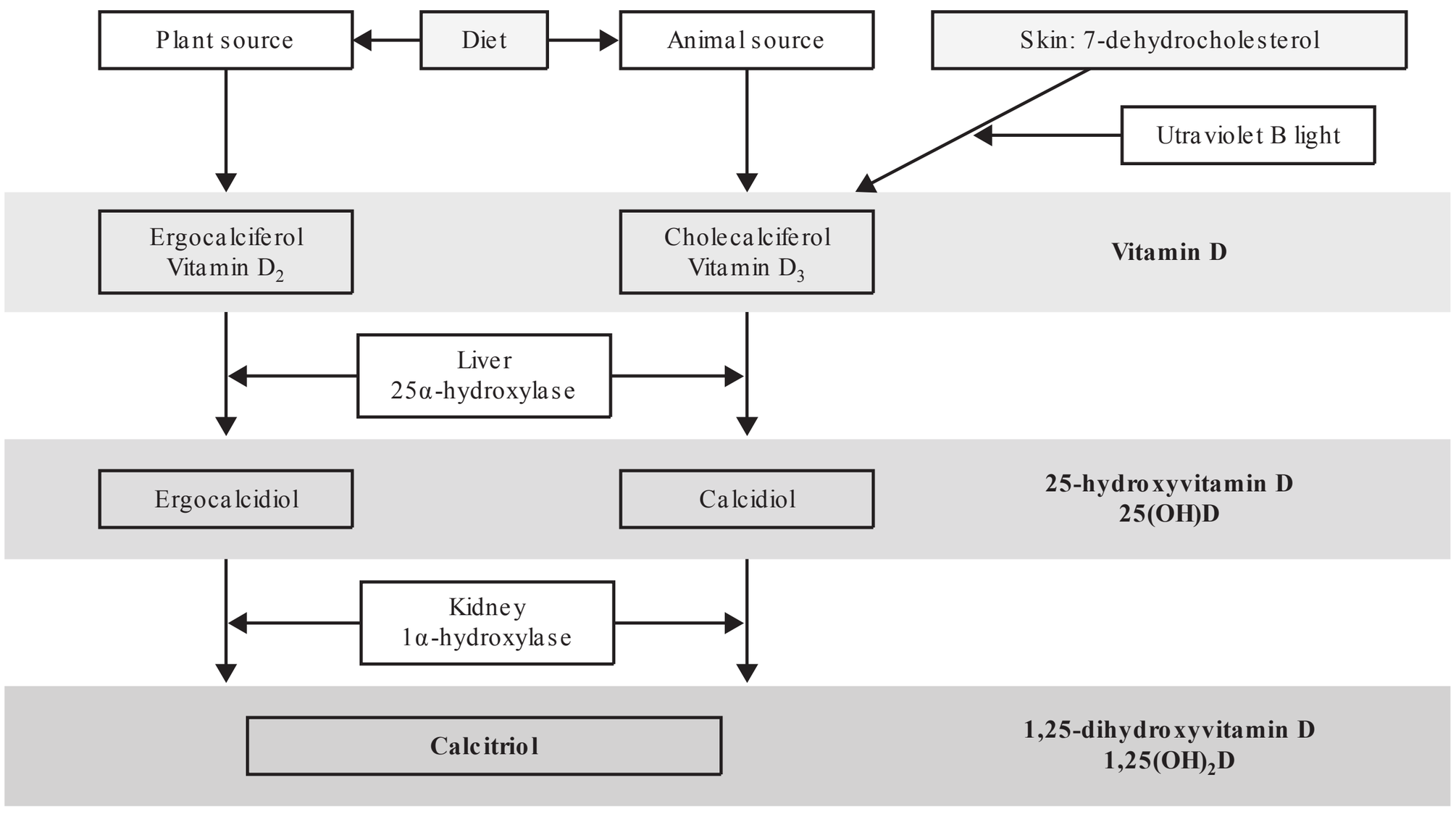

FIGURE 77.5 Sources, pathways of conversion, and classification of vitamin D.

and D_3 undergo hydroxylation by 25α-hydroxylase; and (3) active vitamin D or 1,25-dihydroxyvitamin D or calcitriol ($1,25(OH)_2D$) is produced in the kidneys after additional hydroxylation of 25(OH)D by 1alpha-hydroxylase. The therapeutically available forms of vitamin D include naturally occurring ergocalciferol, cholecalciferol, calcidiol, calcitriol, and synthetic forms such as vitamin D_2 analogs (doxercalciferol, paricalcitol), and vitamin D_3 analogs (alfacalcidol, falecalcitriol, maxacalcitol). Vitamin D analogs do not require 1alpha-hydroxylation for their activity.

Vitamin D deficiency in CKD patients is common and the administration of 25(OH)D to achieve its serum levels above 30 mg per mL (75 nmol/L) has been shown to positively impact elevated levels of PTH in patients with CKD stages 3 to 4.[158,159] Nutritional vitamin D therapy is less effective in reducing PTH[160] and restoring bone histology to normal[161] in hemodialysis patients. Nevertheless, in addition to the role of active vitamin D in bone health and regulation of mineral homeostasis, the local extrarenal tissue conversion of 25(OH)D into $1,25(OH)_2D$ is important for the regulation of immune responses, oxidative stress, cell differentiation, and blood pressure regulation.[162,163] A study of hemodialysis patients demonstrated that cholecalciferol administration was associated with the reduction in production of inflammatory cytokines by circulating monocytes.[164] The recommended by KDOQI ergocalciferol dose is 50,000 units and its frequency ranges from once a week to once a month for a total course of 6 months depending on the severity of vitamin D deficiency.[141]

If despite adequate 25(OH)D level PTH remains elevated, then active vitamin therapy in the form of calcitriol or vitamin D analogs can be successfully used for the treatment of elevated PTH in CKD.[1,141] Calcitriol and vitamin D analogs effectively lower PTH levels in stages 2 to 5 of CKD including patients on RRT, and all can cause hypercalcemia and hyperphosphatemia in a dose-dependent manner.[1] There are no comparative trials on the superiority among different active vitamin D regimens in reducing PTH of CKD patients not yet on RRT; and only two studies that compared calcitriol to maxacalcitol[165] and calcitriol to paricalcitol[166] in hemodialysis patients. These trials revealed similar efficacy of these agents in reducing PTH and comparable adverse profiles, including the incidence of developing elevated Ca and Pi levels and oversuppression of PTH. Therefore, Ca, Pi, and PTH levels need to be closely monitored during vitamin D therapy. In addition to PTH-lowering effect, calcitriol and vitamin D analogs have been shown to improve bone histology,[167] and offered survival benefit for CKD patients in observational studies; however, this hypothesis needs to be confirmed in randomized trials.[168]

Use of Calcimimetics to Suppress Parathyroid Hormone

It is a unique group of drugs that allosterically regulate CaSR and inhibit PTH secretion by sensitizing the parathyroid calcium receptor to extracellular calcium, and hence, "mimic" effects of increased extracellular calcium.[112,169] Cinacalcet is the only drug of this class that is available in clinical practice for the treatment of SHPT in patients with stage 5 CKD on dialysis since its U.S. Food and Drug Administration (FDA) approval in 2004; cinacalcet effectively lowers PTH in ESRD patients (treated with both hemodialysis and peritoneal dialysis).[170,171] In the OPTIMA study, the addition of cinacalcet was shown to increase the proportion of patients achieving serum PTH, Ca, and Pi within KDOQI target levels as compared to conventional therapy (active vitamin D therapy and phosphorus binders) alone.[172] Moreover, cinacalcet is useful for PTH control in patients with elevated calcium and Pi[173]: in hemodialysis patients with PTH controlled by high dose of vitamin D therapy but elevated serum Ca and Pi, addition of cinacalcet to a usual treatment (active vitamin D and phosphorus binders) allowed patients to maintain PTH within KDOQI targets while lowering serum Ca and Pi as compared with the usual treatment alone. The ability of cinacalcet to lower serum Pi in dialysis patients is likely related to PTH reduction and, therefore, reduced Pi translocation from the bone while having no effect on intestinal Pi reabsorption that defer cinacalcet from active vitamin D therapy. In contrast to CKD5D, cinacalcet is not recommended in the treatment of SHPT in patients with earlier CKD stages (3–4)[1] because its use was associated with documented hypocalcemia and paradoxical increase in serum Pi levels and need for Pi-binders.[174] However, the latter phenomenon in that study was likely related to the more frequent vitamin D use in the cinacalcet group.

The data on the effects of calcimimetics on bone histomorphology in patients with CKD are limited. As expected from its ability to suppress PTH, cinacalcet use is associated with higher incidence of development of low turnover bone disease as compared with the placebo.[175] On the other hand, there is a theoretical advantage of using cinacalcet for the prevention of ABD development while treating secondary hyperparathyroidism in patients at high risk for ABD, such as elderly diabetic patients: cinacalcet is able to maintain pulsatile PTH secretion pattern which is anabolic for the bone. In animal CKD models, cinacalcet restored low bone formation[176] and in phase 3 clinical trials use of cinacalcet in combination with active vitamin D analogues reduced fracture risk.[177] Unlike active vitamin D analogues, cinacalcet treatment does not lead to further elevations of circulating FGF23.[178] Current trials are under way that investigate the effects of cinacalcet on mortality in patients with ESRD.

Parathyroidectomy

The surgical correction remains the final therapy of the most severe forms of SHPT which cannot be controlled by medical management. Failure of medical treatment could result from ineffectiveness of medical therapy (combination of low Pi diet, Pi binders, active vitamin D, and cinacalcet)

77.10 Indications for Parathyroidectomy

ESRD patients and severe HPT (generally PTH> 800 pg/mL and elevated AP) **and additional:**
Persistent hypercalcemia
Persistent hyperphosphatemia
Persistently elevated PTH despite adequate treatment
Progressive extraskeletal calcifications, including calciphylaxis
Persistent pruritus
Kidney transplant candidates with
Persistently elevated PTH and parathyroid hyperplasia[a]
Kidney transplant recipients with
Persistently elevated PTH with hypercalcemia
Persistently elevated PTH with unexplained worsening of allograft function

[a]Specific level of PTH is not established.
ESRD, end-stage renal disease; HPT, hyperparathyroidism; PTH, parathyroid hormone; AP, alkaline phosphatase.

leading to the complications of SHPT, or patient intolerance of medical treatment due to its side effects. There is a paucity of data available on effects of parathyroidectomy on cardiovascular, bone histology, biochemical, or other outcomes as discussed previously in clinical manifestation section. General indications for parathyroidectomy are listed in Table 77.10. Most commonly, two types of parathyroidectomy are performed: subtotal parathyroidectomy or total parathyroidectomy with autotransplantation. The presence of severe form of SHPT is ascertained by clinical, biochemical, and radiologic evidence. Clinical symptoms such as pruritus and periarticular pain are nonspecific and cannot be used in isolation as indication for parathyroidectomy. Similarly, hypercalcemia even in presence of soft tissue calcifications is not sufficient to warrant parathyroidectomy, because low turnover bone disease can also be associated with hypercalcemia and elevated Pi. In general, patients requiring parathyroidectomy have PTH levels exceeding 800 pg per mL and with elevation of alkaline phosphatase. Parathyroidectomy is recommended for kidney transplant recipients with persistent PTH elevation associated with hypercalcemia and worsening of kidney function. Additionally, parathyroidectomy can be considered in kidney transplant candidates even without severe symptoms if they have continuously high levels of PTH and parathyroid hyperplasia that is unlikely to regress after kidney transplantation—although no specific level of PTH at which parathyroidectomy would be warranted is established.

Special Consideration for the Treatment of Adynamic Bone Disease

Despite growing prevalence of ABD, its treatment is poorly investigated. The general approach for the treatment of ABD consists of restoration of PTH activity via limiting Ca load by reduction of calcium-containing phosphate-binders and lowering dialysate Ca, and decreasing or discontinuing active vitamin D or cinacalcet therapies. The use of synthetic PTH (1–34) teriparatide as an anabolic agent to restore bone formation in ABD has not been studied in patients with CKD.

Limiting Calcium Load

Ca is the most potent suppressor of PTH release. Several small studies demonstrated that patients treated with Ca-containing phosphate binders exhibited higher rates of development of ABD and were less likely to have an improvement in bone formation during follow-up as compared to non-calcium-containing binders.[179,180] Therefore, sevelamer and lanthanum may be preferable Pi binders for the patients at risk or with already developed ABD. Exposure of ESRD patients to high-calcium dialysate during RRT (both PD and HD) can also contribute to PTH oversuppression. In agreement with this observation, it has been demonstrated that lowering Ca concentration in dialysate for PD or HD improves bone histomorphology and markers of bone turnover.[181–183] Patients treated with PD exhibit higher rates of ABD as compared with HD treated patients. One possible explanation is that PD patients have continuous exposure to high-calcium dialysate versus thrice weekly exposure in HD patients.

Limiting Active Vitamin D Treatment

The use of active vitamin D leads to effective lowering of PTH and improving bone histology in OF via a reduction in bone formation, which, if excessive, can cause ABD. The oversuppression of bone turnover with calcitriol can occur even in presence of relatively normal to high PTH levels suggestive of its possible direct bone suppressive effect.[184,185] However, a recent report that compared effects of calcitriol and doxercalciferol (active vitamin D analog) on changes in bone histomorphology in pediatric ESRD patients treated with peritoneal dialysis did not find any increase in the development of ABD with the careful monitoring of Ca levels.[186] Additionally, there is accumulating evidence from animal models that active vitamin D exerts anabolic effects on the bone by modulating osteoblast and osteoclast activity.[187,188] It is possible that low doses of active vitamin D are beneficial for hyperparathyroid bone disease, whereas in higher doses, vitamin D is more likely to oversuppress bone formation; however, this point of view requires further exploration.

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