

## Secondary Hyperparathyroidism in Chronic Kidney Disease

a report by

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Recent estimates suggest that more than 20 million people have chronic kidney disease (CKD) in the US alone. While it is well known that patients on dialysis are at high risk of cardiovascular death, patients with early stages of kidney dysfunction also experience a high rate of fatal and non-fatal cardiovascular events. In this patient population, death is a more likely outcome than progression to end-stage renal disease (ESRD). Furthermore, recent National Kidney Foundation, American Heart Association, and the Seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guidelines have classified kidney disease as a cardiovascular disease (CVD) risk equivalent. While efforts to delay progression of kidney disease are crucial, it is also known that early and aggressive management of complications secondary to uremia are necessary to reduce the morbidity and mortality of patients with CKD. Among the most relevant secondary complications are hypertension, anemia, secondary hyperparathyroidism (SHPT), and subsequent renal osteodystrophy, hypoalbuminemia and metabolic acidosis (see *Figure 1*).

Secondary hyperparathyroidism is prevalent in most patients with CKD and develops early in the course of the disease before dialysis initiation. Martinez et al. noted a progressive increase in serum parathyroid hormone (PTH) levels with declining kidney function, which became significant at a creatinine clearance of 20ml/min. This increase in PTH is generally associated with calcium and phosphorus levels within the normal range. Once SHPT progresses to an uncontrolled stage it is associated with elevated calcium, phosphorus, and calcium x phosphorus product ( $Ca \times P$ ), and each are independently associated with increased morbidity and mortality. Unfortunately, SHPT is often unrecognized and inadequately treated in patients with early stages of kidney disease when therapy would have greater benefits. This article discusses the pathogenic mechanisms, clinical manifestations, and recent therapeutic advances of SHPT in early stages of CKD.

### Pathogenesis of Secondary Hyperparathyroidism

The principal actions of PTH are to release calcium and

phosphorus from bone, decrease renal excretion of calcium, increase urinary excretion of phosphorus, and stimulate the production of the active form of vitamin D [1,25-dihydroxy vitamin D<sub>3</sub>; (calcitriol)]. In SHPT, both production and secretion of PTH rise.

The pathogenetic mechanisms of SHPT in CKD are multifactorial and include:

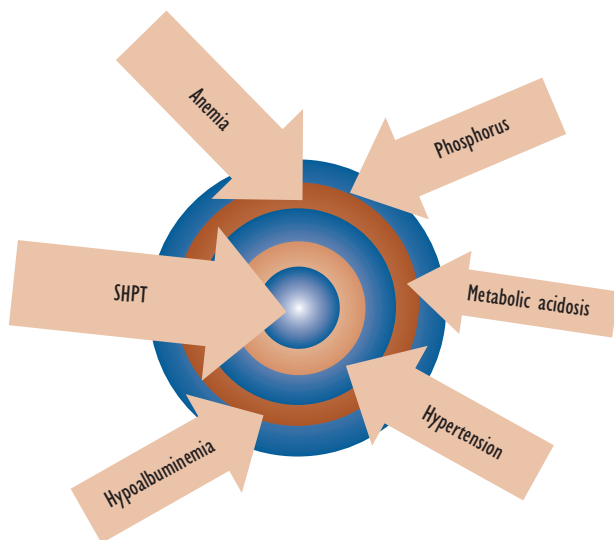
- abnormalities in the regulation of PTH secretion by parathyroid cells;
- disturbances in the control of pre-pro-PTH gene transcription and PTH synthesis;
- dysregulation of cell cycle that lead to parathyroid cell proliferation and parathyroid gland hyperplasia; and
- changes in the intracellular processing and peripheral metabolism of PTH.

Extracellular calcium is an important regulator of PTH secretion, PTH mRNA, and parathyroid cell proliferation. It acts through the calcium-sensing receptor (CaR), which belongs to a large family of G-protein-linked cell membrane receptors. The sigmoidal, inverse relationship between serum levels of PTH and calcium illustrates an exquisitely sensitive control mechanism in which only minute changes in serum calcium are required to induce large changes in PTH. In the long term, hypocalcemia, hyperphosphatemia, and low calcitriol levels promote parathyroid gland hyperplasia and a decrease in both the CaR and vitamin D receptor (VDR) expression levels, exacerbating SHPT. As CaR and VDR expression become downregulated, nodular hyperplasia is established. Nodularly hyperplastic parathyroid glands become increasingly resistant to regulation by serum calcium and calcitriol, and the increasing mass leads to extremely elevated serum PTH levels.

In ESRD, SHPT develops as a result of phosphate retention, as well as the reduced production of calcitriol by the kidney, resulting in hyperphosphatemia, hypocalcemia, and increased PTH levels. The development of SHPT in early stages of kidney dysfunction is less well-established. Martinez et al. have carried out some important work looking at the onset of



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**Figure 1: Treatment Targets for Patients with Chronic Kidney Disease**

SHPT in patients with early kidney disease. They gathered 19 control patients and compared them with 42 patients with known CKD stage one. When compared with controls, patients with established early CKD had elevated PTH even at creatinine clearance >100ml/min. In addition, the investigators noted that calcitriol levels also increased, consistent with increased 1-alpha hydroxylase activity secondary to elevated PTH levels.

These findings suggest that increased PTH levels preceded the elevation of calcitriol, indicating that other mechanisms are responsible for SHPT levels at early stages of kidney disease, including abnormalities of the CaR caused by the uremic milieu. In addition, recent evidence indicates that signaling through the CaR rather than through vitamin D dependent pathways is a more potent regulator of parathyroid gland hyperplasia in certain experimental models. SHPT and parathyroid cell proliferation can be prevented by normalization of blood ionized calcium levels in VDR-ablated mice, strongly suggesting that blood calcium, rather than calcitriol itself, plays a key role in the pathogenesis of hyperparathyroidism. Calcitriol deficiency and hyperphosphatemia are important to the progression of SHPT, and therapies to correct each of these abnormalities of mineral metabolism are important components of disease management. Thus, the data available from experimental animal models and human observational studies suggest that calcium and the CaR are primary regulators of parathyroid gland function and are likely the earliest initiating factors in the SHPT.

#### Clinical Manifestations

An important consequence of SHPT is bone disease, which is a frequent cause of pain and disability among

patients with stage V CKD who require dialysis. Patients with SHPT have abnormalities in bone histology and increased bone resorption beginning at CKD stage three. The classical skeletal abnormality observed in patients with CKD stages III, IV and V is osteitis fibrosa cystica—although adynamic bone disease can also be observed it is less frequently seen.

The treatment of SHPT is mainly undertaken to avoid the unfavorable effects of persistently high PTH levels on bone metabolism and bone micro-architecture. It has been well established that the adverse effects of SHPT are not limited to the skeletal system. Persistently elevated PTH levels and/or hyperphosphatemia can also lead to serious non-skeletal complications, including vascular calcification. Recently, the development of vascular calcifications has gained increased attention because this complication has been linked to increased risk of cardiac and all-cause mortality (see *Figure 2*). In addition, vascular calcification increases with declining kidney function. The incidence of vascular calcification among pre-dialysis patients with CKD is 40%. This increases to 73% in patients who are starting dialysis, and to 83% in patients established on dialysis. Other non-skeletal consequences of SHPT include soft-tissue calcification, calcific uremic arteriolopathy (CUA), abnormalities in endocrine function, impaired erythropoiesis, and neurologic disturbances. Therefore, the potential for adverse clinical outcomes from inadequately controlled SHPT is present throughout the continuum of CKD.

#### Treatment of SHPT in Stages III and IV CKD

The recent National Kidney Foundation (NKF) Kidney Disease Quality Initiative (KDOQI) Clinical Practice Guidelines for Bone Mineral Metabolism and Disease in Chronic Kidney Disease have recommended the measurements of calcium, phosphorus, PTH, and 25-hydroxyvitamin D levels in patients with CKD stages III and IV (see *Table 1*). The rationale for the measurement of 25-hydroxyvitamin D is that low levels of 25-hydroxyvitamin D are likely to play a role in the development of SHPT by limiting the synthesis of calcitriol. Once patients are replete with vitamin D, continued supplementation with a vitamin-D-containing multivitamin preparation should be used with annual reassessment of serum levels of 25-hydroxyvitamin D and the continued assessment of corrected total calcium and phosphorus every three months. Patients with CKD stages III and IV in whom serum levels of 25-hydroxyvitamin D are >30ng/ml (75 nmol/litre) and plasma levels of intact PTH are above the target range for the CKD stage (see *Table 1*) need to be treated with an active oral vitamin D sterol-

calcitriol, alfacalcidol, or doxercalciferol. Active vitamin D sterol should only be initiated in patients with serum calcium < 9.5mg/dl and serum phosphorus < 4.6mg/dl, and should not be prescribed in patients with rapidly worsening kidney function.

The caution in using active vitamin D sterols is due to the potential for hypercalcemia, hyperphosphatemia, and an increase in the calcium-phosphorus product, which may result from active vitamin D sterols intestinal calcium and phosphorus absorption. Therefore, the safe and effective management of SHPT in patients with early stages of CKD remains a challenge for clinicians and better therapeutic interventions that offer the possibility of avoiding these problems are also needed in this patient population.

Manipulation of the CaR impacts synthesis and secretion of PTH and parathyroid gland hyperplasia. Calcimimetics, by modulating CaR, can potentially directly address the pathophysiology of SHPT early in CKD. Charytan et al. recently reported the results of a double-blind, placebo-controlled trial to determine the safety and efficacy of cinacalcet in 54 patients with stages III and IV CKD. Of 54 patients, 27 were randomized to the cinacalcet treatment group and 27 to the placebo (control) group. The first stage of the study—weeks one to 12—consisted of the titration phase, whereby the dose given (between 30 and 180mg/day) to the cinacalcet group was based on concentrations of PTH and serum calcium which were determined weekly. The baseline laboratory parameters were similar between the two groups. The demographics—sex, race, age—also appeared to be well-balanced between the two groups. The second stage of the study, weeks 13 to 18, involved the efficacy assessment phase. Significantly more cinacalcet patients reached the primary end-point—i.e. proportion of subjects with a 30% or greater reduction from baseline in mean PTH concentration (56% compared with 19% in control group). Serum calcium levels in the cinacalcet group dropped over the 18-week study period, whereas the control group showed no significant change in serum calcium. Treatment with cinacalcet did not affect estimated GFR during this study.

In summary, cinacalcet was generally well tolerated. The most common adverse events were nausea, myalgia, and diarrhea, which were generally transient and mild to moderate in severity. Cinacalcet significantly reduced PTH concentrations in stage III and IV CKD patients and SHPT. Reductions in PTH led to mild increases in serum phosphorous, most likely due to renal retention. In addition, to diminishing PTH secretion, calcimimetic compounds have been shown to retard the development of parathyroid gland hyperplasia and

Figure 2: Clinical Consequences of Secondary Hyperparathyroidism

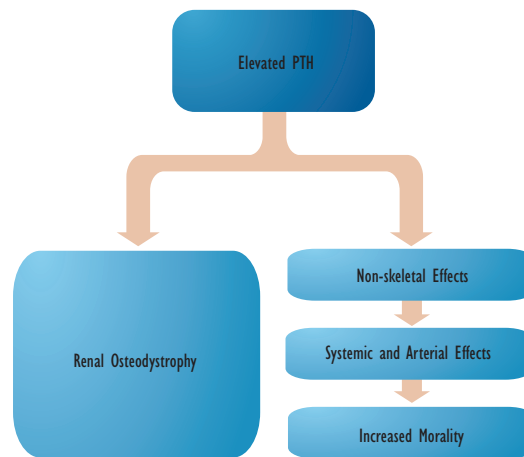


Table 1: NKF-K/DOQI Targets in CKD Stages III, IV and V

	Stage III CKD	Stage IV CKD	Stage V CKD
<i>i</i> PTH(pg/mL)	35–70(o)	70–110(o)	150–300(e)
Serum calcium (mg/dL)	8.4–10.3(o)	8.4–10.3(o)	8.4–9.5(o)
Serum phosphorus (mg/dL)	2.7–4.6(o)	2.7–4.6(o)	3.5–5.5(e)
Ca x P (mg <sup>2</sup> /dL <sup>2</sup> )	Not in guideline	Not in guideline	<55(e)

o=opinion, e=evidence

increase bone mass. These additional clinical qualities of calcimimetic therapy would increase their appeal as an approach for treatment of SHPT in patients with CKD stages III and IV.

Summary

In this review, we have highlighted the central role of serum calcium and the parathyroid CaR in the pathogenesis of SHPT during the early stages of CKD. Uncontrolled SHPT causes numerous skeletal and non-skeletal complications, including vascular calcifications that are present in patients prior to the initiation of dialysis. The traditional management of SHPT with vitamin D sterols involves increased risk, including hypercalcemia and hyperphosphatemia. In one phase II study, cinacalcet significantly reduced PTH levels, suggesting that it will play an important role in the future treatment of SHPT in patients with early stages of CKD. ■

A version of this article containing references can be found in the Reference Section on the website supporting this briefing ([www.touchgenitourinarydisease.com](http://www.touchgenitourinarydisease.com)).