Secondary Hyperparathyroidism: Pathogenesis, Disease Progression, and Therapeutic Options

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Summary
Secondary hyperparathyroidism (SHPT) is a challenge frequently encountered in the management of patients with chronic kidney disease (CKD). Downregulation of the parathyroid vitamin D and calcium-sensing receptors represent critical steps that lead to abnormalities in mineral metabolism: high phosphate, low calcium, and vitamin D deficiency. These imbalances result in parathyroid hyperplasia and contribute to vascular calcification. New studies have established a central role for fibroblast growth factor 23 (FGF-23) in the regulation of phosphate-vitamin D homeostasis. FGF-23 concentration increases in CKD and contributes to SHPT. Achieving current targets for the key mineral parameters in the management of SHPT set by the Kidney Disease Improving Global Outcomes (KDIGO) guidelines can be challenging. This review summarizes the current understanding and evidence supporting strategies for SHPT treatment in CKD patients. Treatment should include a combination of dietary phosphorus restriction, phosphate binders, vitamin D sterols, and calcimetics. Parathyroidectomy is effective in suitable candidates refractory to medical therapy and the standard against which new approaches should be measured. Future strategies may focus on the stimulation of apoptotic activity of hyperplastic parathyroid cells.

Introduction
Secondary hyperparathyroidism (SHPT) is an adaptive and in many cases ultimately maladaptive process that develops in response to declining kidney function, impaired phosphate excretion, and failure to bioactivate vitamin D. Dysregulation of calcium and phosphorous homeostasis leads to decreased renal phosphate excretion, increased serum phosphorous, elevated levels of the phosphatonin fibroblast growth factor 23 (FGF-23), and reduced synthesis of calcitriol, the active form of vitamin D. These changes result in increased synthesis and secretion of parathyroid hormone (PTH) and parathyroid hyperplasia, contributing to the development of a vicious cycle (1). Detailed reviews of the potential role of sustained elevation of PTH to act as an uremic toxin have been published, and in 1979, Massry (2) proposed a set of criteria to be satisfied before establishing a role for PTH or any other proposed toxin in the genesis of uremic toxicity. These criteria included demonstration of elevated blood levels, a relation between the proposed toxin and uremic manifestations, improvement of these manifestations after reduction of the putative toxin blood level, and demonstration of toxicity when administered to experimental animals. Even now, some 30 years later, considerable doubt remains as to the role SHPT and its treatment in relation to bone pain, fracture incidence, muscle function, cardiovascular disease, sexual function, hematoxylin, immune function, pruritis, and calciphylaxis, all of which may influence the length and quality of life (3).

This review will focus on the pathogenesis of SHPT and current treatment options available. Newer therapies, including calcimetics, calcium-free phosphate binders, and advances in surgical intervention will also be highlighted.

Pathogenesis of SHPT
Continuous stimulation of the parathyroid glands by a combination of elevated extracellular phosphate concentration, decreased extracellular ionized calcium concentration, and markedly reduced serum calcitriol leads to increased PTH synthesis and release. At the same time, elevated FGF-23 expression downregulates residual renal 25(OH)-1-hydroxylase, which exacerbates the effective deficiency of calcitriol, acting as an additional driver to SHPT. Even at early stages in the development of hyperparathyroidism, these changes are compounded by variable underexpression of the calcium-sensing receptor (CaSR) and vitamin D receptor (VDR), rendering the parathyroid cells unable to respond appropriately to ambient calcium and/or calcitriol. The resulting increase in proliferative activity in the parathyroid glands eventually leads to parathyroid hyperplasia (Figures 1 and 2) (4–10).

Recent understanding of the molecular mechanisms behind phosphorous homeostasis has shown FGF-23 and its receptor fibroblast growth factor receptor 1 (FGFRI) to be important players (11–16). FGF-23 is a hormone whose production in the osteocytes and osteoblasts is stimulated by phosphate increase and calcitriol elevation. FGF-23 binds to and activates FGFR1, which is functional only if coex-
pressed with the Klotho transmembrane protein, as a Klotho-FGF receptor complex. In the proximal tubule, FGF-23 decreases phosphate reabsorption by reducing the expression of type II sodium phosphate cotransporters (NaPi-2a and NaPi-2c). Thus, increases in both serum FGF-23 and PTH in patients with chronic kidney disease (CKD) decrease the proximal tubular reabsorption of phosphate and maintain normo-phosphatemia in most patients until the GFR falls below 20 ml/min. Inevitably, as CKD progresses, these negative feedback loops are progressively sabotaged and eventually unable to maintain phosphate homeostasis. FGF-23 also reduces PTH synthesis.
directly, whereas indirectly increasing synthesis via reduc-
tion of renal calcitriol production. Correlations between
high FGF-23 levels in dialysis patients, refractory SHPT,
and increased mortality have been observed (17,18). This is
a rapidly evolving area, and further research is needed to
fully understand the role of FGF-23 in SHPT.

High phosphate enhances parathyroid hyperplasia.
There is, however, currently no evidence to suggest the
existence of a phosphorous receptor on the parathyroid
gland. Studies in VDR knock-out mice suggest that vitamin
D pathways play a secondary role in the development of
parathyroid gland hyperplasia and that signaling through
the CaSR is sufficient to prevent parathyroid hyperplasia
in these animals (19–22).

Mechanisms of SHPT Progression

Patients in the early stages of CKD do not usually show
any changes in their serum calcium and phosphate levels,
and their PTH levels may be only slightly higher than
reference values. Some recent publications have reported
increased levels of FGF-23 in these patients, which may
help to regulate serum levels of phosphate and calcium
(23). The stimuli for secretion of FGF-23 in early CKD are
not completely understood, and this is currently an area of
active research. FGF-23 does not seem to be an acute post-
prandial regulator of phosphaturia in CKD, but inappro-
priate postprandial hypocalcemia may represent a previ-
ously unreported mechanism of SHPT in CKD (24). In a
recent study performed in rats, adding phosphate directly
into the small intestine generated a rapid increase in phos-
phate excretion. There were no related changes in FGF-23
or other known phosphatonin (25), indicating that factors
other than FGF-23 appear to be important in the augmen-
tation of postprandial phosphate excretion.

Investigation of the effect of FGF-23 on parathyroid
function in normal and hyperplastic parathyroid glands
showed that FGF-23 decreased PTH secretion (11) and cell
proliferation and increased CaSR and VDR expression in
normal glands (16). Conversely, FGF-23 did not have an
effect on hyperplastic glands (12,16). FGF-23 phospory-
lated extracellular signal–regulated kinase 1/2 in normal
parathyroid glands, although not in hyperplastic ones. In
hyperplastic parathyroid glands, the expression of FGFR1
and Klotho protein were markedly reduced in humans (13)
and experimental animals (16) compared with normal
parathyroid glands (13,16), providing a possible explana-
tion for the lack of response to FGF-23 in uremic animals
(12,16). Thus, reduced expression of FGFR1 and Klotho
precludes control of hyperparathyroidism by FGF-23 in the
presence of renal failure (16).

Parathyroid Hyperplasia

Prolonged parathyroid stimulation leads initially to dif-
fuse polyclonal hyperplasia followed by monoclonal nod-
ular hyperplasia, as shown in Figure 3 (20,27,28). Studies of
genetically modified mice indicate that signal transduction
via the CaSR is a key determinant of parathyroid cell
proliferation and parathyroid gland hyperplasia (29). Ex-
perimental work in normal rats and a rat model of renal
failure has demonstrated that parathyroid cell proliferation
is associated with a decrease in CaSR and VDR expression
(7,16,21,26). It has been questioned whether the receptor
decrease precedes hyperplasia or reduced expression is a
consequence of proliferation. Some data suggest that para-
thyroid cell hyperplasia precedes downregulation of CaSR
expression in a uremic rat model (30), and administration
of calcitriol or calcimimetics resulted in a decrease of para-
thyroid cell proliferation associated with an elevation of
both CaSR and VDR (31,32). There may also be a direct
effect of low calcium and calcitriol levels on the expression
of their receptors. Increasing doses of calcitriol have been
shown to upregulate parathyroid VDR expression in hy-
percalcemic but not hypocalcemic rats (33). Animal studies
have demonstrated that activation of the CaSR by calcimi-
metics induces expression of parathyroid VDR (10). Thus,
in patients receiving calcimimetics, the VDR is upregu-

Figure 3. Development of parathyroid hyperplasia. This figure is reprinted with permission from references 20 and 27.
lated, despite the fact that calcium may be at low levels. It seems likely, therefore, that if a major role of parathyroid cells is the elevation of serum calcium to normal levels, inhibition by calcitriol and prevention of hyperparathyroidism is only possible when serum calcium is controlled. Canadillas et al. (34) proposed a model for the intracellular signaling pathway involved in the CaSR-dependent regulation of VDR expression in parathyroid cells. Extracellular calcium stimulates VDR expression through elevation of cytosolic calcium levels and the stimulation of the phospholipase A2-arachidonic acid-dependent extracellular signal-regulated kinase 1/2 pathway. CaSR activation induces the transcription factor Sp1 to act on the VDR promoter.

Nodular transformation in advanced secondary hyperparathyroidism is accompanied by a reduction in VDR and CaSR expression and decreased sensitivity to the inhibitory effect of calcium and calcitriol on PTH secretion (35). The resulting severe hyperparathyroidism may cause hypercalcemia and hyperphosphatemia driven by calcium and phosphorus efflux from the skeleton.

Vascular Calcification

Elevated calcium and phosphorous levels associated with SHPT have been linked to the development of vascular calcification, which is strongly associated with increased morbidity and mortality. Transcription factors including Cbfa-1/RUNX2 and MSX-2 have been identified in vascular smooth muscle cells adjacent to areas of calcification in CKD patients (36). Bone proteins such as osteopontin, bone sialoprotein, type I collagen, osteonectin, and alkaline phosphatase have also been localized to sites of extraskeletal calcification. Numerous animal models of vascular calcification, including hyperphosphatemia caused by CKD, or those with genetic modifications to key proteins such as FGF-23 have helped to elucidate the complex pathogenesis of vascular calcification. Importantly, these models have also been used to study preventative measures or factors that reduce the severity of the condition (28).

Patient age and duration of dialysis have been linked to an increased risk of vascular calcification. However, not all CKD patients on dialysis go on to develop vascular calcification, despite apparently being exposed to the same risk factors. This implies that naturally occurring protective factors such as matrix Gla protein may play a role and may explain why only certain CKD patient subpopulations are affected (36–39). There are conflicting data regarding an association of fetuin-A with mortality, both in patients with end-stage renal disease and in other settings (40). Identification of factors specific to patients who fail to develop vascular calcification may yield pointers to new therapies.

Guidelines for the Management of SHPT

The absence of standard classification and terminology for bone and mineral disorders led to the development of the Kidney Disease Improving Global Outcomes (KDIGO) guidelines to aid in the management of patients with CKD. However, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF/KDOQI) (41) has also defined CKD and its stages. The more recent KDIGO guidelines on CKD-MBD (42) have taken a stronger “evidence-based” approach than the earlier KDOQI guidance, with fewer and generally less prescriptive recommendations, reflecting the limited availability of high-quality clinical studies in this field. There is currently some debate about how to implement a uniform classification system.

Current Treatment Options

Effective therapeutic interventions are highly desirable if the morbidity and mortality associated with uncontrolled SHPT are to be reduced. However, because of the difficulties associated with lowering PTH while simultaneously controlling serum levels of calcium and phosphorous, traditional therapies for managing SHPT have several limitations. Consequently, achieving the current targets set by the NKF/KDOQI or KDIGO guidelines for the key mineral parameters can be challenging. Interruptions in therapy are common and have the potential to allow disease progression (43). Current widely-used interventions include modulation of calcium and phosphorous balance by dietary intake and dialysis, active vitamin D compounds such as calcitriol and newer vitamin D analogues, phosphate binders, and the more recent calcimimetics. Bisphosphonates, by limiting the high rate of bone resorption in severe SHPT, may have a role, if only as a bridge to more definitive resolution of the SHPT. This use of bisphosphonates falls outside the licensed indications and, because of their very slow removal from bone, carries the risk of inducing low-turnover bone disease, especially in patients ultimately subjected to parathyroidectomy. Surgical intervention in the form of parathyroidectomy is generally only considered in severe SHPT (41). All of these interventions have the potential to improve biochemical profiles and other surrogate markers such as bone histology. All, however, also suffer from the lack of evidence linking the apparently beneficial effects of these therapies on surrogate markers to improved patient outcomes.

Vitamin D Compounds

Deficiency of endogenous calcitriol in CKD patients is managed by treatment with calcitriol or its prodrug, alfacalcidol, doxercalciferol (the vitamin D2 equivalent of alfacalcidol), 22-oxacalcitriol, or paricalcitol. These active vitamin D compounds all activate the VDR, albeit indirectly in the case of alfacalcidol and doxercalciferol. Active vitamin D sterols increase the absorption of both calcium and phosphorous from the gut and reduce the synthesis of PTH. Higher (pharmacologic) doses frequently lead to hypercalcemia and hyperphosphatemia, both of which are associated with ectopic calcification (44,45). In many, although not all, patients, the therapeutic window for active vitamin D use is a narrow one. Newer vitamin D analogues such as doxercalciferol and paricalcitol have been shown to suppress PTH levels at least as well as calcitriol (46). A prospective randomized study showed that calcitriol and paricalcitol lower PTH levels to a similar extent; predefined criteria for efficacy (PTH lowering) and safety (hypercalcemia) showed no difference, although paricalcitol achieved the PTH decrease more rapidly (47).
Contradictory evidence, however, has shown that vitamin D therapy has no effect on parathyroid hyperplasia in animal models (48,49), whereas calcitriol pulse therapy in patients on long-term dialysis induced moderate regression (50). The limited and mixed effects of current vitamin D compounds on parathyroid hyperplasia may be the result of a number of factors, including decreased VDR expression or a change in signal transduction cascades. It has been postulated that the CaSR is more important than the VDR in parathyroid hyperplasia after ablation studies (19). Deletion of the VDR in the parathyroid decreases parathyroid CaSR expression and only moderately increases basal PTH levels, suggesting that the VDR does influence PTH secretion and parathyroid physiology by various mechanisms, albeit with limited effect in this mouse model (22).

Resistance to active vitamin D compounds can also create challenges, especially in patients who have severe SHPT that has progressed to a nodal phenotype (51). Suggested mechanisms for resistance are decreased VDR expression in parathyroid cells or failure of the calcitriol-VDR complex to interact with the vitamin D response element of its target genes (52). A key indicator for the success or failure of treatment is the size of the parathyroid gland. Vitamin D compounds generally control SHPT well in patients with moderately increased glands and less well in patients with enlarged glands (53–55).

Some studies have suggested that vitamin D has a bi-phasic cardiovascular “dose-response” curve, with a propensity to vascular calcification arising not only from vitamin D excess but also from vitamin D deficiency (46). Low active vitamin D exposure results in increased pro-inflammatory cytokines, matrix metalloproteinases, and a decrease in protective factors of endothelial cells, whereas high dosing results in hypercalcemia, medial calcification, arterial stiffness, and left ventricular hypertrophy. The weight of evidence, however, suggests that appropriate exposure to both native and active vitamin D is associated with generally beneficial pleiotropic effects, of which the most obvious is confounding by intention, they mount an important challenge for the renal community to generate appropriately powered and designed prospective studies capable of providing definitive answers.

Phosphate Binders
Persistent hyperphosphatemia has been shown to reduce the effectiveness of vitamin D therapy in certain instances (63), and there is a correlation between phosphorous levels and mortality associated with SHPT (38). The use of calcium salts to treat hyperphosphatemia and return serum phosphorous levels to normal increases the risk of hypercalcemia, calciphylaxis, and vascular calcification (64). Calcium-free phosphate binders, such as sevelamer and lanthanum carbonate, decrease serum phosphate levels but show no related effects on serum calcium and do not significantly reduce circulating PTH levels (65). As such, phosphate binders have limited use as therapy for established SHPT, although hyperphosphatemia is an important factor in the pathogenesis of early SHPT. This is consistent with the minor effect of phosphate binder therapy on SHPT development and treatment. These observations suggest that newer treatments for the control of phosphorous levels, especially as a preventative measure during early CKD, should not be overlooked.

Calcimimetics
Calcimimetics, such as cinacalcet, are positive allosteric modulators of the CaSR, interacting with the membrane-spanning domain of the receptor to induce a conformational change that enhances signal transduction. This change in conformation leads to increased sensitivity to extracellular calcium and subsequently to a decrease in circulating PTH levels (66–68). Studies have shown that calcimimetics administered daily for 1 week upregulate CaSR expression and induce significant decreases in PTH levels in uremic rats (7). It has been suggested that the observed sustained, long-term efficacy of calcimimetics in suppressing PTH levels in dialysis patients might relate to their activity as allosteric activators rather than as agonists at the CaSR (69). Receptor activity may therefore be more important than receptor expression levels. Furthermore, the activation of CaSR increases VDR expression (32). Thus, the addition of vitamin D to calcium may oversuppress PTH, with potential negative consequences (70,71).

Extensive preclinical studies have indicated that the development and progression of parathyroid hyperplasia can be inhibited by calcimimetics. Cinacalcet inhibits parathyroid cell proliferation in the rat 5/6 nephrectomy model, demonstrated by reductions in the numbers of cells in the S phase, proliferating cell nuclear antigen-positive cells, and overall parathyroid cell numbers (72). Calcimimetics consistently prevent increases in parathyroid gland weight...
and/or volume when administered soon after subtotal nephrectomy, and this effect is reversible on treatment withdrawal. Models of severe SHPT, such as animals with established parathyroid hyperplasia, have shown that calcimetics arrest the progression of hyperplasia even under conditions of phosphate loading (72).

The mechanism and time course of the calcimimetic effect on PTH differ from those of vitamin D. Although vitamin D reduces PTH gene transcription and hormone synthesis over a period of several hours or even days (73), cinacalcet inhibits PTH secretion within minutes, with a maximal decrease occurring within 2 hours of dosing in SHPT patients. Metabolism by cytochrome P-450 system enzymes results in a cyclical pattern of serum PTH levels during continued administration of cinacalcet, which may have anabolic effects on bone (74). Other recent data indicate that activation of the CaSR by calcimetics decreases PTH mRNA stability via the post-translational modification of the PTH-mRNA binding protein AUF1 (75,76).

Although parathyroid volume may decrease in cinacalcet-treated patients, there is no evidence that this reflects regression of hyperplasia or upregulation of apoptosis. Treatment with cinacalcet, in combination with existing conventional treatments, led to reduced volume of initially smaller glands in patients with severe SHPT (53–55,77).

One of the most common adverse events seen with calcimetics is hypocalcemia, which is thought to occur after decreased mobilization of calcium from bone caused by reduced PTH levels. In most patients, this hypocalcemia is easily managed with dose adjustment (78) or a combination with low doses of vitamin D sterols in subjects with established parathyroid hyperplasia, have shown that calcitriol inhibits both proliferation and apoptosis but has no net overall effect on the size of the gland (49). However, in glands taken from patients with SHPT, only high concentrations of calcitriol were able to inhibit proliferation or apoptosis.

Recently, no induction of apoptosis of parathyroid cells after CaSR activation by the calcimimetic R-568 could be detected in rats (7). A study on parathyroidectomy patients showed a high oxyphil/chief cell ratio in parathyroid tissue from patients treated with cinacalcet, calcitriol, and phosphate binders compared with patients treated only with calcitriol and phosphate binders (86), suggesting that cinacalcet counteracts SHPT through two synergistic mechanisms: an anti-proliferative effect and a pro-apoptotic effect on chief cells (86). Treatments that can reduce the size of enlarged hyperplastic parathyroid glands through pro-apoptotic methods, or even stop proliferation and thus inhibit the development of hyperplasia through anti-proliferative effects, will be an essential treatment for SHPT in the future.

**Surgical Intervention**

Size reduction of the parathyroid gland via pharmaceutical agents would decrease the number of patients who require surgical intervention. Parathyroidectomy is generally only considered when current pharmacologic intervention has failed. When conservative therapy no longer provides effective control (persistent serum levels of PTH >1000 pg/ml associated with hypercalcemia) or is refractory to medical therapy and when the volume of at least one hyperplastic gland is >500 mm3 (41), parathyroidectomy is performed in suitable candidates. This is a highly effective treatment that remains the standard against which new approaches should be judged. Parathyroidectomy dramatically improves SHPT, increasing survival rates and patient quality of life in suitable candidates (87). However, SHPT may persist or recur because of hyperfunction of the parathyroid remnant or of autotransplanted parathyroid tissue transplanted to avoid hypoparathyroidism. In recent years, surgery has improved through the advance of minimally invasive parathyroidectomy, although there is some debate over the methodologies and criteria used in this procedure. More recent advances in...
surgical procedures have led to the development of endoscopic total parathyroidectomy with autotransplantation, with preoperative preparation by parathyroid ultrasonography and highly-sensitive $^{99m}$Tc-sestamibi radionuclide scans (88). The endoscopic total parathyroidectomy with autotransplantation technique alleviates preoperative symptoms, improves or normalizes mineral levels in most patients, and has been shown to be safe for the treatment of SHPT, offering a short hospital stay and low recurrence rate to patients (88). All of these options may be assisted by an intraoperative parathyroid hormone assay that has been used to guide the surgeon, especially during subtotal parathyroidectomy.

Summary

SHPT is a progressive disease common in patients with CKD and with serious consequences for patient health. If poorly controlled, SHPT progresses and can lead to bone disease, soft tissue calcification, and vascular calcification, all of which adversely influence morbidity and mortality. Traditional therapies that target vitamin D and phosphorous levels are not without drawbacks. The emergence of the calcimimetics and a better understanding of the strengths and limitations of native and active vitamin D compounds have improved the treatment options for patients with SHPT.

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References


42. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl 113: S1–S130, 2010


62. Navas-Diaz M, Alvarez-Hernandez D, Paslick-Deetjen J,


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