In Brief

Secondary hyperparathyroidism (SHPT) describes a complex alteration in bone and mineral metabolism that occurs as a direct result of chronic kidney disease (CKD). Bone disease, a well-recognized complication of SHPT, represents only a small concern in light of the evidence that correlates SHPT with cardiovascular disease and an increased risk of morbidity and mortality in patients with CKD. Patients with mild CKD may be asymptomatic and therefore may not be identified until the pathology of SHPT has begun. Identifying patients at risk and evaluating for SHPT is imperative because early intervention may slow or arrest the progression of both bone and cardiac disease. Dietary concerns, pharmacotherapy, and patient adherence are all important considerations in creating a successful treatment plan.

Secondary Hyperparathyroidism and Chronic Kidney Disease

Sarah Tomasello, PharmD, BCPS

Chronic kidney disease (CKD) is a highly prevalent health issue in the United States and is most often the consequence of chronic diseases, notably diabetes or hypertension. Because ~ 40% of patients with diabetes develop nephropathy, diabetic patients alone will account for 12 million people with CKD. Five stages of CKD are used to stratify patients based on the degree of renal function and act as markers to predict the development of comorbidities of CKD, such as secondary hyperparathyroidism (SHPT). Research has shown that CKD patients who are classified as Stage 3, Stage 4, or Stage 5 are at risk for, or may already have developed, SHPT. The early identification and treatment of SHPT is crucial to preventing or controlling the consequences of this complication.

Pathophysiology of SHPT

The parathyroid glands are four pea-sized glands located on the thyroid gland in the neck. Although their names are similar, the thyroid and parathyroid glands are entirely different glands, each producing distinct hormones with specific functions. The parathyroid glands secrete parathyroid hormone (PTH), a polypeptide that helps maintain the correct balance of calcium and phosphorous in the body. PTH is involved in the homeostasis of bone metabolism by regulating the level of calcium in the blood, release of calcium from bone, absorption of calcium from the intestine, and excretion of calcium in the urine. Consequently, the levels of calcium and other minerals involved in bone metabolism, such as phosphorus and vitamin D, affect the secretion of PTH by the

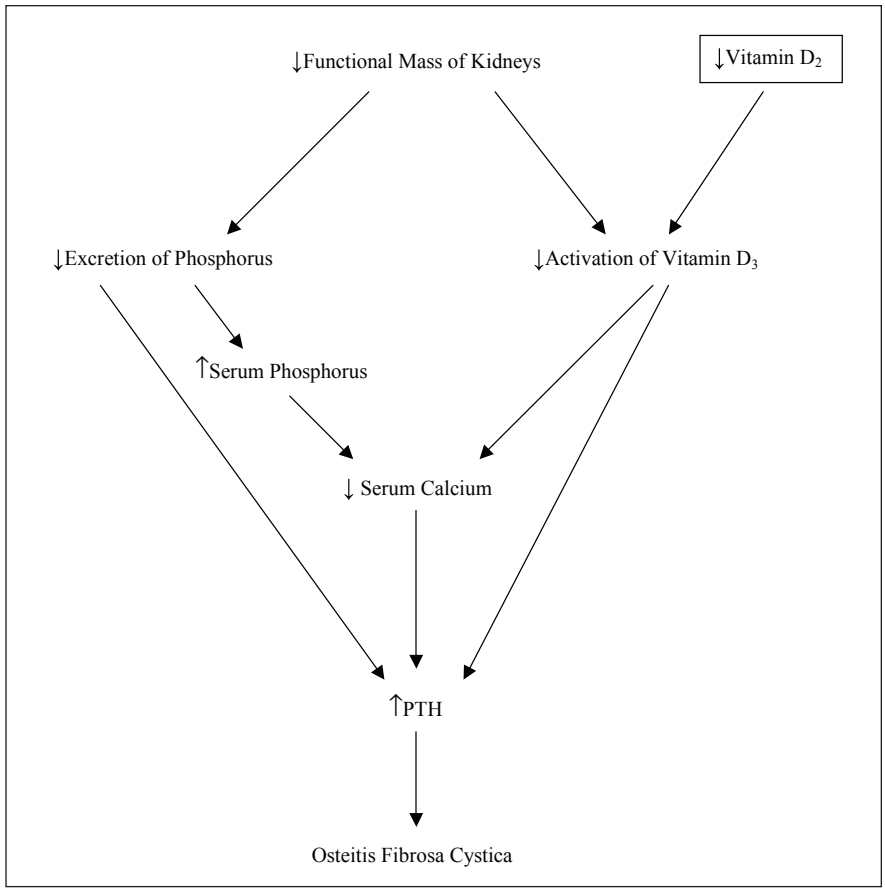

Figure 1. Pathophysiology of secondary hyperparathyroidism.

parathyroid gland. The entire PTH molecule is composed of a sequence of 84 amino acids referred to as the intact hormone (iPTH). Although smaller fragments of this molecule may have unique actions in the body, generally, the iPTH is measured and used to assess bone metabolism and bone disease.

SHPT secondary to CKD is an overproduction of PTH caused by several changes that occur in bone and mineral metabolism as a result of decreased kidney function (Figure 1). The first changes that usually occur with declining kidney function involve the deficiency of activated vitamin D and an increase in phosphorus excretion by the remaining functional nephrons. Both of these changes stimulate an increase in PTH synthesis and secretion.

Vitamin D

The term "vitamin D" is used generically to refer to many substances or forms of vitamin D. In the body, vitamin D_3 is the active form of vitamin D. Precursors to the hormone vitamin D_3 are obtained from food sources and exposure to ultraviolet light. These precursors then undergo two important enzymatic reactions. The resulting calcitriol or active vitamin D_3 [1,25-$(OH)_2D_3$)] molecule is the active form that binds to the vitamin D receptor (VDR).[1] Under normal circumstances, vitamin D_3 plays a vital role in regulating PTH synthesis and release. By stimulating the parathyroid VDR, it down regulates the production of PTH. Vitamin D_3 also decreases PTH indirectly by stimulating VDRs in the gut, thereby increasing calcium absorption and serum calcium.[2,3] As kidney function declines, there is a decrease of renal 1α-hydroxylase activity that is responsible for the final hydroxylation reaction in calcitriol synthesis. In worsening CKD, the kidney becomes less able to perform 1α-hydroxylation and, consequently, active vitamin D_3 levels become deficient and increase PTH concentrations.[4]

Phosphorus Metabolism

As the glomerular filtration rate (GFR) declines to < 60 ml/min/1.73 m^2, phosphorus excretion becomes altered in the nephron. Although half of the nephrons are not working to excrete phosphorus, the remaining nephrons compensate by hyper-excreting the daily phosphorus load to maintain normal serum phosphorus concentrations. Compensation can generally continue until the GFR declines to < 25–40 ml/min/1.73 m^2. With progressive CKD, when the remaining nephrons can no longer sufficiently excrete the phosphorus load, hyperphosphatemia is detected.

Calcium, a divalent cation, and phosphorus, a monovalent anion, have a high binding affinity for each another. In the serum, as the concentration of one or both ions increases, there is an increased risk for an ionic bond to form, creating an insoluble complex. This process may lead to extraskeletal calcification and potentially calciphylaxis or cardiac disease.[5] Additionally, the precipitation may decrease serum calcium concentrations, further stimulating PTH secretion. In fact, PTH production and secretion may be stimulated by hypocalcemia, hyperphosphatemia, and vitamin D deficiency.[6,7] Because PTH is chiefly responsible for preventing hypocalcemia, it stimulates osteoclasts to lyse bone, releasing calcium into the serum. Under normal conditions, there is homeostasis involving osteoclast activity and osteoblast synthetic activity. SHPT produces an imbalance of these activities leading to enhanced bone breakdown that eventuates in renal osteodystrophy.[8,9]

Impact and Consequences of SHPT: Bone Disease

Renal osteodystrophy refers to several bone disorders that accrue from the pathophysiology of bone and mineral metabolism in CKD: osteitis fibrosa cystica, osteomalacia, and adynamic bone disease. Osteitis fibrosa cystica is referred to as high-turnover bone disease and is associated with elevated PTH concentrations that stimulate osteoclast activity, bone breakdown, and resorption. Osteomalacia ("soft bone") is characterized by a low turnover of bone and abnormal mineralization and has historically been associated with aluminum toxicity.[8,10] Adynamic bone disease is referred to as low-turnover disease with normal mineralization and may result from low PTH levels.[11] The prevalence of adynamic bone disease is increasing[11] and may be the consequence of PTH over-suppression from the use of vitamin D agents, calcimimetics,

Table 1. Target Ranges and Monitoring Frequency of Biochemical Parameters*[20]

GFR (ml/min/ 1.73 m^2)	Stage of CKD	Phosphorus (mg/dl)	Corrected Calcium (mg/dl)	Ca × P** (mg^2/dl^2)	Monitoring Frequency of Calcium, Phosphorus and Ca × P	iPTH (pg/ml)	Monitoring of iPTH
30–59	3	2.7–4.6	Within normal limits	< 55	Every year	35–70	Every year
15–29	4	2.7–4.6	Within normal limits	< 55	Every 3 months	70–110	Every 3 months
< 15	5	3.5–5.5	8.4–9.5	< 55	Every month	150–300	Every 3 months

**Target ranges and monitoring frequency of biochemical parameters based on stage of CKD. Once pharmacotherapy is initiated, monitoring may be performed more frequently to assess treatment safety and efficacy.*
***Calcium × phosphorus product calculated by multiplying the corrected calcium concentration by the phosphorus concentration.*

and phosphate binders, singly or in combination.

Impact of Alterations: Extraskeletal Calcification

In addition to bone mineral defects and disease, alterations in calcium, phosphorus, vitamin D, and PTH cause other deleterious consequences in patients with CKD. Extraskeletal calcification (primarily cardiovascular calcification) has been documented in patients with CKD[12] and is directly correlated to an increase in cardiovascular morbidity and mortality.[13] Patients with CKD, especially end-stage renal disease (ESRD), have an increased risk of cardiovascular morbidity and mortality. In fact, research has shown that the primary cause of death in patients with ESRD is cardiovascular disease.[14] A study of patients on hemodialysis found that even when stratified for variables such as sex, race, and presence of diabetes, dialysis patients still had a cardiovascular mortality rate nearly 30 times greater than the general population.[15]

Certainly comorbid disorders, such as diabetes, hypertension, hyperlipidemia, and anemia, play a role in these findings. However, recent research has also identified cardiovascular calcification as a contributing factor. Correlations have been made between cardiovascular calcification and factors such as hyperphosphatemia, increased calcium-phosphorus product (Ca × P), hypercalcemia, vitamin D therapy, and increased doses of calcium-containing phosphate binders and calcium supplements.

The balance of calcium, phosphorus, vitamin D, and iPTH is complex and interrelated. Patients must adhere to dietary restrictions, dialysis therapies, and complicated medication regimens. These factors create barriers to achieving and maintaining control of SHPT. In fact, one study of nearly 200 chronic hemodialysis outpatients revealed that < 10% of patients could be simultaneously maintained within the target ranges of the above parameters.[16]

Goals of SHPT Treatment

The ultimate goals of treating SHPT are to normalize mineral metabolism, prevent bone disease, and prevent extraskeletal manifestations of the altered biochemical processes. The markers of calcium, phosphorus, vitamin D, and iPTH are used as surrogate measures of disease progression. It is important to identify SHPT early. Abnormalities can occur subtly, usually without any symptoms, and may progress to cause more complications if not detected early. Until recently, it was thought that hyperphosphatemia was the earliest sign of SHPT and bone metabolism disorders. However, when patients reach Stage 3 CKD, it is highly probable that none of the biochemical parameters routinely assessed will be abnormal. In fact, the iPTH level is often increased before clinical hyperphosphatemia occurs.[17–19] For this reason, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KQODI) guidelines recommend that all patients with a GFR < 60 ml/min/1.73 m^2 undergo evaluation of serum calcium, phosphorus, and iPTH levels (Table 1). Additionally, if the iPTH concentration exceeds the CKD stage-specific target, the 25(OH)D level (precursor of activated vitamin $D_{2,3}$) should be assessed and treated. Hopefully, earlier identification and assessment of SHPT will improve bone and mineral metabolism in CKD and reduce its associated complications (e.g., fractures, pain, and cardiovascular calcification).

Management of SHPT

Vitamin D therapy in Stages 3 and 4 CKD

For patients with Stage 3 or Stage 4 CKD, one of the first abnormalities noted on evaluation may be an isolated increase in iPTH. If the iPTH concentration exceeds the target range, the serum 25(OH)D concentration should be measured, and if that is found to be < 30 ng/ml, ergocalciferol (vitamin D_2) therapy should be initiated (Table 2). If the concentration of 25(OH)D is > 30 ng/ml and the iPTH concentration exceeds the target range, an activated vitamin D agent should be initiated (Table 3).[20] Regardless of which vitamin D agent is used, the calcium and phosphorus concentrations must be monitored and maintained within the target range to

Table 2. Dosing of Oral Ergocalciferol in Patients With CKD Stages 3 and 4[20]*

25(OH) vitamin D concentration	Oral ergocalciferol dose (international units)
< 5 ng/ml	50,000 weekly for 12 doses, then monthly for 3 doses
5–15 ng/ml	50,000 weekly for 4 doses, then monthly for 5 doses
16–30 ng/ml	50,000 monthly for 6 doses

**Evaluation of 25(OH)D concentrations should be conducted in Stages 3 and 4 CKD if the iPTH is greater than the target range. Oral ergocalciferol should be initiated to decrease the iPTH to the normal range. Calcium and phosphorus concentrations should be in target range before therapy is started.*

prevent the precipitation of calcium in soft tissue and vasculature.

Dietary phosphate restriction

Hyperphosphatemia generally becomes prevalent as the GFR declines to < 30 ml/min/1.73 m^2.

Dietary phosphate restriction is one of the first interventions recommended to lower serum phosphate concentrations. Foods that are high in phosphate content include dairy products, meats, beans, dark sodas, beer, and nuts. Many foods that are high in phosphorus are also primary sources of protein, particularly meats. Generally, patients are instructed to reduce their intake of or avoid foods that are high in phosphorus but not high in protein. Examples of foods to avoid include cheese, milk, ice cream, beer, and dark sodas. Protein sources are not withheld because poor nutrition can lead to hypoalbuminemia, which has been associated with increased morbidity and mortality in CKD. Dietary phosphate restriction alone is often insufficient to maintain serum phosphorus concentrations in the target range. In this case, phosphate binders may be used to prevent hyperphosphatemia.

Phosphate binding agents

Phosphate binding agents decrease serum phosphate concentrations by binding to dietary phosphate in the gut, forming an insoluble complex that is excreted in the feces. Optimally, these agents are administered with food and are generally taken three times daily with meals. Patients requiring enteral feedings may need more frequent administration. The greatest challenge to successful use of phosphate binders is patient acceptance and adherence. Patient education is imperative because these medications must be taken several times a day and may significantly increase patients' medication burden. Table 4 lists some of the more commonly used products and dosage forms.

Phosphate binders from different classes may be combined to achieve target concentrations of phosphorus and calcium. In fact, the combined use of a calcium-containing phosphate binder and a non–calcium-containing phosphate binder may reduce the serum phosphorus level while maintaining the calcium concentration. Likewise, the use of one or more non–calcium-containing phosphate binders (e.g., sevelamer hydrochloride, lanthanum carbonate, and aluminum) may be needed for patients with hyperphosphatemia with concurrent hypercalcemia. Frequently, CKD patients will require therapy to lower iPTH and serum phosphorus concentrations. 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 × P, and iPTH).

Vitamin D therapy in Stage 5 CKD

As described earlier, vitamin D is essential for many physiological processes. Therapy with ergocalciferol should be initiated during any CKD stage if 25(OH)D concentrations are < 30 ng/ml. For all patients in Stage 5 CKD, as well as patients in Stages 3 and 4 with normal or elevated 25(OH)D concentrations, an activated vitamin D agent should be initiated when iPTH levels exceed the target range.[20]

Currently, there are three commercially available vitamin D agents in the United States. Calcitriol was the first agent available. It has the same structure as endogenous activated vitamin D_3 [1,25(OH)D_3] and therefore the same pharmacological actions. It stimulates gut and parathyroid VDR receptors. Because of its affinity for intestinal VDR, calcitriol has the greatest propensity to increase serum calcium concentrations of the three vitamin D agents.[21,22] Both oral and injectable formulations are available generically. Generally, calcitriol is the least expensive oral or injectable product available and is a first-line agent. It is especially useful when the

Table 3. Initial Dosing of Oral Vitamin D Sterol Therapy to Treat Elevated iPTH Concentrations in Patients With CKD Stages 3 and 4[33]*

Agent	Initial Dose	Titration
Calcitriol	0.25 µg daily or every other day	Increase by 0.25 µg at 4- to 8-week intervals
Doxercalciferol	1 µg daily or every other day	Increase by 0.5–1 µg every 2 weeks
Paricalcitol	1–2 µg daily or every other day	Increase by 1–2 µg every 2–4 weeks

**Patients with normal or elevated 25(OH)D concentration but increased iPTH concentration require a vitamin D_3 agent. Vitamin D therapy should be decreased or discontinued if the calcium, phosphorus, or Ca × P concentrations are higher than the target range for each stage of CKD.*

Table 4. Examples of Phosphate-Binding Medications and Initial Dosing Information

Agent	Dosage Form	Initial Dose
Calcium-Containing Phosphate Binders		
Calcium acetate (prescription only)	667-mg capsules	667–1,334 mg
Calcium carbonate (nonprescription products; not preferred)	250- to 1,000-mg tablets	500–1,000 mg
Aluminum-Containing Agents		
Aluminum hydroxide (nonprescription products)	300 mg/5 ml suspension 600 mg/5 ml suspension 300- to 600-mg tablets	1,200–1,800 mg
Newer Agents		
Sevelamer hydrochloride (prescription only)	400- and 800-mg tablets	800–1,600 mg
Lanthanum carbonate (prescription only)	250-, 500-, 750-, and 1,000-mg chewable tablets	500–1,000 mg

All doses should be administered three times a day with meals and also with snacks if necessary.

serum calcium level is less than the mid-point of the target range.

Paricalcitol and doxercalciferol are vitamin D agents that have less affinity for the intestinal receptors and, therefore, have been shown to cause a lower incidence of hypercalcemia.[23] Some studies have shown that doxercalciferol causes more hypercalcemia than paricalcitol. This finding is controversial; the studies were difficult to interpret because of the use of concurrent medications, specifically calcium-containing products.[24,25] One notable difference between the two agents is that doxercalciferol is a vitamin D_2 pro-drug, 1-α(OH)D_2, and requires activation by hepatic 25-hydroxylase. Therefore, doxercalciferol should not be used in patients with hepatic dysfunction.

With any vitamin D agent, the risk of increasing serum calcium concentrations is greater during oral drug administration than when administered intravenously. All vitamin D agents should be titrated to maintain iPTH, calcium, phosphorus, and Ca × P within KDOQI target ranges. Because of the risk of hypercalcemia, unavailability of a specific agent, or other factors, it may be necessary to switch products and convert doses. Therapy with any vitamin D agent should only be initiated when the serum calcium and phosphorus concentrations are within target range. The vitamin D dose should be decreased or temporarily discontinued if the Ca × P is > 55 mg^2/dl^2 to minimize the risk of extraskeletal calcification. Likewise, the vitamin D dose should be decreased or temporarily discontinued if the iPTH concentration falls below the lower

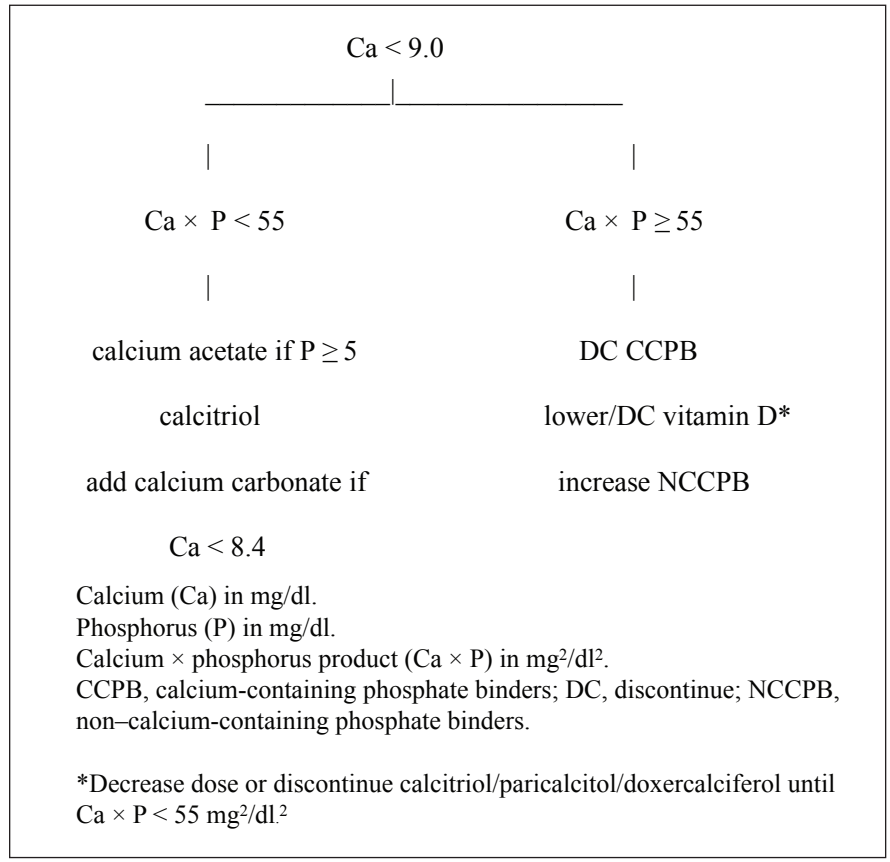

Figure 2. Example algorithm for the management of CKD mineral and bone disorders for patients with elevated iPTH and normal/low calcium concentrations.

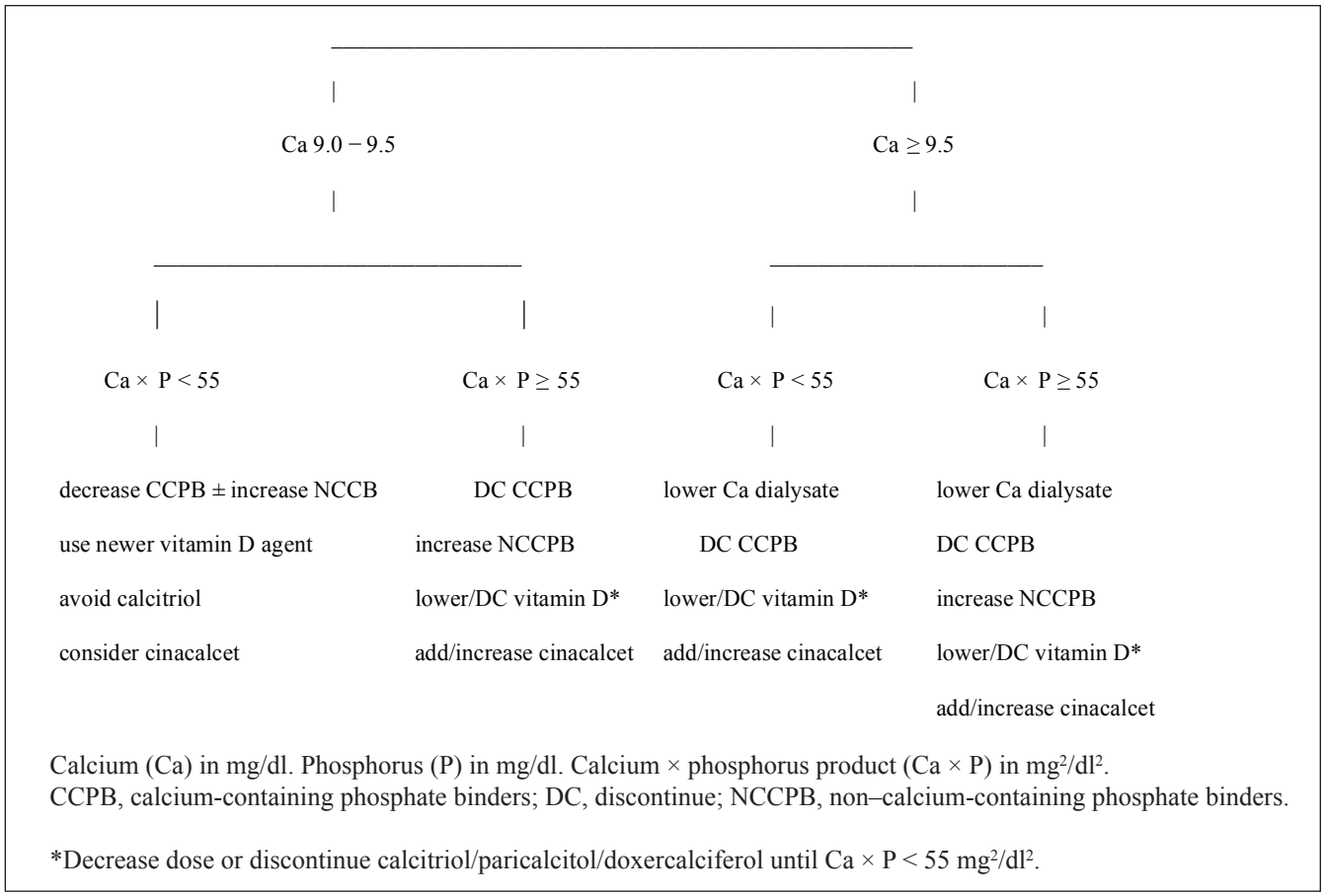

Figure 3. Example algorithm for the management of CKD mineral and bone disorders for patients with elevated iPTH concentrations and normal/high calcium concentrations.

limit of the target range to avoid the risk over adynamic bone disease.

Calcimimetic agents

Cinacalcet is the first calcimimetic agent available in the United States.[26,27] Cinacalcet was approved for use after publication of the 2003 KDOQI guidelines and does not appear in any of the guidelines or algorithms. It acts by binding to and modifying the calcium sensing receptor on the chief cell of the parathyroid gland. This change causes an increased sensitivity of the receptor to serum calcium. Cinacalcet is effective in decreasing iPTH concentrations and maintaining calcium and phosphorus concentrations.[28,29] It can be used in combination with phosphate binders and 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 or a maximum dose of 180 mg per day has been achieved.

Patients may experience transient nausea and vomiting. However, the most important side effect of cinacalcet therapy is the risk of hypocalcemia, the direct result of cinacalcet's mechanism of action. Thus, cinacalcet should not be initiated in patients if the corrected serum calcium concentration is < 8.4 mg/dl. Additionally, calcium and phosphate concentrations should be obtained within 1 week of initiation or dose change. The iPTH concentration should be monitored between 1 week and 1 month of initiation or after a dose change. Because cinacalcet lowers serum calcium levels, it may also reduce Ca × P. As with all 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.[30–32]

Cinacalcet offers a new treatment strategy when used alone, with phosphate binders, or in combination with phosphate binders and vitamin D therapy. Figures 2 and 3 depict possible algorithms for the use of pharmacotherapy.

Conclusion

SHPT is a complex and challenging condition. Metabolic parameters such as calcium, phosphate, Ca × P, iPTH, and vitamin D must be maintained within target ranges to prevent bone disease and extraskeletal calcification, decrease cardiac disease risk, and maintain homeostasis of other body systems. Additionally, all of these parameters need to be controlled simultaneously to be successful.

Perhaps the most difficult challenge in the treatment of SHPT is that of patient acceptance and adherence. Complicated medication regimens that involve taking medicines multiple times each day, a high pill burden, comorbid conditions, financial constraints, psychosocial issues, and dietary restrictions are all factors that increase the rate of nonadherence and thwart treatment success. Maintaining bone and mineral metabolism is a challenge for all health care providers and requires a multidisciplinary team approach. Dietitians may play a crucial role in the management of SHPT by working with patients to design nutrition plans that restrict the amount of phosphorus while providing optimal protein intake.

They also may recommend protein supplements or other dietary aids for optimal nutritional balance. Pharmacists and social workers are often involved in the complicated process of obtaining drugs for patients with limited resources or prescription drug benefits that have restrictions on certain agents. Some might work with insurance companies and physicians to obtain prior authorizations or access patient assistance programs through the pharmaceutical industry or community resources. Physicians, nurses, pharmacists, social workers, physical therapists, and nearly all other health care professionals can play a role in managing SHPT. Reinforcing adherence to medications, diet, and exercise and providing positive reinforcement across disciplines is crucial to the successful management of SHPT.

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Sarah Tomasello, PharmD, BCPS, is a clinical assistant professor of pharmacy and a clinical specialist in nephrology at the Ernest Mario School of Pharmacy at Rutgers University in Piscataway, N.J.