Abbreviations

Nephrology II

Abbreviations

PSAP

BONE METABOLISM AND DISEASE IN CHRONIC KIDNEY DISEASE

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Learning Objectives

1. Analyze the alterations in phosphorus, calcium, vitamin D, and parathyroid hormone regulation that occur in patients with chronic kidney disease (CKD).
2. Classify the type of bone disease that occurs in patients with CKD based on the evaluation of biochemical markers.
3. Construct a therapeutic plan individualized for the stage of CKD to monitor bone metabolism and the effects of treatment.
4. Assess the role of various treatment options such as phosphorus restriction, phosphate binders, calcium supplements, vitamin D agents, and calcimimetics based on the pathophysiology of the disease state.
5. Devise a therapeutic plan for a specific patient with alterations of phosphorus, calcium, vitamin D, and intact parathyroid hormone concentrations.
6. Evaluate therapeutic nonadherence as a potential cause of treatment failure.
7. Devise strategies to increase patient adherence and optimize pharmaceutical care.

Introduction

Abnormalities of bone metabolism in patients with chronic kidney disease (CKD) are a result of a series of alterations in the homeostasis of calcium, phosphorus, activated vitamin D, and parathyroid hormone (PTH) concentrations, or a consequence of the medical treatment of these disturbances. Renal osteodystrophy refers to several patterns of defective bone mineralization, including osteitis fibrosa cystica, osteomalacia, and adynamic bone disease. Osteitis fibrosa cystica is referred to as high turnover bone disease. It is associated with elevated concentrations of PTH, which stimulates osteoclast activity, bone breakdown, and resorption. Osteomalacia is described as a low turnover bone disease with abnormal mineralization that leads to softening of bone and has historically been associated with aluminum toxicity. Adynamic bone disease is referred to as low turnover disease with normal mineralization. This disorder may be caused by excessive suppression of PTH through the use of vitamin D agents, calcimimetics, or phosphate binders. In addition to bone effects, alterations in calcium, phosphorus, vitamin D and PTH cause other deleterious consequences in patients with CKD. Of these, extra-skeletal calcification and increased left ventricular mass have been documented and directly correlated to an increase in cardiovascular morbidity and mortality. The goal of treatment in patients with CKD and abnormalities of bone metabolism is to normalize mineral metabolism, prevent bone disease, and prevent extraskeletal manifestations of the altered biochemical processes.

In 2003, a non-profit international organization, Kidney Disease: Improving Global Outcomes, was created. Their mission is to improve care and outcomes for patients with CKD worldwide by promoting, coordinating, collaborating, and integrating initiatives to develop and implement clinical practice guidelines. As part of this initiative, the group acknowledged the awkward and inconsistent nomenclature used in the scientific community to discuss disorders of bone and mineral metabolism due to CKD. They propose the term CKD-Mineral and Bone Disorder (CKD-MBD) to refer to these disorders manifested by abnormalities in bone and mineral metabolism and/or extraskeletal calcification. This term can be used to replace previous terms such as bone metabolism disorder, secondary hyperparathyroidism, renal osteodystrophy, and vascular calcification secondary to CKD. Improving the terminology will enhance communication and create much-needed consistency for both patient care and research.

Pathophysiology

Derangements of Phosphorus, Calcium, Vitamin D, and PTH Balance

The derangements in mineral metabolism that occur in patients with CKD are complex and interrelated. Figure 1-1 provides a simplified diagram of the pathophysiology that

Abbreviations in this Chapter

Ca X P	Calcium-phosphorus product
CCPB	Calcium-containing phosphate binder
CKD	Chronic kidney disease
CKD-MBD	CKD-Mineral and Bone Disorder
GFR	Glomerular filtration rate
iPTH	Intact parathyroid hormone
KDOQI	Kidney Disease Outcomes Quality Initiative
PTH	Parathyroid hormone

highlights the targets of current therapies. Typically, the initial alteration is impaired excretion of phosphate. Hyperphosphatemia stimulates the parathyroid gland to produce and secrete PTH. In patients with healthy kidneys, PTH decreases the reabsorption of phosphorus in the proximal tubule and enhances phosphorus excretion in the distal tubules. Unfortunately, with the decrease in kidney function (usually Stage 4 or 5 CKD), the kidneys are not able to increase the amount of phosphorus excreted and hyperphosphatemia persists despite elevations in PTH concentrations. It is particularly important to note that although serum phosphate concentrations may not rise significantly until the estimated glomerular filtration rate (GFR) decreases below 30 mL/minute/1.73 m^2, PTH concentrations may begin to increase much sooner. Patients may develop secondary hyperparathyroidism as early as stage 3 CKD when the GFR is less than 60 mL/minute/ 1.73 m^2. This increase is due to the fact that the parathyroid gland is sensitive to minute changes in the excretion of phosphorus by the kidneys and to deficiencies in vitamin D that occur concurrently in patients with CKD. As CKD progresses, there are fewer functioning nephrons and the single nephron load of phosphate excretion increases. The parathyroid gland reacts by increasing synthesis and release of intact PTH. Chronic kidney disease-mineral and bone disorder may begin even before hyperphosphatemia is observed. This series of events highlights the importance of early screening.

Once hyperphosphatemia occurs, there are many complications that ensue. Phosphorus has a high affinity for calcium. As the concentration of phosphorus in the blood increases, there is a higher likelihood that calcium and phosphate will bind and precipitate. This process is of concern, both from the perspective of increased precipitation and vascular calcification, as well as resultant hypocalcemia, which is a potent stimulus for further PTH production and secretion. Hyperphosphatemia also inhibits the activation of vitamin D. Both the deceased functional mass of the kidneys and hyperphosphatemia cause a decrease in activity of 1α-hydroxylase in the kidney, which is responsible for the final hydroxylation reaction that forms activated vitamin D_3 (calcitriol). Due to this deficiency of vitamin D_3, there is less intestinal absorption of calcium leading to further decreases in serum calcium concentrations. The parathyroid gland, sensing all of these alterations (decreased activated vitamin D_3, hypocalcemia, and hyperphosphatemia), increases the production and secretion of PTH. Parathyroid hormone stimulates osteoclast activity to break down bone and release calcium into the serum. These changes lead to further metabolic abnormalities of calcium and phosphorus, and may ultimately lead to CKD-MBD.

To further complicate the management of these metabolic derangements, it is imperative that the PTH concentrations be maintained within a target range. Concentrations that are too high will lead to osteitis fibrosa cystica, whereas concentrations that are too low may cause adynamic bone disease. Oversuppression of PTH with the subsequent development of adynamic bone disease places patients at risk for vascular calcification as well. In fact, patients with CKD need PTH concentrations higher than normal values to maintain proper bone metabolism. This increased requirement may be due to skeletal resistance to PTH with worsening kidney function. It is for this reason that the target ranges for intact PTH are incrementally higher as the degree of kidney function decreases (see Table 1-1).

Diagnosis of Bone Disease

The gold standard test to assess bone disease in patients with CKD is a trans-iliac bone biopsy for histologic analysis. This is an expensive and invasive procedure and may not be readily available in clinical practice. Intact parathyroid hormone (iPTH) concentration has been well correlated to histologic findings. Therefore, for the majority of patients with CKD, the routine analysis of iPTH, calcium, phosphorus, and vitamin D concentrations are sufficient to assess bone health and CKD-MBD. In the United States, the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines for the management of bone metabolism and bone disease provide information on the target ranges and monitoring of these biochemical markers (see Table 1-1 and Table 1-2).

Some controversy exists regarding the most accurate, reliable test to measure PTH concentrations in patients with CKD. The full-length iPTH molecule contains 84 amino acids with an amino, N terminus (position 1) and a carboxyl, C terminus (position 84). Cellular degradation and metabolism can cause fragmentation of the molecule producing smaller molecules known as N-terminally truncated fragments [i.e., iPTH(19-84), iPTH(7-84), iPTH(39-84)]. Although the radioimmunoassays were the first methods created to detect iPTH (1-84), they cross-reacted with many of these fragments and were found to be particularly inaccurate in predicting bone disease in the CKD patient population. This inaccuracy led to the advent of the immunometric assays or first-generation intact assays that are typically used today. The first immunometric assay was developed to detect only the full-length iPTH molecule. The results obtained from this type of assay were well correlated with bone histology from biopsy. In the late 1990s, research showed that these assays were actually detecting iPTH fragments that end at the amino terminus as well. This detection of fragments would overestimate the concentration of iPTH (1-84) by about 40%–50%. In addition, the other fragments measured have variable

physiologic effects. For example, iPTH (7-84) has hypocalcemic effects whereas iPTH (1-34) has calcemic effects. In an effort to better assess the active iPTH, second-generation assays were developed. These tests measure iPTH (1-84) and other fragments that end at the carboxyl terminus, but not iPTH (7-84). Although the second-generation assays have less cross-reactivity with the N-terminal fragments, they may not be more accurate in predicting bone disease in patients with Stage 5 CKD. There have been only a few studies comparing the results of first-generation tests with second-generation tests. Although the sample sizes were small, the results indicated that both assays produced similar information regarding CKD-MBD in comparison with bone histology. In conclusion, despite the increased specificity for iPTH (1-84) of the second-generation assays, at this time there is insufficient evidence to warrant a change in assays.

Vitamin D

Vitamin D_3 deficiency plays a large role in the pathogenesis of CKD-MBD. Vitamin D is produced through the reaction of endogenous 7-dehydrocholesterol present in the skin and ultraviolet B light. This reaction forms the precursor to active Vitamin D_3. Vitamin D_2 is another precursor that is contained in certain foods and supplements. Vitamins D_2 and D_3 are transported to the liver and hydroxylated at the 25 position to 25-hydroxyvitamin D (both D_2 and D_3). 25-Hydroxyvitamin D is the major circulating moiety that is measured to assess vitamin D deficiency. It is bound to vitamin D binding protein and carried to the renal tubule where it undergoes a second hydroxylase reaction to become the final active form, 1,25-dihydroxyvitamin D_3.

Although certain foods contain significant concentrations of vitamin D and many foods in the United States are fortified with vitamin D (to prevent rickets), it is still estimated that nearly 90%–95% of the total requirement for this vitamin is derived through the ultraviolet B light reaction in the skin. Sunscreens and the deteriorating ozone layer are both barriers to the production of vitamin D. Melanin, a natural skin pigment, is also a barrier and accounts for the fact that people with darker skin require more sunlight exposure to produce similar quantities of vitamin D than fair-skinned counterparts.

With regard to bone metabolism, vitamin D interacts with vitamin D receptors in the intestine to increase the absorption of calcium. Vitamin D also interacts with vitamin D receptors on the parathyroid gland, causing down- regulation of the synthesis and release of iPTH, inhibition of parathyroid gland hyperplasia, increased expression of the calcium sensing receptor, and increased osteoblast activity. Although the role of vitamin D in the abnormalities of CKD-MBD is well known, research is continuing to elucidate the many functions of vitamin D beyond these traditional effects. Vitamin D receptors are located throughout the body and the presence of vitamin D is essential to a wide array of homeostatic functions. For instance, vitamin D is an immunomodulator, regulating cellular apoptosis, proliferation, and differentiation. It decreases the inflammatory response associated with atherosclerosis and modulates cardiac and vascular smooth muscle function. It is also a negative endocrine regulator of the renin-angiotensin system. Vitamin D deficiency has

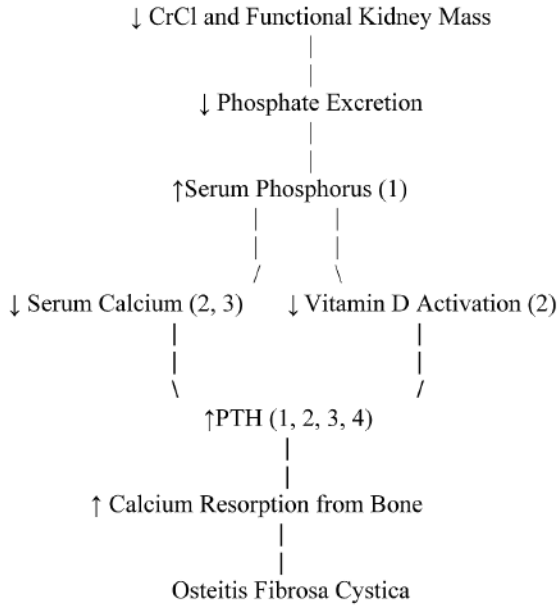

Figure 1-1. Pathophysiology of chronic kidney disease-mineral and bone disorder.
The numbers represent current strategies (below) that may be employed to attenuate the progression and prevent bone disease and potentially extraskeletal calcification. It should be noted that this is a simplified depiction. The interplay between all of the systems is complex. Please refer to the text for a more detailed description.
1. Phosphate binders and dietary restriction
2. Vitamin D therapy
3. Calcium supplements
4. Calcimimetics
CrCl = creatinine clearance; PTH = parathyroid hormone.

Table 1-1. KDOQI Target Ranges of Biochemical Markers in Stages 3, 4, and 5 CKD

Stage of CKD	Phosphorus (mg/dL)	Corrected Calcium (mg/dL)	Ca X P (mg^2/dL^2)	Serum iPTH (pg/mL)
3 (30–59 mL/minute/1.73 m^2)	2.7–4.6	Normal Range	Less than 55	35–70
4 (15–29 mL/minute/1.73 m^2)	2.7–4.6	Normal Range	Less than 55	70–110
5 (< 15 mL/minute/1.73 m^2)	3.5–5.5	8.4–9.5	Less than 55	150–300

Ca X P = calcium-phosphate product; CKD = chronic kidney disease; iPTH = intact parathyroid hormone; KDOQI = Kidney Disease Outcomes Quality Initiative.
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Abbreviations

Table 1-2. Monitoring Frequency of Calcium, Phosphorus, and Intact Parathyroid Hormone (iPTH) Based on Stage of Kidney Disease

Stage of CKD	Measurement of iPTH	Measurement of Calcium and Phosphorus
3 (30–59 mL/minute/1.73 m^2)	Every 12 months	Every 12 months
4 (15–29 mL/minute/1.73 m^2)	Every 3 months	Every 3 months
5 (< 15 mL/minute/1.73 m^2)	Every 3 months	Every month

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been associated with the development of several systemic disorders such as diabetes mellitus, hypertension, coronary artery disease, and colon cancer. Developing research in this area may lead to new recommendations for use of vitamin D therapy in patients with CKD in the future.

Prevalence of CKD-MBD

The majority of patients with CKD and an eGFR less than 60 mL/minute/1.73 m^2 (Stage 3 or worse) will show signs of CKD-MBD. Early assessment by a general practitioner or early referral to a nephrologist is paramount as patients often have CKD-MBD before hyperphosphatemia is observed. Once the cycle of metabolic alterations begins, it is very challenging to correct and maintain normal homeostasis. In fact, in two recent studies of patients with kidney failure treated by dialysis, fewer than 10% of the study populations were within KDOQI target ranges for all of the metabolic parameters assessed: calcium, phosphorus, calcium-phosphorus product (Ca X P), and iPTH.

Consequences of CKD-MBD

It has long been known that patients with CKD, especially those treated by dialysis, have an increased cardiovascular morbidity and mortality. One study found that even when stratified for sex, race, and presence of diabetes, dialysis patients had a cardiovascular mortality rate up to 30 times greater than the general population. Recent research of cardiovascular calcification in patients with CKD is the subject of much debate. Correlations have been made between cardiovascular calcification and factors such as time on dialysis, hyperphosphatemia, increased Ca X P, hypercalcemia, vitamin D therapy, and increased doses of calcium-containing phosphate binders (CCPB) and calcium supplements. While there has been a good deal of focus on promoters of atherosclerosis and calcification, new research is also focusing on identifying inhibitors of cardiovascular calcification. Unfortunately, no pharmacotherapeutic agents have been identified at this time to arrest this process. For the purposes of bone metabolism and alterations in associated biochemical parameters, it is clear that the best treatment plan at this time is to maintain serum phosphorus, calcium, Ca X P, and iPTH within the target ranges.

Quality of Life

Chronic kidney disease-mineral and bone disorder is relatively asymptomatic until there is a profound event. Although some patients may complain of bone pain or pruritus, most do not have any complaints. Unfortunately, being a silent disease, CKD-MBD can progress and cause an increased risk of fracture. Patients on dialysis have an increased relative risk of hip fracture as compared with the general population. In addition, patients on dialysis also have a much higher mortality rate post-fracture than patients without CKD who sustain a fracture.

Mortality

Numerous studies have shown a correlation between increased risk of mortality and increases in many of the biochemical parameters involved in bone metabolism. Evaluation of the results from these studies is complicated by the increased mortality rate of the CKD population, especially cardiovascular mortality. Although it is difficult to control for all confounding variables, many studies showed a significantly increased mortality risk in patients. Although it is difficult to control for all confounding variables, many studies showed a significantly increased mortality risk in patients with CKD with hyperphosphatemia or an increased Ca X P as compared to patients with CKD who had phosphorus and Ca X P concentrations that were lower or within the target range. Although the upper end of the normal ranges for each parameter differed in these studies, it is clear that maintaining the serum phosphorus and Ca X P within the target ranges as proposed in the KDOQI guidelines would be beneficial. One study showed a significant increase in both all-cause mortality as well as cardiovascular mortality associated with relatively small increases in each parameter (1 mg/dL for phosphorus and calcium, 5 mg^2/dL^2 for Ca X P, and 100 pg/mL for iPTH). Although most studies demonstrated an increase in mortality risk due to increased concentrations of phosphorus and Ca X P, only a few have shown a similar risk for increased iPTH or calcium concentrations. More research is required before conclusions can be drawn; however, given the interrelatedness of these parameters, it is prudent to maintain them within the KDOQI ranges.

Goals of Therapy

The ultimate goal of drug therapy in the management of CKD-MBD is to prevent complications of the abnormalities caused by CKD, specifically bone disease and extraskeletal calcification. In October 2003, the first guidelines for the treatment of bone metabolism and bone disease were published. These guidelines provide recommendations for the evaluation, treatment, and monitoring of bone

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metabolism to prevent secondary hyperparathyroidism and renal osteodystrophy. At Stage 3 CKD, serum calcium, phosphorus, and iPTH concentrations should be evaluated. After the initial assessment, routine monitoring should be performed according to the timetable shown in Table 1-2. As discussed, there are many parameters involved in the homeostasis of bone. The KDOQI provides guidelines for achievement of target calcium, phosphate, iPTH, and Ca X P (see Table 1-1).

Restriction of Dietary Phosphorus

If the patient is hyperphosphatemic, dietary restriction of phosphorus is the first intervention recommended. Many foods high in phosphorus are also primary sources of protein (i.e., meat, beans, and dairy). As hypoalbuminemia has been associated with a higher incidence of morbidity and mortality in the CKD population, it is imperative that patients receive nutritional counseling to avoid malnutrition when maintaining phosphorus restriction. Patients are instructed to restrict non-protein sources of phosphorus like dark sodas and beer, but to not necessarily reduce their intake of protein-containing foods. The average dietary intake of phosphorus in the United States is about 1000–1200 mg/day. Of this, patients with kidney failure absorb about one-half. Diets incorporating more processed foods may contain even more phosphorus. Patients with CKD stages 3 and 4 require strict dietary adherence and often phosphate binders to maintain calcium and phosphorus concentrations within the normal range. For patients with kidney failure, dialytic therapies remove some phosphorus, but are frequently inadequate alone to achieve target phosphorus concentrations. For instance, a 4-hour hemodialysis session with a high-flux dialyzer will remove about 900 mg of phosphorus. Even with optimal dialysis, a typical 3 times/week hemodialysis regimen still leaves the patient with a significant positive phosphorus balance. Therefore, in most instances, dietary restriction and dialysis alone are insufficient to maintain goal phosphorus concentration and phosphate-binding agents will be required.

Pharmacotherapy

Phosphate-Binding Agents

The proper use of phosphate-binding agents is essential for management of hyperphosphatemia. Table 1-3 lists some of the different drugs used to treat CKD-MBD. These medications are given with food (meals ± snacks) to bind the intestinal phosphorus from dietary intake before it is absorbed. Most likely, the greatest challenge to the successful use of phosphate binders will be patient adherence. Patient education is imperative as these medications must be taken routinely and multiple times a day, which may significantly increase the patient's pill burden. Patients requiring alternate enteral feeding modalities such as continuous feeding via nasogastric tubes or other meals via percutaneous gastrostomy tubes will have additional needs to consider. If feedings are given continuously, the frequency of administration of the binder will need to be increased. In addition, some agents (e.g., sevelamer) should not be crushed and administered through a tube.

Aluminum-Containing Phosphate Binders

The ideal phosphorus-binding agent is not commercially available. The first agents used to treat hyperphosphatemia contained divalent or trivalent ions such as calcium, magnesium, or aluminum. Magnesium and aluminum are very effective phosphate binders; however, they may accumulate in patients with decreased kidney function. Due to serious central nervous system toxicities, hyperkalemia, and diarrhea, magnesium is seldom used. The toxicities of aluminum include constipation, osteomalacia, central nervous system toxicity, and potentially decreased responsiveness to erythropoietic agents. Aluminum is reserved for situations in which the phosphorus concentration is very high (greater than 7.0 mg/dL) and the Ca X P is greater than 55 mg^2/dL^2. Baseline concentrations of aluminum should be assessed and should be below 20 mcg/L. Short courses may be used when the Ca X P precludes the use of CCPB and when other

Table 1-3. Examples of Phosphate-Binding Medications: Product and Initial Dosing Information

	Dosage Form	Usual Initial Dose
Calcium-Containing Phosphate Binders		
Calcium carbonate Trade names: Os-Cal, Tums Generic preparations	250–1000 mg tablets	500–1000 mg
Calcium acetate Trade name: PhosLo	667 mg capsules	667–1334 mg
Aluminum-Containing Agents		
Aluminum hydroxide Trade names: ALternaGEL, Alamag Generic preparations	300 mg/5 mL suspension 600 mg/5 mL suspension 300–600 mg tablets	600–1200 mg
New Agents		
Sevelamer hydrochloride Trade name: Renagel	400 mg tablets 800 mg tablets	800–1600 mg
Lanthanum carbonate Trade name: Fosrenol	250, 500, 750, 1000 mg Chewable tablets	500–1000 mg

All doses should be administered 3 times/day with meals and also with snacks, if necessary.

Abbreviations

Table 1-4. Dosing of Oral Ergocalciferol (Chronic Kidney Disease Stages 3 and 4)

25(OH) vitamin D concentration	Oral ergocalciferol dose (IU)
< 5 (ng/mL)	50,000 weekly for 12 doses, then monthly for three doses
5–15 (ng/mL)	50,000 weekly for four doses, then monthly for five doses
16–30 (ng/mL)	50,000 monthly for six doses

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non-calcium-containing binders are not available, too expensive, or otherwise not indicated. Because aluminum has a very high affinity for phosphorus it is usually effective in several days to 1 week. The KDOQI guidelines recommend the judicious use of aluminum-containing binders for a maximum of 30 days. It should be noted that the coadministration of citrate increases the absorption of aluminum, so use of products containing citrate should be avoided in patients with CKD. Another caution about aluminum is that it is a common component of over-the-counter antacids and anti-diarrheal products, and can also be found in some prescription drugs such as sucralfate.

A recent study found that routine testing of aluminum in all patients might not be necessary or cost-effective. In this survey, less than 1% of patients were found to have an elevated aluminum concentration, and almost all of those patients were taking aluminum-containing phosphate binders. Given this information, frequent monitoring of aluminum concentrations in the general CKD population is not warranted. The KDOQI guidelines suggest monitoring aluminum concentrations at least yearly, and every 3 months for patients taking an aluminum-containing medication.

Calcium-Containing Phosphate Binders

Calcium-containing phosphate binders are relatively inexpensive and are often used as initial therapy for hyperphosphatemia. Although maintaining calcium concentrations within the target range may cause a decrease in iPTH synthesis and release, the use of CCPB is limited by the concern for metastatic calcification. For this reason, KDOQI recommends limiting calcium intake to less than 2000 mg/day. Of this amount, about 1500 mg may be from phosphate binders and 500 mg from dietary sources. In addition, CCPB use should be reevaluated if the serum calcium increases above 10.2 mg/dL or if the Ca X P is greater than 55 mg^2/dL^2.

There are several different calcium salts for oral use. These products differ in the amount of elemental calcium that they contain as well as adverse effect profiles or the potential to cause adverse events. The three most common CCPBs are calcium carbonate, calcium acetate, and calcium citrate. Calcium citrate should be avoided in patients with CKD, as citrate is known to enhance the absorption of aluminum in the gastrointestinal tract. There are several differences between calcium carbonate and calcium acetate. Although calcium acetate contains a lower amount of elemental calcium than calcium carbonate (25.3% vs. 40%, respectively), it has been shown to be a more efficient phosphorus binder. The increased binding of calcium to phosphorus with the acetate salt may be due to a decrease in gastrointestinal absorption of the calcium as well as an increased solubility and dissociation of the acetate moiety. It has been shown that when calcium carbonate and calcium acetate are given in doses that are equivalent with regard to elemental calcium content, that calcium acetate not only lowers the serum phosphorus concentration more effectively, but is also associated with a lower incidence of hypercalcemia than the calcium carbonate product. The first pharmaceutical preparations of calcium acetate were unpalatable and caused uncomfortable gastrointestinal effects such as nausea and vomiting. These effects may have led to poor compliance among patients. This issue appears to be somewhat resolved with a more recent formulation.

Any of the calcium salts may interact with certain antimicrobial agents, specifically fluoroquinolones and tetracyclines. These agents should be administered at least 1 hour before or 3 hours after the calcium product. Oral iron preparations should also be administered at least 1 hour before or 3 hours after the calcium product to optimize the absorption of iron. Another consideration that may deter the use of calcium carbonate products is that they are commercially available without a prescription as dietary supplements. The Food and Drug Administration does not regulate dietary supplements; therefore, strength, purity, and bioavailability may be variable among preparations. Lastly, if a patient has prescription insurance, the pharmaceutical preparation of calcium acetate may well be more cost-effective. This affordability is important, especially in light of the large number of tablets (e.g., 7–8) of calcium carbonate that a patient may need to consume each day.

Research has clearly demonstrated that extraskeletal calcification leads to increased morbidity and mortality in patients with CKD, especially those patients treated with dialysis. Risk factors have been identified that correlate with this calcification. Some of these factors especially important in the management of CKD-MBD include hypercalcemia, hyperphosphatemia, an increased iPTH concentration, a very low iPTH concentration, and an increased Ca X P. It is interesting to note that the current KDOQI guidelines on the management of bone metabolism recommend that the Ca X P should be maintained less than 55 mg^2/dL^2. Before the guidelines were published in 2003, it was thought that the product should be less than 70 mg^2/dL^2. Today there is still controversy regarding the optimal goal; however, from the research that has been done to date it appears that the lower the product the better. This idea may be disconcerting to practitioners who are struggling to meet the current guidelines.

Given the difficulties of controlling calcium, phosphorus, and iPTH concentrations and the extreme consequences of failure, it is no surprise that there is considerable debate regarding the use of any CCPB. Having options besides

Abbreviations

Table 1-5. Initial Dosing of Oral Vitamin D Sterol Therapy To Treat Elevated Intact Parathyroid Hormone (iPTH) Concentrations in Patients With Stages 3 and 4 Chronic Kidney Disease

Drug	Initial Dose	Titration
Calcitriol	0.25 mcg/day or every other day	Increase at 4–8-week intervals
Doxercalciferol	1 mcg/day	Increase by 0.5 mcg every 2 weeks
Paricalcitol	iPTH ≤ 500–1 mcg/day or 2 mcg every other day iPTH >500–2 mcg/day or 4 mcg every other day	Increase every 2–4 weeks

It is recommended that vitamin D therapy should be decreased or discontinued if the concentrations of calcium, phosphorus, or the calcium-phosphate product are higher than the upper limit of the target range for each stage of chronic kidney disease.
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Table 1-6. Recommended Initial Dosing for Vitamin D Therapy for Patients with Stage 5 Chronic Kidney Disease[c]

iPTH (pg/mL)	Ca (mg/dL)	P (mg/dL)	Ca X P (mg^2/dL^2)	Calcitriol	Paricalcitol[a,b,]	Doxercalciferol
300–600	< 9.5	< 5.5	< 55	IV 0.5–1.5 mcg	IV 2.5–5 mcg	IV 2 mcg
				Oral 0.5–1.5 mcg	Oral None[a]	Oral 5 mcg
600–1000	< 9.5	< 5.5	< 55	IV 1–3 mcg	IV 6–10 mcg	IV 2–4 mcg
				Oral 1–4 mcg	Oral None[a]	Oral 5–10 mcg
> 1000	< 10.0	< 5.5	< 55	IV 3–5 mcg	IV 10–15 mcg	IV 4–8 mcg
				Oral 3–7 mcg	Oral None[a]	Oral 10–20 mcg

[a]The oral formulation was not approved at the time that the KDOQI guidelines were written.
[b]The oral formulation is not labeled for use in patients with stage 5 chronic kidney disease.
[c]Dosing is generally 3 times/week with hemodialysis.
Ca = corrected calcium; P = phosphorus; Ca X P = calcium-phosphate product; iPTH = intact parathyroid hormone; KDOQI = Kidney Disease Outcomes Quality Initiative.
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CCPBs is important in treating hyperphosphatemia. Excessive calcium intake has been directly correlated with the development of vascular calcification. In a long-term study of sevelamer hydrochloride versus calcium carbonate, nearly one-third of the patients receiving calcium displayed evidence of aortic and coronary artery calcification, a finding not observed in the sevelamer group. Although CCPBs may be a better binder for phosphorus, hypercalcemia or especially an increased Ca X P is also dangerous. Although hyperphosphatemia is an independent risk factor for death in hemodialysis patients, it may be that the treatments for the abnormality are actually increasing the risk of death.

The optimal regimen of phosphate-binding agents will depend on the characteristics of each situation. The properties of the binders, the acuity of the situation, as well as the specific needs of the patient must be evaluated. Drug-related considerations include adverse effect profile and toxicity, calcium content, and efficacy. Patient factors to consider include biochemical parameters (calcium, phosphorus, and Ca X P), preference for swallowing or chewing pills, finances or prescription insurance issues, and tolerance of adverse effects.

Newer Phosphate Binders

The search for safe, effective, and palatable phosphate binders is ongoing. Alternatives to calcium-, magnesium-, and aluminum-based products include sevelamer or lanthanum carbonate. Sevelamer is a non-absorbed polymer that binds to phosphorus in exchange for chloride ion. It may be effective as monotherapy or combined with other binders as necessary to control phosphorus concentrations. The doses used in some trials were large (6–6.9 g/day), and there has been some concern of the increased pill burden and increased adverse effects with these doses. Adverse effects may include nausea, vomiting, bloating, and constipation. Recently, there has been some concern about the possible increased incidence of colonic obstruction and perforation associated with the use of sevelamer. Although a clear relationship between the use of sevelamer and intestinal obstruction has not been well established, caution is warranted when using large doses. Sevelamer is insoluble in water and expands upon contact with water. Tablets or capsules should not be crushed, split, chewed, or taken apart before swallowing. These characteristics make sevelamer inappropriate for alternative routes of administration such as nasogastric, oral-gastric, or percutaneous entero-gastric feeding tubes. Another concern with the use of sevelamer is an increased incidence of metabolic acidosis associated with the exchange of chloride ion for short-chain fatty acid ions. Some research has shown that among other complications, metabolic acidosis is associated with an increase in iPTH concentrations and bone disease.

Despite concerns, there are several advantages to using sevelamer to control hyperphosphatemia associated with CKD. As sevelamer does not contain calcium, it does not

cause hypercalcemia. In addition, it reduces phosphorus concentrations leading to a decrease in the Ca X P. Of interest, sevelamer has been shown to have lipid-lowering effects. Although it has not been shown to be cost-effective when compared with the combination of calcium carbonate and atorvastatin, the effect on lipid concentrations may be of benefit in a population with hyperlipidemia as a comorbid condition. Sevelamer has been shown to significantly decrease the bioavailability of ciprofloxacin. Although other fluoroquinolone antibiotics have not been tested, it would be prudent to give any of these agents either 1 hour before or 3 hours after the administration of sevelamer. Many drugs have not been tested to determine an interaction when given concomitantly with sevelamer. It is recommended to separate doses of sevelamer and any drug that may be less safe or efficacious if the bioavailability were decreased due to an interaction.

Lanthanum is a relatively new agent that, like sevelamer, does not contain calcium, aluminum, or magnesium. This is a promising agent in that it appears to be non-toxic, not well absorbed, does not bind to other drugs, and has high affinity for phosphorus. There are no studies directly comparing the efficacy of sevelamer with lanthanum. Some studies have shown that sevelamer is not very effective as monotherapy for hyperphosphatemia whereas lanthanum is. Unfortunately, although not substantiated in human models, two studies have shown that lanthanum appears to accumulate in rats. To further confound the situation, the serum concentrations did not correlate well with tissue concentrations and lanthanum accumulated in liver, lung, and kidney tissue. Lanthanum has not been extensively evaluated for drug-drug interactions. It is not a substrate or inhibitor of any of the cytochrome P450 isozymes and is not absorbed systemically. Like sevelamer, many drugs have not been tested to determine an interaction when given concomitantly with lanthanum.

Phosphate binders from different classes may be combined to achieve target concentrations of phosphorus and calcium. In fact, the combined use of a CCPB and a non-calcium-containing phosphate binder may reduce the phosphorus concentration while maintaining the calcium concentration. Similarly, the use of one or more non-calcium-containing phosphate binders (such as sevelamer, lanthanum, or short-term aluminum) may be needed for patients with hyperphosphatemia and concomitant hypercalcemia. Please refer to Table 1-3 for example of phosphate binders. Frequently, patients with CKD will require therapy to lower the iPTH concentration as well as the phosphorus concentration. The phosphate binders are typically used concurrently with vitamin D therapy or a calcimimetic agent to control all of the biochemical parameters involved (i.e., calcium, phosphorus, Ca X P, and iPTH).

Vitamin D Therapy

As described earlier in the chapter, vitamin D is essential for many physiologic processes. Because vitamin D deficiency is prevalent in the CKD population, patients with Stage 3 or 4 CKD should be screened for Vitamin D deficiency if the iPTH concentration is above the range recommended by KDOQI based on the stage of CKD. This is an evidence-based recommendation from the KDOQI guidelines. In this situation, if the serum concentration of 25-hydroxyvitamin D is less than 30 ng/mL, supplementation with vitamin D_2 (ergocalciferol) may be initiated (KDOQI opinion based) (see Table 1-4). If the serum concentration of 25-hydroxyvitamin D is greater than 30 ng/mL and the iPTH concentration is greater than the target range, the patient should receive an activated vitamin D sterol. Once the patient reaches stage 5 CKD, active vitamin D or a vitamin D analog should be initiated to achieve the target iPTH.

Since the publication of the KDOQI guidelines in 2003 there have been a number of studies using vitamin D agents in stages 3 and 4 CKD. Originally, there was some concern regarding the safety of these agents. Specifically, there was question that the use of vitamin D could accelerate the decline in kidney function. In the past several years, studies have not shown any irreversible decline in kidney function while using vitamin D. The KDOQI guidelines recommend using active vitamin D or an analog in patients with persistent hyperparathyroidism despite correction of 25-hydroxyvitamin D deficiency.

Currently, there are three commercially available vitamin D agents in the United States. Calcitriol has the same structure as endogenous activated vitamin D_3 (1,25-dihydroxycholecalciferol). Both oral and injectable formulations are available generically. In general, calcitriol is the least expensive oral or injectable product currently available. Because calcitriol is the same as endogenous vitamin D_3, it has the same functions. Similar to endogenous vitamin D_3, calcitriol has affinity for both intestinal and parathyroid gland vitamin D receptors and has the propensity to increase serum calcium concentrations. Paricalcitol and doxercalciferol are vitamin D analogs that have less affinity for the intestinal receptors and therefore have been shown to cause a lower incidence of hypercalcemia. Some studies showed that doxercalciferol might cause more hypercalcemia than paricalcitol. This is still an issue of controversy as the studies were difficult to interpret because of concomitant medications (especially CCPB use). A difference between the two agents is that doxercalciferol is a vitamin D_2 prodrug, 1α-hydroxyvitamin D_2. Doxercalciferol requires activation in the liver by 25-hydroxylase and should only be used in patients with normal hepatic function. It should also be noted that hypercalcemia has been reported more frequently in patients receiving daily, oral dosing of vitamin D compared with intermittent, intravenous therapy.

There is little research directly comparing the three vitamin D agents. Studies comparing doxercalciferol or paricalcitol to calcitriol have clearly shown that the former two agents cause less hypercalcemia than the latter. One study showed a lower risk of mortality in hemodialysis patients who received paricalcitol compared with calcitriol. This finding was observed independent of the calcium, phosphorus, or Ca X P. Another trial showed a survival benefit for dialysis patients who received vitamin D (either calcitriol or paricalcitol) compared with patients who received no vitamin D therapy. No prospective studies have been designed to verify this observation. Although advantages of the analogs compared with calcitriol have

been elucidated, there are few studies comparing paricalcitol directly to doxercalciferol. Although a few studies tried to show differences in the incidence of hypercalcemia and increases in serum phosphate concentrations, the evidence from human trials is not conclusive. Clinically, the choice between the analogs may be based on patient-specific information, cost, formulary issues, and indication. As calcitriol is commonly the least expensive vitamin D drug available, it is a potentially attractive first-line drug provided that the calcium concentration is within the target range. If the calcium concentration is not well controlled, a newer vitamin D drug (paricalcitol or doxercalciferol) should be recommended. The KDOQI guidelines and package insert information for each agent provide suggested initial doses for each of the vitamin D agents based on the level of secondary hyperparathyroidism (refer to Tables 1-5 and 1-6). All of the agents should be titrated to maintain iPTH, Ca, P, and Ca X P within KDOQI target ranges.

As the vitamin D agents are similar (especially doxercalciferol and paricalcitol), it may be necessary to switch from one agent to another for reasons such as hypercalcemia or formulary restraints. There is no set guide for converting between agents. One study showed that, when converting a patient from paricalcitol to doxercalciferol, the dose should be reduced by 40%. In other words, the doxercalciferol dose should be about 60% of the paricalcitol dose. Other sources have suggested a ratio of 1:4:5 between the agents calcitriol:doxercalciferol:paricalcitol, respectively. A 1:3 ratio of calcitriol: pericalcitol has also been recommended. In the event of a conversion between agents, the iPTH, calcium, and phosphorus concentrations should be monitored monthly until the dose is stable. Adjustments in the vitamin D agent, phosphate binders, and/or calcimimetics may be necessary after the conversion.

Therapy with any vitamin D sterol should only be initiated when the serum calcium and phosphorus concentrations are within target range. A decrease in dose or temporarily withholding vitamin D therapies may be considered if the Ca X P is greater than 55 mg^2/dL^2 or if the iPTH concentration falls below the lower limit of the KDOQI range. It is imperative that vitamin D therapy be stopped if the iPTH concentration is below goal as over-suppression may lead to adynamic bone disease. In fact, as CKD progresses, iPTH concentrations must be maintained at higher concentrations as there appears to be increasing skeletal resistance to iPTH. Research has shown that during the altered bone metabolism of adynamic disease, patients are also at a higher risk for vascular calcification.

Calcimimetics

A relatively new strategy to control secondary hyperparathyroidism is the use of the calcimimetic agent, cinacalcet. Cinacalcet acts by binding to and allosterically modifying the calcium-sensing receptor on the chief cell of the parathyroid gland. This causes an increased sensitivity of the receptor to extracellular calcium. The calcium-sensing receptor is a G-coupled receptor and, through a series of second messenger pathways, the parathyroid gland down-regulates gene transcription and release of iPTH. Cinacalcet is beneficial in decreasing iPTH concentrations and maintaining calcium and phosphorus concentrations with or without concomitant treatment with vitamin D agents.

The initial dosage of cinacalcet is 30 mg by mouth once a day. The dose may be titrated in increments of 30 mg every 2–4 weeks until the iPTH is within the target range to a maximum of 180 mg/day. In studies, cinacalcet was well tolerated by patients. There was a slightly higher incidence of nausea and vomiting in the cinacalcet group compared with the placebo group but this was generally self-limiting. The most concerning untoward effect of cinacalcet is hypocalcemia, and careful monitoring should be undertaken to assure safety upon initiation of the drug and at every dose increase. Cinacalcet should not be initiated in patients if their corrected serum calcium concentration is less than 8.4 mg/dL. Calcium and phosphate concentrations should be obtained within 1 week of initiation or a dose increase. The iPTH concentration can be monitored between 1 week and 1 month after initiation or dose change. As noted, cinacalcet can be used concomitantly with vitamin D agents and phosphate binders. In fact, the hypocalcemia that can result from cinacalcet use may be beneficial to offset increases in calcium produced by other therapies such as CCPB or vitamin D agents. Cinacalcet has been shown to reduce serum calcium, phosphorus (slightly), Ca X P, and iPTH concentrations. As with vitamin D agents, the dosage of cinacalcet should be decreased or discontinued if the iPTH concentration falls below the target range to prevent adynamic bone disease. There is some concern for drug interactions with cinacalcet. Azole antifungals, especially ketoconazole, may cause a doubling of cinacalcet concentrations. A dose reduction may be required for drugs metabolized by the cytochrome P450 isozyme 2D6 that have a narrow therapeutic range. Examples include flecainide, thioridazine, vinblastine, and most of the tricyclic antidepressants.

Cinacalcet offers a new treatment strategy when used alone, with phosphate binders, or in combination with phosphate binders and vitamin D therapy. As cinacalcet was approved for use after the KDOQI guidelines were published in 2003, it does not appear in any of the guidelines or algorithms (see Figures 1-2 and 1-3 for proposed use).

Parathyroidectomy

A parathyroidectomy is the last-line treatment for hyperparathyroidism. It is indicated when iPTH concentrations are consistently greater than 800 pg/mL and calcium and phosphorus concentrations are above the target range despite all attempts at medical management. The surgical procedure is neither completely safe nor effective. Surgical complications may occur. Occasionally, a portion of the gland remains intact after surgery and hyperparathyroidism will recur. In addition, the removal of the parathyroid gland can cause precipitous, persistent decreases in serum calcium and possibly phosphorus. This is sometimes known as “hungry bone syndrome” as the bone reabsorbs as much calcium and phosphorus as possible. Frequent monitoring and calcium supplementation is essential following surgery. Intravenous calcium should be

given as a continuous intravenous admixture to maintain the ionized calcium concentration within the normal range. Once the patient is stable, oral calcium supplements and calcitriol should be initiated to maintain calcium concentrations.

Therapeutic Challenges

Adherence

Despite evidence showing the deleterious effect of secondary hyperparathyroidism, the disorder remains uncontrolled in many patients with CKD. A recent study found that, despite the use of phosphate binders, 70% of hemodialysis patients still had hyperphosphatemia. A separate study showed that nearly 40% of patients take less than 80% of their prescribed dose of phosphate binders. In addition, only 11 out of the 177 patients (6%) were within the target range for all biochemical parameters: calcium, phosphorus, iPTH, and Ca X P. It is clear that therapy for hyperphosphatemia and hyperparathyroidism will not be effective unless aggressive efforts are made to educate both patients and providers on appropriate use of these agents. Such therapies must be accompanied by both patient and provider education to ensure compliance and better outcomes. There are many patient-specific factors to consider in developing a therapeutic regimen to treat disorders of calcium, phosphorus, and iPTH. It is important to realize that, although one agent may be more efficacious in theory, the agent that helps the patient is the one he or she will actually use as prescribed. The CKD population (especially patients on dialysis) is at high risk for nonadherence and treatment failure. Psychosocial issues of taking medications, issues of prescription insurance, pill burden, palatability, comorbid diseases (including depression), adverse effects, and portability must be considered when choosing medications. Compliance rates fall with the increased frequency of administration and increased number of pills per day. Designing an optimal drug regimen should take all of these factors into account. Patients who fail to achieve secondary outcomes such as maintaining biochemical parameters within the KDOQI guidelines despite an optimal pharmacotherapeutic regimen

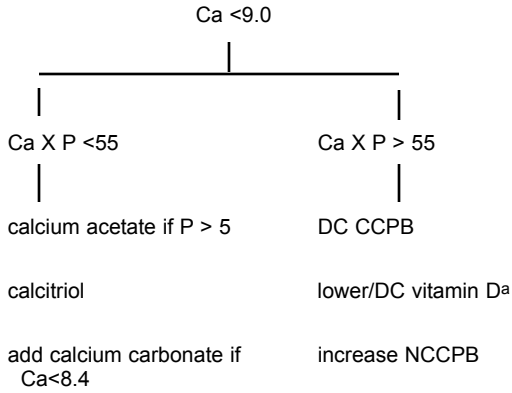

Figure 1-2. Options for managing chronic kidney disease-mineral and bone disorder for patients with elevated iPTH and **normal/low** calcium concentrations.
[a]Lower/DC vitamin D = decrease dose or discontinue calcitriol /paricalcitol/doxercalciferol until Ca X P <55 mg^2/dL^2.
Ca = calcium mg/dL; Ca X P = calcium/phosphorus product mg^2/dL^2; CCPB = calcium-containing phosphate binder; DC = discontinue; NCCPB = non-calcium containing phosphate binder; P = phosphorus in mg/dL.

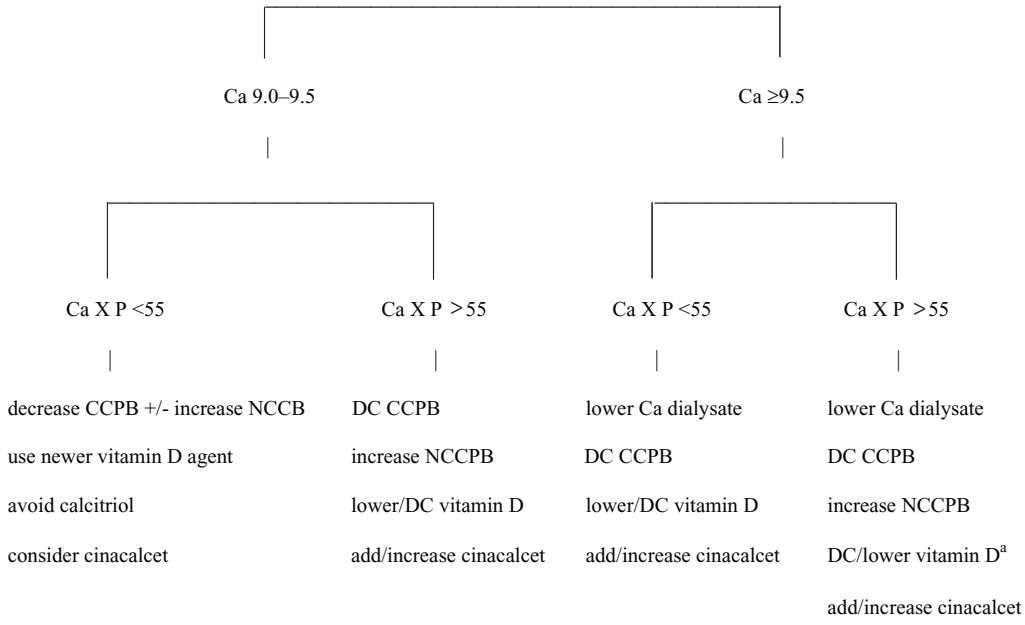

Figure 1-3. Options for managing chronic kidney disease-mineral and bone disorders for patients with elevated iPTH concentrations and **normal/high** calcium concentrations.
[a]Lower/DC vitamin D = Decrease dose or discontinue calcitriol/paricalcitol/doxercalciferol until Ca X P <55 mg^2/dL^2.
Ca = calcium in mg/dL; Ca X P = calcium/phosphorus product in mg/dL; DC = discontinue; CCPB = calcium-containing phosphate binder; iPTH = intact parathyroid hormone; NCCPB = non-calcium containing phosphate binder; P = phosphorus in mg/dL.

should be evaluated for potential nonadherence. Direct questioning, pill counts, and obtaining pharmacy prescription profiles and refill histories may all be necessary to determine the cause of nonadherence. Patients may not understand that they must take their phosphate binders with food. They may be under false impressions about the phosphate binders. Examples include thinking that calcium carbonate is only for indigestion or that they only take binders with meals, not with snacks. There may be language barriers that make verbal communication or reading prescription labels difficult. Educational barriers or development delays may make comprehension impossible. Physical barriers such as blindness (or near-blindness), arthritis, or difficulty swallowing may impede adherence. Financial difficulties may cause patients to discontinue medications, and patients may not report such issues for fear of judgment by providers.

In addition to recommending optimal agents for these patients, a multidisciplinary team approach may be helpful to increase adherence rates. Physicians, nurses, pharmacists, dieticians, and social workers should cooperate and communicate to provide the best care. Using an interdisciplinary approach to work with other health care providers, insurance companies, drug manufacturers, and other agencies may provide options for patients with limited financial resources to obtain drugs. Other strategies that may be used to enhance and ensure compliance include frequent education (dietary as well as taking phosphate binders with food), reinforcement (possibly through incentive programs), feedback sessions, pill counts, providing portable medication containers, and communication with direct caregivers.

Conclusion

Chronic kidney disease-mineral and bone disorders present a very challenging situation for the clinician and patient. Research thus far has shown that the metabolic parameters such as calcium, phosphate, Ca X P, iPTH, and vitamin D must be maintained within fairly narrow ranges to prevent negative consequences. In addition, all of these parameters need to be controlled simultaneously to really be successful. Last and perhaps the most difficult challenge of all is patient acceptance and adherence. Complicated regimens, multiple doses per day, a high pill burden, and comorbid disease states are all factors that increase the rate of nonadherence and therefore treatment failure. Pharmacists can play an important role in the management of CKD-MBD. Routine monitoring of biochemical markers, patient education and reinforcement, ensuring compliance, monitoring for adverse effects of pharmacotherapy, and making recommendations to optimize drug therapy are among the important roles.

Annotated Bibliography

1. National Kidney Foundation. Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease. Am J Kidney Dis 2003;42(4 suppl 3):S1–S201.

   This evidence-based clinical practice guideline elucidates the prevalence and consequences of secondary hyperparathyroidism and associated metabolic abnormalities as well the role that mineral homeostasis plays in the development of extraskeletal calcification and increased cardiovascular morbidity and mortality in patients with CKD. New developments in the area of bone metabolism in patients with CKD have led to new recommendations for optimal management of bone metabolism and bone disease for these patients in the United States. A panel of experts reviewed the relevant literature and created guidelines for patient management. Guidelines are evidence-based when possible although opinion-based recommendations are provided when the literature is insufficient.

2. Friedman PA, Goodman WG. PTH(1-84)/PTH(7-84): a balance of power. Am J Physiol Renal Physiol 2006;290:975–84.

   This article provides an excellent review of the molecular structure of the parathyroid molecule, its important biologic fragments, and the different assays that have been created to measure parathyroid hormone concentrations. Evidence supporting the use of different assays is explored. Most assays employed in clinical practice are first-generation immunometric assays. Although they were designed to detect intact parathyroid hormone, PTH (1-84), they also detect some fragments as well. Ideally, only iPTH would be measured and correlated to histologic findings. The discussion and summary support utilizing the current assays until further evidence of superiority is available for the new second-generation iPTH tests, and it is demonstrated that results of the assays are better correlated with clinical and histologic findings.

3. Chertow GM, Burke SK, Raggi P, for the Treat To Goal Working Group. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. Kidney Int 2002;62:245–52.

   The authors conducted an international study involving 200 patients on chronic hemodialysis. Patients were randomized to receive either sevelamer (about 8 of the 800 mg tablets/day) or a calcium-containing phosphate binder (about 7 667 mg or 500 mg tablets/day) for 1 year. A significant reduction in coronary and aortic artery calcification was found in the sevelamer group. This group also had a significant reduction in low density lipid concentrations. Although it was not highlighted in the article, on average, patients receiving calcium had a final iPTH concentration below the recommended level of 150 pg/mL, placing them at risk for adynamic bone disease. This condition has also been associated with an increase in extraskeletal calcification. The calcium group also had a greater incidence of hypercalcemia (43% vs. 17%). Another finding was 12% of patients in the sevelamer group required aluminum supplementation to maintain calcium and phosphorus levels compared with only 4% in the calcium group. This study is difficult to interpret as the specific vitamin D supplementation was not identified, although the investigators report that overall a lower dose of vitamin D was used in the sevelamer group.

4. Qunibi W, Hootkins RE, McDowell LL, Meyer MS, Simon M, Garza RO, et al. Treatment of hyperphosphatemia in hemodialysis patients: The Calcium Acetate Renagel Evaluation (CARE Study). Kidney Int 2004;65:1914–26.

One hundred patients received either calcium acetate 667 mg tablets or sevelamer 403 mg capsules 3 times/day with meals in an 8-week, randomized, double-blind, multicenter study. Average numbers of capsules used per day were 10.7 in the calcium arm and 17.2 in the sevelamer arm, although compliance rates (weekly pill counts) were similar in both arms. The primary efficacy end points were phosphorus and calcium concentrations, and the Ca X P. At each week, patients were more likely to attain goal phosphorus concentrations and Ca X P in the calcium acetate group than in the sevelamer group. There were 18 cases of hypercalcemia in the calcium arm and none in the sevelamer arm, although all patients who experienced hypercalcemia were also on vitamin D therapy. Patients in the sevelamer group had greater reductions in serum bicarbonate concentrations. This study also provided a cost-benefit analysis showing that, in the absence of hypercalcemia calcium acetate, should be the treatment of choice.

5. Moe SM, Chertow GM, Coburn JW, Quarles LD, Goodman WG, Block GA, et al. Achieving NKF-KDOQI bone metabolism and disease treatment goals with cinacalcet hydrochloride. Kidney Int 2005;67:760–71.

   This report is an analysis of three placebo-controlled, double-blind, 26-week studies. More than 1000 subjects on chronic dialysis were randomized to receive placebo or cinacalcet in addition to phosphate binders and vitamin D therapy. Doses were titrated based on bone mineral metabolism biochemical parameters according to a predetermined protocol for each study. Compilation of the data demonstrated that patients who received cinacalcet were more likely to meet the target ranges for phosphorus, calcium, iPTH, Ca X P, and simultaneous Ca X P and iPTH outcomes than subjects who received placebo.

6. Zisman A, Ghantous W, Schinleber P, Roberts L, Sprague SM. Inhibition of parathyroid hormone: a dose equivalency study of paricalcitol and doxercalciferol. Am J Nephrol 2005;25:591–5.

   Little information has been published regarding the dose equivalency between the three active, intravenous vitamin D agents, calcitriol, doxercalciferol, and paricalcitol. Although these agents are titrated based on the concentrations of iPTH, calcium, and phosphorus, the question of dose equivalence is one of interest when the need arises to switch from one vitamin D agent to another. Because both paricalcitol and doxercalciferol are associated with a lower incidence of hypercalcemia as compared with calcitriol, these agents are often used interchangeably. This article suggests that in the hemodialysis population, a dose conversion factor of 0.57 be used when switching from paricalcitol to doxercalciferol. In other words, the doxercalciferol dose should be 55%–60% of the paricalcitol dose. Although this was a relatively small study, it provides a guide to interchanging the doses of paricalcitol and doxercalciferol. Using this conversion as an initial dose, and then monitoring calcium, phosphorus, and iPTH concentrations within 1 month and titrating the analog based on the concentrations appears to be an effective means of dose conversion.

7. Sprague SM, Llach F, Amdahl M, Taccetta C, Batlle D. Paricalcitol versus calcitriol in the treatment of secondary hyperparathyroidism. Kidney Int 2003;63:1483–90.

   In a well-designed trial of 263 patients receiving hemodialysis, Sprague and colleagues showed that paricalcitol lowers iPTH concentrations faster (target achieved in 18 weeks) than calcitriol. In fact, as a group, the majority of the patients in the calcitriol arm did not attain the target goals of 100–300 pg/mL for iPTH. Patients in the calcitriol arm also had a higher incidence of sustained hypercalcemia (on more than two occasions) or sustained increases in Ca X P (on more than four occasions). This study highlights the findings that paricalcitol is associated with a lower incidence of hypercalcemia than calcitriol.

8. Noordzij M, Korevaar J, Boeschoten E, Dekker FW, Bos WJ, Krediet RT; Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) Study Group. The Kidney Disease Outcomes Initiative (K/DOQI) Guideline for Bone Metabolism and Disease in CKD: association with mortality in dialysis patients. Am J Kidney Dis 2005;46:925–32.

   This study, conducted in the Netherlands, included 1629 patients receiving dialysis. It showed that patients receiving hemodialysis and peritoneal dialysis experienced an increased risk of mortality if they had a phosphorus concentration greater than 5.5 mg/dL (40% and 60%, respectively). In addition, patients with a Ca X P greater than 55 mg^2/dL^2 also experienced a significant increase in all-cause mortality risk, 40% in hemodialysis and 50% in peritoneal dialysis. This study provides further evidence for the need for adherence to the KDOQI guidelines and the potential effects of uncontrolled bone and mineral metabolism in these patients.

9. Loghman-Adham M. Medication noncompliance in patients with chronic kidney disease: issues in dialysis and renal transplantation. Am J Manag Care 2003;9:155–71.

   This is a well-written review article detailing the research that has been performed in the area of noncompliance in the CKD and transplant populations. Many creative ideas are presented to enhance compliance such as incentives, simplification, visual reminders, patient education, and feedback sessions. With bone metabolism and bone disease, compliance with dietary and pharmaceutical regimens is essential for success. Only a small fraction of the CKD population is actually meeting the KDOQI targets for all the biochemical parameters for bone mineral metabolism. Even the most carefully designed treatment plan will fail without patient acceptance and compliance. This article highlights this sentiment and gives practical ideas to assist caregivers of patients on dialysis.

10. Coyne D, Acharya M, Qiu P, Abboud H, Batlle D, Rosansky S, et al. Paricalcitol capsule for the treatment of secondary hyperparathyroidism in Stages 3 and 4 CKD. Am J Kidney Dis 2006;47(2):263–76.

    This is the compilation of three Phase 3 trials using oral paricalcitol capsules to control iPTH and calcium concentrations, and Ca X P in patients with CKD Stages 3 and 4. When used as daily or thrice-weekly therapy, 91% of patients receiving paricalcitol achieved a 30% decrease in iPTH and 75% of patients had concentrations below 110 pg/mL at the end of study. Mean calcium concentrations and Ca X P did not differ significantly between groups. This study provides data for the safety and efficacy of oral paricalcitol in pre-dialysis patients.

11. Coburn JW, Maung HM, Elangovan L, Germain MJ, Sprague SM, Williams ME, et al. Doxercalciferol safely suppresses PTH levels in patients with secondary hyperparathyroidism

associated with chronic kidney disease stages 3 and 4. Am J Kidney Dis 2004;43:877–90.

A study similar to the above study by Coyne and colleagues, this study provides evidence for the use of oral doxercalciferol in patients with Stages 3 and 4 CKD. Fifty-five adults with CKD Stages 3 and 4 were randomized to receive either daily oral doxercalciferol or placebo. After 6 weeks of therapy and at all subsequent weeks, the decrease in iPTH was greater with doxercalciferol than with placebo. In addition, iPTH concentrations decreased by 46% from baseline to the end of the study at 24 weeks. There were no clinically significant differences in change of other biochemical parameters, such as calcium and phosphorus concentrations or Ca X P. This study provides data for the safety and efficacy of oral doxercalciferol in patients with Stages 3 and 4 CKD.

Abbreviations

Self-Assessment Questions

Please start new PSAP-VI online test.

Questions 1–5 pertain to the following case.
J.J. is a 47-year-old African-American man who has just been diagnosed with diabetic nephropathy. He is unemployed and has no health insurance or prescription coverage. His estimated glomerular filtration rate (eGFR) is stable at 34 mL/minute/1.73 m^2 (Stage 3 chronic kidney disease [CKD]). His primary physician refers him to see a nephrologist. The nephrologist orders a complete work-up with the following laboratory results: calcium 8.5 mg/dL, albumin 3.8 g/dL, phosphorus 4.1 mg/dL, and intact parathyroid hormone (iPTH) 52 pg/mL.

1. Which one of the following best represents J.J.'s condition and best recommendation for management at this time?
   A. J.J. has secondary hyperparathyroidism and requires aggressive vitamin D therapy.
   B. Given J.J.'s calcium, phosphorus, and intact parathyroid concentrations, he probably already has bone disease and should be evaluated by bone biopsy.
   C. J.J.'s phosphorus level is above the recommended range for Stage 3 kidney disease and J.J. should be placed on a calcium-containing phosphate binder with meals.
   D. All of J.J.'s laboratory parameters are within the normal range for Stage 3 CKD. The levels should be rechecked in 1 year.

J.J. has been followed in the CKD clinic for the past year although he has missed several appointments. During this time, his health has declined. He is still unemployed and is currently staying with his sister. He has newly diagnosed hypertension and his estimated GFR today is 27 mL/minute/1.73 m^2. Today in clinic, you review his recent laboratory results: hemoglobin A1c 9.1%, blood glucose 315 mg/dL, calcium 8.4 mg/dL, phosphorus 9.8 mg/dL, and albumin 2.4 g/dL. He is not currently taking any phosphate-binding agents.

2. In addition to dietary phosphorus restriction, the addition of which one of the following phosphate-binding agents is most appropriate at this time?
   A. Calcium acetate 667 mg by mouth 3 times/day with meals.
   B. Sevelamer 800 mg by mouth 3 times/day with meals.
   C. Aluminum hydroxide 1200 mg by mouth 3 times/day with meals.
   D. Calcium carbonate 1250 mg by mouth twice a day spaced between meals.

J.J.'s iPTH concentration was not available at the time of his clinic visit. Five days later, the result came back at 148 pg/mL. His 25-hydroxyvitamin D concentration was greater than 30 ng/mL (ruling out vitamin D deficiency and the use of ergocalciferol).

3. Assuming that the other laboratory values are still valid, which one of the following recommendations should be made at this time?
   A. Initiate calcitriol 0.5 mcg by mouth once a day.
   B. Do not treat the elevated iPTH value until J.J.'s Ca X P is less than 55 mg^2/dL^2.
   C. Initiate paricalcitol 5 mcg intravenously 3 times/week.
   D. Initiate paricalcitol 1 mcg by mouth once a day.

Sadly, J.J. suffered from a catastrophic stroke secondary to his uncontrolled hypertension 5 days ago. He is on a ventilator and has left-sided hemiparesis and severe neurological damage. He has acute tubular necrosis secondary to prolonged hypotension and hypoperfusion and has been anuric for the past 3 days. The nephrology team is starting hemodialysis today. His laboratory results reveal the following: blood urea nitrogen 158 mg/dL, serum creatinine 6.2 mg/dL, calcium 8.5 mg/dL, and phosphorus 9.0 mg/dL. The intensive care unit team is holding a family meeting today to discuss outcomes. They will wait until the family's wishes are known to put in a nasogastric tube and begin tube feedings. Currently, J.J.'s drugs include phenytoin 100 mg intravenously 3 times/day, esomeprazole 40 mg intravenous push once a day, and midazolam 4 mg/hour continuous intravenous infusion. The intensive care unit team asks for the best recommendation regarding the calcium and phosphorus concentrations.

4. Which one of the following recommendations should be made at this time?
   A. Wait until after hemodialysis and re-evaluate the phosphorus and calcium concentrations.
   B. Give calcium chloride 1 g intravenous push now before hemodialysis is initiated.
   C. Give aluminum hydroxide 1200 mg by mouth 3 times/day.
   D. Give calcium gluconate 1 g intravenous push now before hemodialysis is initiated.

One month later, J.J.'s condition has stabilized; however, he is ventilator dependent, hemodialysis dependent, has left-sided hemiparesis, and is receiving continuous feedings via nasogastric tube at 40 mL/hour (1.2 g protein/kg/day). He is in the subacute unit of the hospital, awaiting placement in a nursing home. His drugs include phenytoin 100 mg 3 times/day, atorvastatin 10 mg once a day, clopidogrel 75 mg once a day, aspirin 81 mg once a day, sucralfate 1 g 4 times/day, and a renal vitamin once a day, all given via nasogastric tube, and heparin 5000 units subcutaneously twice a day. His laboratory values are as follows: calcium 7.2 mg/dL, phosphorus 1.2 mg/dL, iPTH 37 pg/ml, albumin 1.6 g/dL, and free phenytoin 1.3 ng/mL. An infusion of

sodium phosphate 20 mmol via intravenous piggyback over 6 hours was started.

5. Which one of the following options is best to treat J.J.'s phosphorus disorder?
   A. Discontinue phenytoin as it is binding phosphorus. Consult neurology.
   B. Discontinue sucralfate as it is binding phosphorus. Add famotidine 20 mg via nasogastric tube once a day.
   C. Discontinue atorvastatin as it is decreasing the gastrointestinal absorption of phosphorus.
   D. Increase the rate of the tube feeds to 80 mL/hour as J.J. is not getting enough protein.

Questions 6 and 7 pertain to the following case.

C.J. is a 54-year-old woman with kidney failure secondary to diabetic nephropathy. She has been maintained on hemodialysis for the past 4 years. Her most recent laboratory values reveal the following levels: calcium 9.0 mg/dL, phosphorus 5.1 mg/dL, albumin 2.8 g/dL, and iPTH 882 pg/mL. She is currently taking the following drugs: calcium acetate 1334 mg by mouth 3 times/day with meals and doxercalciferol 4 mcg intravenous push 3 times/week at the end of hemodialysis. She has never been prescribed aluminum-containing phosphate binders.

6. Which one of the following options is best at this time to treat C.J.'s chronic kidney disease-mineral and bone disorder?
   A. Osteitis fibrosa cystica.
   B. Osteomalacia.
   C. Rickets.
   D. Adynamic bone disease.

7. What is the best recommendation for C.J.'s CKD-Mineral and Bone Disorder?
   A. Stop calcium acetate. Add sevelamer 403 mg with meals.
   B. Stop calcium acetate. Add lanthanum 500 mg with meals.
   C. Add cinacalcet 30 mg by mouth once a day.
   D. Increase doxercalciferol to 6 mcg intravenously 3 times/week.

Questions 8–10 pertain to the following case.

F.F. is a 22-year-old African-American woman with kidney failure secondary to systemic lupus erythematosus. She has been on peritoneal dialysis for 6 years. At her clinic visit, she has no complaints except a worsening of indigestion. Her monthly calcium and phosphorus levels showed a corrected calcium of 10.0 mg/dL and phosphorus of 3.1 mg/dL. Her last iPTH level was 891 pg/mL. Her drugs have been constant in the past 3 months and include prednisone 20 mg by mouth once a day, pantoprazole 20 mg by mouth once a day, hydroxychloroquine 200 mg by mouth once a day, sevelamer 800 mg by mouth 3 times/day with meals, and paricalcitol 5 mcg by mouth once a day.

8. Which one of the following recommendations is best at this time to treat F.F.'s chronic kidney disease-mineral and bone disorder?
   A. Increase paricalcitol to 10 mcg by mouth once a day.
   B. Discontinue paricalcitol. Start doxercalciferol 4 mcg by mouth once a day.
   C. Discontinue paricalcitol. Start calcitriol 1 mcg by mouth once a day.
   D. Start cinacalcet 30 mg by mouth once a day.

Three months later, F.F. returns to the clinic. Her laboratory parameters include corrected calcium 8.8 mg/dL, phosphorus 7.6 mg/dL, and iPTH 289 pg/mL. She reports that she has not been taking her sevelamer (800 mg by mouth 3 times/day with meals) regularly as she thinks it is contributing to her indigestion (she feels much better when she does not take it). She reports that she is still taking her other drugs as prescribed.

9. Which one of the following recommendations is best to address F.F.'s symptoms at this time?
   A. Decrease the sevelamer dose to 400 mg by mouth 3 times/day with meals.
   B. Discontinue sevelamer; start calcium carbonate 500 mg by mouth 2 times/day and at bedtime.
   C. Increase pantoprazole to 20 mg by mouth 2 times/day with breakfast and dinner.
   D. Discontinue sevelamer; start lanthanum 500 mg by mouth 3 times/day with meals.

F.F. returns to clinic in 3 months. Although F.F. states that she is taking all of her drugs as instructed, her calcium concentration is very high (10.2 mg/dL) while her phosphorus is a little low (3.1 mg/dL).

10. Which one of the following hypotheses could adequately explain F.F.'s calcium and phosphorus concentrations?
    A. F.F. has been chewing her lanthanum tablets instead of swallowing them whole.
    B. F.F. has been chewing Alamag (aluminum and magnesium hydroxide) tablets several times a day for indigestion.
    C. F.F. has been chewing Tums (calcium carbonate) tablets several times a day for indigestion.
    D. F.F. has been eating yogurt every day because she heard it was good for her bones.

Questions 11 and 12 pertain to the following case.

H.H. is a 54-year-old Hispanic man who presented to the hospital last week with kidney failure. Despite having health insurance, he has never had any health care and it appears that his kidney failure is secondary to long-standing uncontrolled hypertension. He started hemodialysis and a full work-up was initiated. He will probably remain as an inpatient for a week or more until he is stabilized and arrangements are made for outpatient hemodialysis. His laboratory values today are calcium 9.0 mg/dL, albumin 3.1 g/dL, phosphorus 12.2 mg/dL, and iPTH 1201 pg/mL.

The nephrologist is going to order dietary phosphate restriction and use a low calcium concentration in the dialysate solution.

11. In addition, which one of the following regimens would be best to correct the metabolic abnormalities and prevent extraskeletal calcification and bone disease at this time?
    A. Aluminum hydroxide 1200 mg by mouth 3 times/day with meals and paricalcitol 10 mcg intravenous push 3 times/week with hemodialysis.
    B. Lanthanum 1000 mg by mouth 3 times/day with meals and paricalcitol 10 mcg intravenous push 3 times/week with hemodialysis.
    C. Lanthanum 1000 mg by mouth 3 times/day with meals and cinacalcet 30 mg by mouth once a day.
    D. Aluminum 1200 mg by mouth 3 times/day with meals and cinacalcet 30 mg by mouth once a day.

12. One week later, H.H.'s laboratory results show calcium 7.8 mg/dL, phosphorus 6.5 mg/dL, and albumin 3.2g/dL. Which one of the following options is best for H.H. at this time?
    A. Add calcium carbonate 1000 mg by mouth twice a day between meals.
    B. Add calcium acetate 667 mg by mouth 3 times/day with meals.
    C. Add sevelamer 403 mg by mouth 3 times/day with meals.
    D. Maximize the calcium concentration in the dialysate.

Questions 13 and 14 pertain to the following case.
C.H. is a 75-year-old man on chronic hemodialysis with a history of calciphylaxis and uncontrolled hyperphosphatemia. He has just transferred into your dialysis unit. His most recent laboratory results from the other dialysis center show a corrected serum calcium of 9.5 mg/dL and a phosphorus concentration of 8.6 mg/dL. He had been receiving paricalcitol 8 mcg intravenously 3 times/week during hemodialysis. In addition, you note that last year he experienced significant gastrointestinal effects from sevelamer necessitating discontinuation. You cannot find a recent iPTH concentration so you ask C.H. to go to the laboratory before his next appointment to have it drawn. In the meantime, you want to try to lower his phosphorus concentration.

13. Which one of the following recommendations should be made at this time?
    A. Initiate aluminum hydroxide 1200 mg by mouth 3 times/day.
    B. Initiate sevelamer 800 mg by mouth 3 times/day with meals.
    C. Increase the calcium acetate dose to 2001 mg by mouth 3 times/day with meals.
    D. Initiate lanthanum 500 mg by mouth 3 times/day with meals.

C.H. returns to the clinic today. The tests you ordered last month are back. His laboratory results are calcium 9.2 mg/dL, phosphorus 4.1 mg/dL, and iPTH 423 pg/mL. You note that his phosphorus concentration has improved, but would like to lower his iPTH concentration into the target range. He had previously been maintained on paricalcitol 8 mg intravenously 3 times/week at hemodialysis. Your facility does not carry paricalcitol, only calcitriol or doxercalciferol.

14. Which one of the following recommendations is the best option?
    A. Calcitriol 0.5 mcg intravenously 3 times/week at the end of hemodialysis.
    B. Petition pharmacy to order paricalcitol, resume prior dose.
    C. Doxercalciferol 5 mcg by mouth once a day.
    D. Doxercalciferol 5 mcg intravenously 3 times/week at the end of hemodialysis.

15. G.D. is a 63-year-old woman on chronic peritoneal dialysis for the past 11 years. She has multiple comorbidities including diabetes, congestive heart failure, hyperlipidemia, peripheral vascular disease, hypertension, anemia, and secondary hyperparathyroidism. Her laboratory results are calcium 8.8 mg/dL, phosphorus 6.2 mg/dL, and iPTH 278 pg/mL. Her most recent low-density lipoprotein concentration was 162 mg/dL, high-density lipoprotein concentration 30 mg/dL, triglycerides less than 500 mg/dL, and total cholesterol of 218 mg/dL. She has been maintained on calcium acetate 667 mg by mouth 3 times/day with meals, paricalcitol 5 mcg by mouth once a day, aspirin 81 mg by mouth once a day, epoetin alfa 10,000 units subcutaneously once a week, glipizide 5 mg by mouth once a day, and metoprolol 25 mg by mouth 2 times/day. Which one of the following strategies has the potential to lower her risk factors for cardiovascular disease?
    A. Increase calcium acetate to 1334 mg by mouth 3 times/day with meals.
    B. Add sevelamer 403 mg by mouth 3 times/day with meals.
    C. Add lanthanum 500 mg by mouth 3 times/day with meals.
    D. Discontinue paricalcitol 5 mcg by mouth once a day.

Questions 16–19 pertain to the following case.
H.K. is a 63-year-old man with a history of hypertension, hyperlipidemia, and benign prostatic hypertrophy. He has been referred to the CKD clinic because his serum creatinine has been increasing over the past several years. Today you estimate his GFR to be about 38 mL/minute/1.73 m^2. His laboratory values reveal calcium 8.6 mg/dL, albumin 4.0 g/dL, phosphorus 3.9 mg/dL, and iPTH 139 pg/mL, and 25-hydroxyvitamin D 42 ng/mL.

16. Which one of the following recommendations is best to treat the H.K.'s metabolic abnormalities?
    A. Calcitriol 0.25 mcg by mouth once a day.
    B. Doxercalciferol 4 mcg by mouth once a day.
    C. Cinacalcet 30 mg by mouth once a day.
    D. Sevelamer 403 mg by mouth 3 times/day with meals.

Two years have passed since H.K. first came to your clinic. His estimated GFR today is 31 mL/minute/1.73 m^2. His laboratory results today show calcium 9.8 mg/dL, albumin 3.6 g/dL, phosphorus 5.1 mg/dL, and iPTH 59 pg/mL. His current medications include calcium acetate 667 mg by mouth 3 times/day with meals, sevelamer 403 mg by mouth 3 times/day with meals, paricalcitol 1 mcg by mouth once a day, lisinopril 20 mg by mouth once a day, and hydrochlorothiazide 25 mg by mouth once a day.

17. Which one of the following recommendations is optimal at this time?
    A. Discontinue calcium acetate. Increase sevelamer to 800 mg by mouth 3 times/day with meals.
    B. Discontinue paricalcitol. Increase sevelamer to 800 mg by mouth 3 times/day with meals.
    C. Discontinue sevelamer. Increase paricalcitol to 2 mcg by mouth once a day.
    D. Discontinue paricalcitol. Add doxercalciferol 2 mcg by mouth once a day.

H.K.'s wife who had been his primary caregiver passed away about 6 months ago. Since that time, he seems to be very sad and despondent. He appears unkempt and unclean. His primary care physician referred him to a psychiatrist for depression and anxiety. He was started on paroxetine 20 mg by mouth once a day and buspirone 5 mg by mouth 3 times/day. His current drugs also include calcium acetate 667 mg by mouth 3 times/day with meals, sevelamer 403 mg by mouth 3 times/day with meals, cinacalcet 60 mg by mouth once a day, lisinopril 20 mg by mouth once a day, and hydrochlorothiazide 25 mg by mouth once a day. His estimated GFR today is 20 mL/minute/1.73 m^2. His laboratory values are calcium 7.9 mg/dL, phosphorus 8.9 mg/dL, and iPTH 220 pg/mL. The dietician noticed that H.K.'s albumin was decreasing (now 2.5 g/dL). He conducts a food recall with H.K. and finds that since his wife's death H.K. has been eating out for every meal. He does not cook for himself. The dietician prescribes a high-protein, liquid nutritional supplement to be taken twice daily.

18. Which one of the following changes should be made at this time to optimize H.K.'s pharmacotherapy?
    A. Discontinue sevelamer.
    B. Discontinue cinacalcet.
    C. Add lanthanum 500 mg by mouth with each liquid protein supplement.
    D. Remind H.K. to take calcium acetate and sevelamer with him when he goes out to eat.

Since his wife's death 2 years ago, H.K. has become very unreliable. He often misses his appointments. Although a psychiatrist is treating him, he still seems very sad and despondent. Today in the clinic you notice that his blood pressure is uncontrolled (178/94 mm Hg) and his heart rate is 92 beats/minute. His estimated GFR is 19 mL/minute/1.73 m^2. He had an arteriovenous fistula placed last month in preparation for hemodialysis. His drugs at this time are sevelamer 2400 mg by mouth 3 times/day with meals, cinacalcet 120 mg by mouth once a day, metoprolol 100 mg by mouth 2 times/day, lisinopril 20 mg by mouth 2 times/day, amlodipine 10 mg by mouth once a day, furosemide 80 mg by mouth once a day, paroxetine 20 mg by mouth once a day, ferrous sulfate 325 mg by mouth 3 times/day with meals, and darbepoetin alfa 100 mcg subcutaneously every month. His laboratory results today show calcium 10.6 mg/dL, albumin 2.1 g/dL, phosphorus 8.7 mg/dL, and iPTH 199 pg/mL.

19. Which one of the following interventions is best for H.K. at this time?
    A. Increase sevelamer to 3200 mg by mouth 3 times/day with meals.
    B. Add lanthanum 500 mg by mouth 3 times/day with meals.
    C. Increase cinacalcet to 180 mg by mouth once daily.
    D. Call H.K.'s pharmacy to get his profile history.

20. Y.L. is a 14-year-old girl who received a cadaveric kidney transplant almost 3 years ago. Unfortunately, over the past 3 years, her kidney function has declined and she is now back on chronic hemodialysis. Currently, her drugs include cyclosporine 50 mg by mouth 2 times/day, prednisone 5 mg by mouth once daily, amlodipine 5 mg by mouth once daily, clonidine transdermal patch 0.1 mg/day, epoetin alfa 6000 units intravenously 3 times/week at the end of hemodialysis, iron sucrose 100 mg intravenously every Monday at the end of hemodialysis, and a renal vitamin by mouth once a day. Her laboratory values today are calcium 8.8 mg/dL, phosphorus 6.0 mg/dL, iPTH 176 pg/mL, and albumin 3.9 g/dL. Which one of the following therapies is most appropriate for Y.L. today?
    A. Sevelamer 403 mg by mouth 3 times/day with meals.
    B. Calcium acetate 667 mg by mouth 3 times/day with meals.
    C. Lanthanum 500 mg by mouth 3 times/day with meals.
    D. Cinacalcet 30 mg by mouth once a day.