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CKD Series: Disturbances of Mineral Metabolism in Chronic Kidney Disease

Robert F. Reilly, MD

Chronic kidney disease (CKD) afflicts between 2.5 and 18 million Americans, with millions more at increased risk for the disorder.^{1,2} Recently, the National Kidney Foundation (NKF) published a series of clinical practice guidelines for CKD, defining the disorder as the presence of kidney damage or a decreased level of kidney function for 3 months or more.² Kidney damage is further defined as a structural or functional abnormality present for at least 3 months that can lead to a decreased glomerular filtration rate (GFR). As GFR declines, the incidence of comorbid conditions such as hypertension, anemia, left ventricular hypertrophy, hypoalbuminemia, exercise intolerance, hyperphosphatemia, hypocalcemia, and secondary hyperparathyroidism increases.

Disturbances of mineral metabolism are common in CKD. Increases in serum phosphate and decreases in 1,25-dihydroxyvitamin D₃ occur early in the course of the disease (GFR \leq 60 mL/min/1.73 m²), whereas hypocalcemia is a relatively late finding (GFR \leq 20 mL/min/1.73 m²). All 3 abnormalities contribute to both the elevation of the parathyroid hormone level and the secondary hyperparathyroidism that are near universal outcomes of CKD. Secondary hyperparathyroidism results in parathyroid gland hyperplasia. As the parathyroid mass increases, hyperplasia progresses from a diffuse to a nodular form. Larger, nodular glands are more resistant to suppressive therapy with vitamin D.³ Suppression of parathyroid hormone (PTH) production and parathyroid growth before nodular hyperplasia ensues may ensure responsiveness to medical therapy and reduce the need for future parathyroidectomy.

Metabolic bone disorders known collectively as renal osteodystrophy also are associated with renal dysfunction. Patients with renal osteodystrophy are at increased risk for hip and vertebral fractures.⁴⁻⁷ Early intervention may help preserve bone mass.

Finally, the recent association of an elevated serum phosphate level with an increased mortality in hemodialysis patients, along with concerns that hyperphosphatemia may promote vascular calcification, emphasizes the key role that disturbances of mineral metabolism play in patients with end-stage renal disease (ESRD).⁸ Consequently, identification and treatment of mineral metabolism disturbances at an early stage of CKD may reduce many of their adverse outcomes. This article, the third in a 6-part series on CKD, provides information on the pathophysiology and consequences of these disturbances of mineral metabolism in order to enhance a fuller understanding of them. Treatment strategies to correct such disturbances are also discussed.

PATHOPHYSIOLOGY OF SECONDARY HYPERPARATHYROIDISM PTH Level and GFR

As mentioned earlier, secondary hyperparathyroidism is an almost universal complication of CKD that develops early in the course of the disease. PTH production and secretion are regulated by 1,25-dihydroxyvitamin D₃, phosphate, and calcium.⁹ Regulation occurs at a variety of levels, including the transcriptional level, posttranscriptional level (ie, stabilization of PTH messenger RNA [mRNA]), and release or degradation within the cell. In general, PTH level begins to increase as GFR falls below 40 mL/min/1.73 m² (**Figure 1**).¹⁰ More specifically, PTH level is greater than 95 pg/mL in 20% of patients with a

Dr. Reilly is an Associate Professor of Medicine, Section of Nephrology, Department of Medicine, Yale University School of Medicine, New Haven, CT. Dr. Perazella is an Associate Professor of Medicine, Section of Nephrology, and Director, Acute Dialysis Program, Yale University School of Medicine, New Haven, CT; he is also a member of the Hospital Physician Editorial Board.

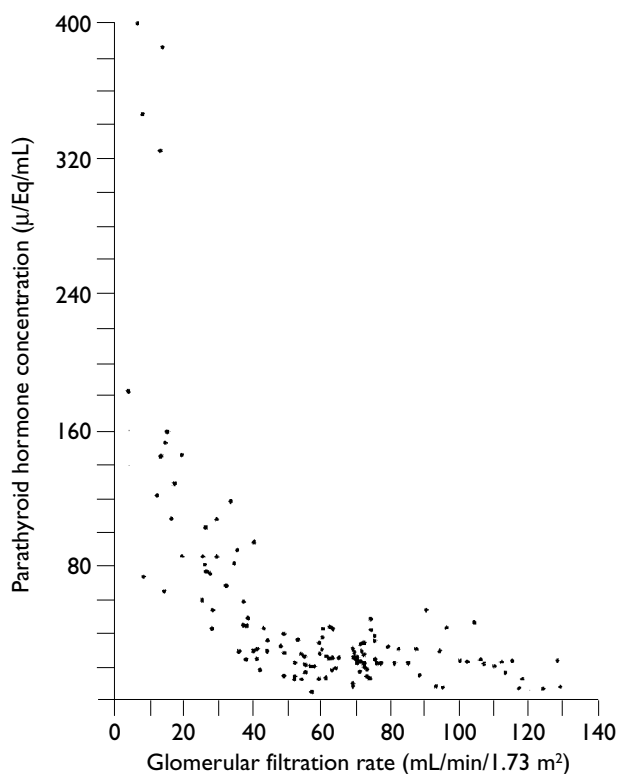


Figure 1. Relationship between parathyroid hormone concentration and glomerular filtration rate. As glomerular filtration rate falls below 40 mL/min/1.73 m², the parathyroid hormone concentration begins to increase. (Adapted with permission from Arnaud CD. Hyperparathyroidism and renal failure. *Kidney Int* 1973;4:89.)

GFR of 30 to 44 mL/min/1.73 m², 60% of patients with a GFR of 15 to 29 mL/min/1.73 m², and 80% of patients with a GFR of less than 15 mL/min/1.73 m²; it is greater than 190 pg/mL in 5% of patients with a GFR of 30 to 44 mL/min/1.73 m², 20% of patients with a GFR of 15 to 29 mL/min/1.73 m², and 60% of patients with a GFR of less than 15 mL/min/1.73 m².²

The Role of Phosphate

Multiple studies have examined the relationship between serum phosphate level and kidney function, and most show that serum phosphate level increases as GFR declines. Phosphate retention begins as GFR falls below 60 mL/min/1.73 m².¹¹ Approximately 15% of patients with a GFR of 15 to 30 mL/min/1.73 m² and 50% of those with a GFR of less than 15 mL/min/1.73 m² have a serum phosphate level that is greater than 4.5 mg/dL.²

PTH increases renal excretion of phosphate by inhibiting proximal tubular phosphate reabsorption, thus returning serum phosphate level toward normal. In the short-term, PTH maintains phosphate homeostasis. As GFR falls below 30 mL/min/1.73 m², however, renal phosphate excretion reaches a maximum. In the long-term, secondary hyperparathyroidism is quite deleterious, resulting in bone disease (ie, renal osteodystrophy) and possibly contributing to dysfunction of various other organ systems.

Hyperphosphatemia directly increases PTH secretion and stimulates parathyroid cell proliferation and hyperplasia. PTH level and parathyroid gland weight increase in animal models of renal failure, and a high-phosphate diet results in a further increase.¹² Phosphate restriction, independent of changes in ionized calcium or 1,25-dihydroxyvitamin D₃ levels, prevents this increase in PTH.^{13,14}

Hyperphosphatemia also decreases expression of the calcium-sensing receptor.¹⁵ The calcium-sensing receptor is expressed in the plasma membrane of parathyroid cells and senses the extracellular fluid calcium concentration. High serum calcium levels activate the receptor, and its message is transduced to the PTH secretory mechanism by phospholipase C and indirectly by phospholipases D and A₂. Arachidonic acid is then metabolized to leukotrienes that inhibit PTH secretion.¹⁶ There is an inverse sigmoidal relationship between serum calcium level and PTH level, with a nonsuppressible component of PTH secretion even at high serum calcium levels (**Figure 2**). The set point is defined as the extracellular fluid ionized calcium concentration at which PTH secretion is 50% of maximum. The PTH calcium response curve and set point are shifted to the right in patients with secondary hyperparathyroidism. This decreased calcium sensing may result from reduced expression of the calcium-sensing receptor.^{17,18}

The Role of 1,25-Dihydroxyvitamin D₃

1,25-Dihydroxyvitamin D₃ level decreases early in the course of CKD when GFR is 60 mL/min/1.73 m² or less, prior to the increase in PTH.¹⁹ Under normal circumstances, 1,25-dihydroxyvitamin D₃ is a potent suppressor of PTH gene transcription.²⁰ The vitamin D receptor is activated by 1,25-dihydroxyvitamin D₃ binding and dimerizes with the retinoid X receptor. The resultant heterodimer binds to vitamin D response elements in the PTH gene promoter and suppresses transcription. The vitamin D receptor in the parathyroid gland is down-regulated in cases of renal failure,^{21,22} in part because, under normal circumstances, the receptor is stabilized and its half-life increased by binding to

1,25-dihydroxyvitamin D₃.²³ Because 1,25-dihydroxyvitamin D₃ is a major inhibitor of parathyroid growth, decreased levels allow parathyroid cells to proliferate; moreover, parathyroid hyperplasia is inhibited but not reversed by 1,25-dihydroxyvitamin D₃.²⁴ Low levels of vitamin D receptor expression have been found in hyperplastic regions of surgically excised parathyroid tissue from dialysis patients²²; areas with nodular hyperplasia had the lowest levels of receptor expression. There is significant correlation between decreased vitamin D receptor expression and increased parathyroid gland weight. Therapeutic administration of 1,25-dihydroxyvitamin D₃ increases vitamin D receptor expression in the parathyroid gland, allowing for better suppression of both PTH and parathyroid growth.

Calcium-sensing receptor expression is also regulated by 1,25-dihydroxyvitamin D₃. Vitamin D deficiency reduces calcium-sensing receptor mRNA, whereas 1,25-dihydroxyvitamin D₃ administration increases it.²⁵ A reduction in calcium-sensing receptor expression decreases the responsiveness of the parathyroid gland to inhibition by calcium.

The Role of Calcium

Data from the Third National Health and Nutrition Examination Survey found no relationship between serum calcium and GFR.¹¹ However, most studies report that serum calcium level decreases as GFR decreases. For example, the Canadian Longitudinal Multicenter Cohort found that 7% of patients with a GFR of 15 to 30 mL/min/1.73 m² and 25% of patients with a GFR of less than 15 mL/min/1.73 m² were hypocalcemic.² Hypocalcemia occurs late in the course of renal dysfunction, after changes in serum phosphate, 1,25-dihydroxyvitamin D₃, and PTH levels.

Hypocalcemia dramatically increases PTH by prolonging the half-life of PTH mRNA.^{14,26} Cytosolic proteins from the parathyroid gland bind to sequences in the 3'-untranslated region that are sensitive to degradation and stabilize the transcript.²⁷

Although decreases in serum calcium and 1,25-dihydroxyvitamin D₃ and increases in serum phosphate all play a role in secondary hyperparathyroidism, the initial increase in PTH is more likely related to decreases in 1,25-dihydroxyvitamin D₃ or hyperphosphatemia than to hypocalcemia. Therapy in patients with CKD (and ESRD) is directed at reversing these abnormalities.

RENAL OSTEODYSTROPHY

Forms of Renal Osteodystrophy

Renal osteodystrophy comprises a group of metabolic bone disorders that are a consequence of CKD.

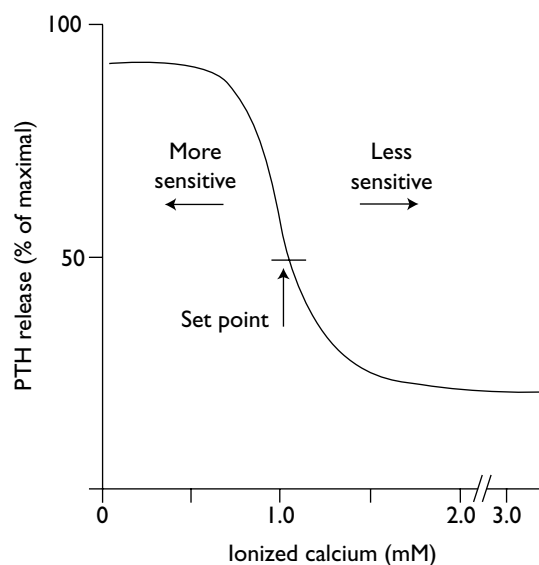


Figure 2. Parathyroid hormone–calcium response curve. The “set point” is the ionized calcium concentration at which parathyroid hormone secretion is 50% of maximal. Even at high ionized calcium concentrations, parathyroid hormone is not completely suppressed. As calcium-sensing receptor expression decreases, the curve shifts to the right, and parathyroid hormone secretion is less sensitive to inhibition at physiologic ionized calcium concentrations. (Adapted with permission from Brown EM. The extracellular Ca²⁺-sensing receptor: central mediator of systemic calcium homeostasis. *Annu Rev Nutr* 2000;20:512.)

These disorders include osteitis fibrosa, osteomalacia, mixed uremic osteodystrophy, and adynamic bone disease. Osteitis fibrosa develops as a result of increased PTH level, which in turn increases osteoblast and osteoclast number and activity (ie, high bone turnover). Osteomalacia is caused by 1,25-dihydroxyvitamin D₃ deficiency and is characterized by low bone turnover, wide unmineralized osteoid seams, and the absence of osteoclasts and erosive surfaces. The major defect is in bone mineralization. Mixed uremic osteodystrophy has features of both osteitis fibrosa and osteomalacia.

Adynamic bone disease is distinguished by a marked reduction in bone formation and resorption; histologic manifestations are thin osteoid seams with little or no evidence of cellular activity (ie, low turnover). This form of renal osteodystrophy is associated with peritoneal dialysis, higher doses of calcium carbonate (administered as a phosphate binder), the presence of diabetes mellitus, treatment with 1,25-dihydroxyvitamin D₃, and older age.²⁸ PTH level is generally normal or

Table I. Spectrum of Renal Osteodystrophy in Studies of Chronic Kidney Disease

Source (year)	Patients (N)	GFR*	Treatment	Histologic Results of Bone Biopsy				
				Normal	OF	MUO	OM	ABD
Lafage et al ²⁹ (1992)	17	≤ 20	None	4/17 (23.5%)	9/17 (53%)	4/17 (23.5%)	0/17	0/17
Cohen-Solal et al ³⁶ (1992)	27	19 ± 3	None	9/27 (33%)	10/27 (37%)	5/27 (19%)	3/27 (11%)	0/27
Hutchinson et al ³⁰ (1993)	30	≤ 5	Calcium carbonate	1/30 (3%)	15/30 (50%)	4/30 (13%)	2/30 (7%)	8/30 (27%)
Hernandez et al ³¹ (1994)	92	< 10	Calcium carbonate (no vitamin D)	0/92	52/92 (56%)	0/92	10/92 (11%)	30/92 (33%)
Bianchi et al ³² (1994)	17	48.2 (mean)	None	0/17	5/17 (29%)	9/17 (53%)	3/17 (18%)	0/17
Hamdy et al ³³ (1995)	176	15–50	24 patients treated with calcium carbonate (no vitamin D)	44/176 (25%)	98/176 (56%)	24/176 (13.6%)	1/176 (< 1%)	9/176 (5%)
Torres et al ³⁴ (1995)	38	< 10	Calcium carbonate (no vitamin D)	0/38	15/38 (39%)	4/38 (11%)	1/38 (3%)	18/38 (47%)
Coen et al ³⁵ (1996)	76	19.5 ± 11.9	None	10/76 (13%)	2/76 (3%)	48/76 (63%)	7/76 (9%)	9/76 (12%)
Total	473	—	—	68/473 (14%)	206/473 (43.5%)	98/473 (21%)	27/473 (6%)	74/473 (15.5%)

ABD = adynamic bone disease; GFR = glomerular filtration rate; MUO = mixed uremic osteodystrophy; OF = osteitis fibrosa; OM = osteomalacia.

*In mL/min/1.73 m².

slightly elevated, yet bone turnover remains low. The reasons for this absolute or relative hypoparathyroidism are unclear. Down-regulation of the PTH receptor in bone, uremic inhibitors of osteoblast function, or changes in cytokines necessary for osteoblast function may all contribute to the PTH resistance.

The Spectrum of Renal Osteodystrophy in CKD

Since 1990, 8 studies have used bone biopsy results to examine the spectrum of renal osteodystrophy in CKD.^{29–36} A summary of these studies is shown in **Table 1**. In 3 of the studies performed in the immediate predialysis period, the spectrum of renal osteodystrophy was similar to that observed in patients with ESRD.^{30,31,34} More specifically, osteitis fibrosa was seen in 39% to 56% of patients, osteomalacia in 3% to 11%, and adynamic bone disease in 27% to 47%; very few patients had normal bone histology.

Five of these studies included patients with milder disease.^{29,32,33,35,36} Osteitis fibrosa and mixed uremic osteodystrophy were the most common histologic findings, occurring in 40% and 30% of patients, respectively. As in patients with ESRD, osteomalacia was the least common abnormality, affecting only 4.5% of patients. Two important differences, however, distinguished these patients with milder disease from patients immediately predialysis. In the first place, normal bone histology, which is rarely seen immediately predialysis, was found in 21% of those with less severe disease. Secondly, adynamic bone disease, a common form of renal osteodystrophy in the ESRD population, was found in only 6% of those with milder CKD. This finding seems to support concerns that the later form of osteodystrophy may be related to treatment with high doses of vitamin D in the ESRD population.

Adynamic bone disease was associated with higher GFR levels, normal to mildly elevated PTH levels, and normal serum calcium levels.³⁵ Osteomalacia occurred in patients with more severe renal dysfunction, hypocalcemia, acidosis, and increased PTH levels. In the largest of these 5 studies, which examined 176 patients with CKD via bone biopsy, osteitis fibrosa occurred in 56% of patients, mixed uremic osteodystrophy in 13.6%, and adynamic bone disease in 5%; osteomalacia was observed in only 1 patient (< 1%).³³ Normal histology was seen in 25% of patients. Of note, patients whose biopsy results showed normal histology had a significantly higher GFR than did those with abnormal results on bone biopsy.³³

Differentiation of High and Low Bone Turnover

Renal osteodystrophy can be further divided into

2 subgroups, namely high-turnover disease (eg, osteitis fibrosa) and low-turnover disease (eg, adynamic bone disease, osteomalacia). It is worth noting that the frequency of osteomalacia has declined dramatically in recent years because of decreased use of aluminum-containing phosphate binders.

PTH level is the most common biomarker used for the assessment of bone turnover. Hutchison and colleagues showed that PTH levels of less than 65 pg/mL had a sensitivity of 88% and a specificity of 91% for diagnosing adynamic bone disease, whereas a PTH level of more than 200 pg/mL had a sensitivity of 83% and a specificity of 88% for diagnosing osteitis fibrosa.³⁰ Torres and colleagues compared patients immediately predialysis to those on dialysis for more than 8 months.³⁴ A PTH level of less than 120 pg/mL was 39% specific and 95% sensitive for diagnosing low bone turnover, whereas a PTH level of more than 450 pg/mL was 53% sensitive and 100% specific for diagnosing high bone turnover disease.

Only a single recent report addressed the relationship between bone disease and PTH at higher levels of GFR. Coen and colleagues studied 76 patients with a mean GFR of 19.54 ± 11.87 mL/min/1.73 m² and found that patients with normal bone biopsy results had an average intact PTH level that was lower than that of all other histologic groups, even lower than those with adynamic bone disease; the GFRs of these patients were, however, significantly higher than those of patients with any form of renal osteodystrophy.³⁵ The authors concluded that intact PTH level was not a good marker of bone turnover in mild renal failure. Target levels for PTH level in CKD have been proposed (**Table 2**) but are based on little data.³⁷

Bone biopsy is required to definitively determine which form of renal osteodystrophy is present. This technique, however, has not gained wide acceptance for a variety of reasons. The NKF Working Group concluded that there were no convincing data to suggest a benefit of routinely obtaining bone biopsy or a bone densitometry study in patients with CKD.² It was recommended that biomarkers such as PTH be followed longitudinally in patients in whom abnormalities may develop or become more severe as kidney function deteriorates. Optimal target PTH values have not been established for patients with mild to moderate CKD.

Morbidity of Renal Osteodystrophy

Patients with ESRD are at increased risk for hip and vertebral fractures, and those with adynamic bone disease may be at highest risk. Analysis of the United States Renal Data System (USRDS) database of Caucasians

Table 2. Suggested Ranges for Parathyroid Hormone in Relation to Glomerular Filtration Rate

Glomerular Filtration Rate	Suggested Parathyroid Hormone Range
> 50 mL/min/1.73 m ²	Upper limit of normal
20–50 mL/min/1.73 m ²	1.0–1.5 times the upper limit of normal
< 20 mL/min/1.73 m ²	1.5–2.0 times the upper limit of normal
On dialysis	2.0–3.0 times the upper limit of normal

who started dialysis between 1989 and 1996 showed that the risk for hip fracture in women was 13.63 per 1000 patient years and in men was 7.45 per 1000 patient years.⁵ The relative risk for hip fracture in men and women was 4.44 and 4.40 times higher, respectively, in dialysis patients compared with age- and sex-matched controls. Although the age-specific relative risk was highest in the youngest age groups, the added risk for fracture associated with dialysis increased steadily with advancing age. A similar study found that risk factors for hip fracture included age, white race, female sex, low body mass index, peripheral vascular disease, inability to ambulate, low albumin level, and smoking.³⁸ In patients on dialysis at Montefiore Medical Center in the period from 1988 through 1998, the risk for hip fracture was 14.2-fold higher in women and 17.2-fold higher in men compared with the general population.⁴ Hip fractures occurred at a much younger age in patients on dialysis than in the general population (64.4 versus 80 years in men; 61.4 versus 74 years in women). Patients with PTH levels of less than 65 pg/mL and, presumably, adynamic bone disease were at the highest risk for hip fracture. Risk factors for fracture included white race, increased age, an elevated alkaline phosphatase level, and a PTH level of less than 195 pg/mL. The risk for vertebral fracture was 2.4-fold higher in men with a PTH level in the lowest tertile (5–61 pg/mL) than in men in the middle PTH tertile (62–202 pg/mL) and 1.6-fold higher than in men in the highest PTH tertile (203–1818 pg/mL).⁷

TREATMENT

Correction of Hyperphosphatemia

Hyperphosphatemia can be controlled initially with dietary restriction. Ingestion of foods high in phosphate (eg, dairy products) should be minimized. In 23 patients with CKD, phosphate restriction decreased PTH levels from 168.2 pg/mL to 116.6 pg/mL over a

3-month period.³⁹ Unfortunately, phosphate intake is directly proportional to protein intake, and it is difficult to restrict phosphorus without restricting protein.⁴⁰ Malnutrition is common in patients starting dialysis and is a powerful predictor of increased mortality. Therefore, serum albumin level should be followed carefully in patients with CKD to ensure that malnutrition does not result.

As CKD worsens, orally administered phosphate binders are frequently required. The current goal of therapy in patients with ESRD is to maintain the calcium-phosphorus product below 72 and the serum phosphate level below 6.5 mg/dL. According to Block and colleagues, levels higher than these increase the relative risk for mortality in patients with ESRD.⁸ Recently, these same authors advocated reducing these goals to a serum phosphate level of 5.5 mg/dL or lower and a calcium-phosphorus product of 55 or lower.⁴¹ Similar studies in patients with CKD have not been performed.

The use of calcium-containing phosphate binders results in a net positive calcium balance in patients with ESRD. This calcium, however, may deposit in the vasculature and contribute to increased morbidity and mortality from ischemic coronary disease. In patients with ESRD, vascular calcification also has been associated with increased oral intake of calcium.⁴² After treatment for one year, calcification in the coronary arteries, as measured by electron beam computed tomography, increased in patients on hemodialysis who were treated with calcium-containing phosphate binders but did not change in patients who were treated with sevelamer, a non-calcium-containing binder.⁴³ However, there were no differences in mortality between the 2 groups, raising questions about the significance of the increase in calcification.

An ideal phosphate binder would have the following characteristics: efficient phosphate binding, minimal effects on comorbid conditions, low cost, and a favorable adverse effect profile. Unfortunately, no currently available phosphate binder fulfills all of these criteria. Calcium-containing binders, although efficient binders and low in cost, may contribute to excess total-body calcium burden. Sevelamer, a synthetic calcium-free polymer, has a favorable adverse effect profile but is costly. Aluminum is the most efficient binder and is relatively inexpensive; however, it has prohibitive long-term toxicity (eg, aluminum-related osteomalacia, dementia). Aluminum-containing phosphate binders should only be used for short-term management of severe hyperphosphatemia (ie, a phosphate level \geq 8.5 mg/dL). In choosing between a calcium-containing binder and sevelamer, one must balance the higher cost of

sevelamer against the potential benefits of a decreased risk for vascular calcification. Findings of a recent survey of a drugstore Web site listing approximate costs of the starting dose of the more common phosphate binders are presented in **Table 3**.

Correction of Hypocalcemia

Hypocalcemia is a potent stimulator of PTH secretion. The therapeutic goal in patients with CKD should be to increase the serum calcium level to the low-normal range. This goal can be achieved with an orally administered calcium preparation. In one study, serum PTH level in CKD patients was reduced by 50% (from 183 ± 149 pg/mL to 85 ± 61 pg/mL) with oral administration of calcium carbonate alone.⁴⁴ The dose should be given either 2 hours before or after a meal or at bedtime in order to maximize absorption. This therapy may, however, place the patient at increased risk for vascular calcification and the development of adynamic bone disease.

Correction of Acidosis

Acidosis increases bone loss, potentiates the effect of PTH, and—most importantly—decreases production of 1,25-dihydroxyvitamin D₃. Correction of acidosis, on the other hand, slows the progression of secondary hyperparathyroidism; such correction can be achieved with administration of 1 to 4 g of sodium bicarbonate daily, provided that fluid balance and blood pressure control are not compromised by the sodium load.

Monitoring of PTH Levels and Control of Renal Osteodystrophy

The optimal PTH level in patients with CKD has not been established. If, however, PTH level is more than 2 to 4 times the upper limit of normal, one should first determine whether hyperphosphatemia or hypocalcemia is present. If either condition is found, it should be corrected. If PTH level remains elevated after correction or if both of these conditions are absent, then vitamin D therapy will likely be required. Small doses of orally administered calcitriol (0.25–0.50 µg daily) can stabilize and decrease PTH levels,⁴⁵ with decreases primarily occurring in patients with a PTH level that is less than 200 pg/mL.⁴⁶ Pulse calcitriol therapy (2 µg/wk), however, may be more effective and is associated with a lower risk for hypercalcemia.⁴⁷ It has been suggested that vitamin D therapy may cause a deterioration in renal function.⁴⁸ In the absence of hypercalcemia, however, the preponderance of evidence would argue that such deterioration does not occur.^{46,49}

Hamdy and colleagues randomized 87 patients with CKD to treatment with placebo and 89 patients with

Table 3. Comparative Cost of Common Phosphate Binders

Preparation	Starting Dose	Approximate Monthly Cost
Calcium carbonate (500 mg)	2 with meals	\$5
Calcium acetate (667 mg)	1 with meals	\$13
Sevelamer (800 mg)	1 with meals	\$100

CKD to treatment with alfacalcidol.³³ (Alfacalcidol, or 1 α -hydroxyvitamin D₃, is converted to 1,25-dihydroxyvitamin D₃ by 25-hydroxylation in the liver.) In this largest study to date of CKD patients who had a bone biopsy both before and after treatment with vitamin D, there was no difference in the decline of renal function between alfacalcidol and placebo groups, indicating that treatment does not worsen renal function. Thirteen patients developed mild hypercalcemia (3 in the placebo group and 10 in the alfacalcidol group); those in the alfacalcidol group responded to a reduction of the dose. Only 1 patient developed severe hypercalcemia, which also responded to a reduction in the alfacalcidol dose. Moreover, alfacalcidol reversed the histologic features of secondary hyperparathyroidism in some patients. Abnormal histology was present in 76% of the alfacalcidol group at the start of therapy and in 73% of the placebo group; bone disease resolved in 42% of those in the treatment group but only 4% of those in the placebo group ($P < .001$) after treatment.³³

Whether alfacalcidol therapy results in adynamic bone disease is unclear. Adynamic bone disease developed in 8 of 89 patients who received alfacalcidol therapy and in 4 of 87 patients in the placebo group.³³ The authors do not state whether this difference was statistically significant. At the start of the study, adynamic bone disease was present in 6 patients in the alfacalcidol group and 3 in the placebo group.³³ Interestingly, it resolved in 4 of the patients who received alfacalcidol and in 2 of the patients in the placebo group.

MANAGEMENT SUMMARY

Correction of hyperphosphatemia, hypocalcemia, and acidosis will help reduce increases in PTH levels that are associated with CKD. Serum phosphate level can be reduced by dietary restriction, but care must be taken not to induce protein malnutrition. If hyperphosphatemia persists, a phosphate binder is required. Hypocalcemia should be corrected so that

serum calcium level in affected patients is in the low-normal range. Acidosis can be reversed with oral administration of sodium bicarbonate, with careful attention paid to volume status and blood pressure. If the PTH level remains elevated despite these interventions, small doses of daily orally administered calcitriol (0.25–0.5 µg) can be added, but hypercalcemia must be avoided. The target value for PTH suppression remains unclear in patients with CKD. The next article in this series will examine cardiovascular risk factors in patients with CKD. **HP**

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