From Research to Practice / Diabetic Kidney Disease

Secondary Hyperparathyroidism and Chronic Kidney Disease

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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
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 D₃ is the active form of vitamin D. Precursors to the hormone vitamin D₃ are obtained from food sources and exposure to ultraviolet light. These precursors then undergo two important enzymatic reactions. The resulting calcitriol or active vitamin D₃ [1,25-(OH)₂D₃] molecule is the active form that binds to the vitamin D receptor (VDR). Under normal circumstances, vitamin D₃ plays a vital role in regulating PTH synthesis and release. By stimulating the parathyroid VDR, it downregulates the production of PTH. Vitamin D₃ also decreases PTH indirectly by stimulating VDRs in the gut, thereby increasing calcium absorption and serum calcium.

Phosphorus Metabolism
As the glomerular filtration rate (GFR) declines to < 60 ml/min/1.73 m², 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 m². 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. 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. 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.

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. Adynamic bone disease is referred to as low-turnover disease with normal mineralization and may result from low PTH levels. The prevalence of adynamic bone disease is increasing and may be the consequence of PTH over-suppression from the use of vitamin D agents, calcimimetics,
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 and is directly correlated to an increase in cardiovascular morbidity and mortality. Patients with CKD, especially end-stage renal disease (ESRD), have an increased risk of cardiovascular morbidity and mortality. 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.

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.

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. 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 m² 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 D₃) 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 D₂) 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). Regardless of which vitamin D agent is used, the calcium and phosphorus concentrations must be monitored and maintained within the target range to

<table>
<thead>
<tr>
<th>GFR (ml/min/1.73 m²)</th>
<th>Stage of CKD</th>
<th>Phosphorus (mg/dl)</th>
<th>Corrected Calcium (mg/dl)</th>
<th>Ca × P**</th>
<th>Monitoring Frequency of Calcium, Phosphorus and Ca × P</th>
<th>iPTH (pg/ml)</th>
<th>Monitoring of iPTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>30–59</td>
<td>3</td>
<td>2.7–4.6</td>
<td>Within normal limits</td>
<td>&lt; 55</td>
<td>Every year</td>
<td>35–70</td>
<td>Every year</td>
</tr>
<tr>
<td>15–29</td>
<td>4</td>
<td>2.7–4.6</td>
<td>Within normal limits</td>
<td>&lt; 55</td>
<td>Every 3 months</td>
<td>70–110</td>
<td>Every 3 months</td>
</tr>
<tr>
<td>&lt; 15</td>
<td>5</td>
<td>3.5–5.5</td>
<td>8.4–9.5</td>
<td>&lt; 55</td>
<td>Every month</td>
<td>150–300</td>
<td>Every 3 months</td>
</tr>
</tbody>
</table>

*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.

Table 1. Target Ranges and Monitoring Frequency of Biochemical Parameters*20
Table 2. Dosing of Oral Ergocalciferol in Patients With CKD Stages 3 and 420*

<table>
<thead>
<tr>
<th>25(OH) vitamin D concentration</th>
<th>Oral ergocalciferol dose (international units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5 ng/ml</td>
<td>50,000 weekly for 12 doses, then monthly for 3 doses</td>
</tr>
<tr>
<td>5–15 ng/ml</td>
<td>50,000 weekly for 4 doses, then monthly for 5 doses</td>
</tr>
<tr>
<td>16–30 ng/ml</td>
<td>50,000 monthly for 6 doses</td>
</tr>
</tbody>
</table>

*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.

Table 3. Initial Dosing of Oral Vitamin D Sterol Therapy to Treat Elevated iPTH Concentrations in Patients With CKD Stages 3 and 433*

<table>
<thead>
<tr>
<th>Agent</th>
<th>Initial Dose</th>
<th>Titration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcitriol</td>
<td>0.25 µg daily or every other day</td>
<td>Increase by 0.25 µg at 4- to 8-week intervals</td>
</tr>
<tr>
<td>Doxercalciferol</td>
<td>1 µg daily or every other day</td>
<td>Increase by 0.5–1 µg every 2 weeks</td>
</tr>
<tr>
<td>Paricalcitol</td>
<td>1–2 µg daily or every other day</td>
<td>Increase by 1–2 µg every 2–4 weeks</td>
</tr>
</tbody>
</table>

*Patients with normal or elevated 25(OH)D concentration but increased iPTH concentration require a vitamin D3 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.
The 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. 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. One notable difference between the two agents is that doxercalciferol is a vitamin D₂ pro-drug, 1\(\alpha\)(OH)D₂, 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 KDQI 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 mg²/dl² 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

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

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosage Form</th>
<th>Initial Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium acetate (prescription only)</td>
<td>667-mg capsules</td>
<td>667–1,334 mg</td>
</tr>
<tr>
<td>Calcium carbonate (nonprescription products; not preferred)</td>
<td>250- to 1,000-mg tablets</td>
<td>500–1,000 mg</td>
</tr>
</tbody>
</table>

**Aluminum-Containing Agents**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosage Form</th>
<th>Initial Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminum hydroxide (nonprescription products)</td>
<td>300 mg/5 ml suspension</td>
<td>1,200–1,800 mg</td>
</tr>
<tr>
<td></td>
<td>600 mg/5 ml suspension</td>
<td></td>
</tr>
<tr>
<td></td>
<td>300- to 600-mg tablets</td>
<td></td>
</tr>
</tbody>
</table>

**Newer Agents**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosage Form</th>
<th>Initial Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sevelamer hydrochloride (prescription only)</td>
<td>400- and 800-mg tablets</td>
<td>800–1,600 mg</td>
</tr>
<tr>
<td>Lanthanum carbonate (prescription only)</td>
<td>250-, 500-, 750-, and 1,000-mg chewable tablets</td>
<td>500–1,000 mg</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Ca &lt; 9.0</th>
<th>Ca × P &lt; 55</th>
<th>Ca × P ≥ 55</th>
</tr>
</thead>
<tbody>
<tr>
<td>calcium acetate if P ≥ 5</td>
<td>DC CCPB</td>
<td></td>
</tr>
<tr>
<td>calcitriol</td>
<td>lower/DC vitamin D*</td>
<td></td>
</tr>
<tr>
<td>add calcium carbonate if</td>
<td>increase NCCPB</td>
<td></td>
</tr>
</tbody>
</table>

Ca < 8.4

Calcium (Ca) in mg/dl.
Phosphorus (P) in mg/dl.
Calcium × phosphorus product (Ca × P) in mg²/dl².
CCPB, calcium-containing phosphate binders; DC, discontinue; NCCPB, non–calcium-containing phosphate binders.

*Decrease dose or discontinue calcitriol/paricalcitol/doxercalciferol until Ca × P < 55 mg²/dl².

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

**Calcimimetic agents**

Cinacalcet is the first calcimimetic agent available in the United States. 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. 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.

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.

References

7. Qinibi WY: Consequences of hyperphosphatemia in patients with end-stage renal disease (ESRD). Kidney Int 64 (Suppl.):S8–S12, 2004

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