

Outcomes of Secondary Hyperparathyroidism in Chronic Kidney Disease and the Direct Costs of Treatment

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ABSTRACT

BACKGROUND: There has been an emphasis over the last several years to identify and treat chronic kidney disease (CKD) and its complications as they evolve rather than waiting until the patient reaches end-stage renal disease (ESRD), also known as CKD stage 5. The number of patients who will be identified and prescribed therapies for complications such as secondary hyperparathyroidism (SHPT) is greater than initially proposed.

OBJECTIVE: To review the pathways, complications, management, and estimated treatment costs of CKD-related SHPT.

METHODS: An electronic literature search of MEDLINE (January 1980 through January 2007) was conducted for English-language publications using the base search term *secondary hyperparathyroidism*. To refine subsequent searches, the authors added Boolean operators to the following secondary and tertiary search terms: *parathyroid hormone, chronic kidney disease, renal osteodystrophy, adynamic bone disease, vascular calcification, cardiovascular disease, vitamin D, vitamin D analogs, hypercalcemia, hyperphosphatemia, calcimimetics, costs, prevalence, and economics*.

RESULTS: The initial MEDLINE search produced 278 relevant articles. After refining the search terms, the authors triaged the results for English-language publications relevant to the discussion of SHPT and its complications in CKD, eliminating 149 publications. The remaining 129 publications were accepted for review. These articles represent a growing body of primarily observational evidence that demonstrates that elevated intact parathyroid hormone (PTH) levels cause deleterious physiological results across a variety of organ systems, including the cardiovascular and skeletal systems. Specific complications associated with SHPT are left ventricular hypertrophy (LVH), renal osteodystrophy (ROD), and extraskeletal calcification. Medical management of the PTH/vitamin D/calcium and phosphorus imbalances in SHPT focus on regulating PTH levels via vitamin D therapy. The class of calcimimetics is a newer treatment modality that has favorable effects on biochemical laboratory values, such as serum calcium and phosphorus levels, but current data do not show differences on hard endpoint patient-oriented outcomes compared with standard generic agents.

The direct drug costs in April 2007 U.S. dollars of treating CKD-associated elevations in PTH in predialysis patients range from \$8.40 per patient per week (\$437 per year) for oral generic calcitriol to \$88.90 per patient per week (\$4,623 per year) for oral paricalcitol (expressed as 85% of average wholesale price [AWP] for brand drugs or 70% of AWP for generic drugs). The direct drug costs of treating SHPT in hemodialysis patients range from \$80.20 per patient per week (\$4,170 per year) for generic calcitriol (IV) to \$278.46 per patient per week (\$14,480 per year) for oral cinacalcet.

CONCLUSIONS: SHPT causes skeletal and cardiovascular complications in CKD patients. Calcitriol therapy is effective in managing PTH levels, but efforts to reduce the associated hypercalcemia and hyperphosphatemia have led to the development of newer, yet more expensive, vitamin D analogs. With the lack of evidence to support comparative superior outcomes in end-organ disease among SHPT therapy alternatives, future research is still needed to clearly identify which newer agents are most competitive with the historical gold standard of calcitriol therapy.

KEYWORDS: Secondary hyperparathyroidism, Renal osteodystrophy, Cardiovascular disease, Direct costs, Vitamin D

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What is already known about this subject

- SHPT is highly prevalent in the hemodialysis patient population. It is often treated with vitamin D analogs. There is a need for evidence of the treatment effect of vitamin D analogs on hard endpoint skeletal and cardiovascular outcomes in predialysis CKD patients.

What this study adds

- The financial expense of treating SHPT (as a complication of CKD) may be cost effective, based on observational data. In addition to the need to establish a causal link between drug therapy for SHPT and reduction in hard endpoint cardiovascular outcomes, future randomized studies are needed to determine the preferred agent, PTH treatment goal, stage of the disease at which to initiate treatment, and impact on mortality.

According to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) Workgroup on the Diagnosis and Treatment of Chronic Kidney Disease (CKD), CKD is defined as functional abnormalities of the kidney lasting longer than 3 months, with or without reduced glomerular filtration rate (GFR).¹ CKD can also be defined by the presence of urinary albumin with an excretion rate higher than 300 mg per 24 hours or in a ratio of more than 200 mg of albumin to 1 g of creatinine.¹ As it is currently defined, CKD affects as many as 19 million adults in the United States, with 20 million more at risk.² More than 6 million Americans have significant reductions in kidney function, and nearly 400,000 require dialysis to prevent death.^{1,3-5} The National Health and Nutrition Examination Survey (conducted 1999-2000) estimated that 80,000 people are diagnosed annually with CKD.⁶

CKD staging is categorized by kidney damage and reductions in GFR, as shown in Table 1. Between 1990 and 2002, diabetes mellitus and hypertension accounted for the majority of new kidney failure cases (44.6% due to diabetes mellitus and 26.9% to hypertension). Other disorders that can lead to CKD include glomerulonephritis, ischemia, infection, polycystic kidney disease, obstruction, toxins, and autoimmune and infiltrative diseases.⁶

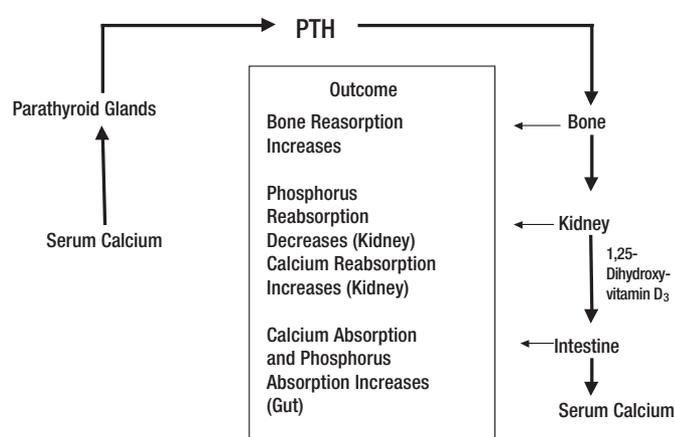
Adding to the burden of CKD is the development of secondary hyperparathyroidism (SHPT), a common complication manifested in elevated parathyroid hormone (PTH) levels as a direct result of decreased renal function, vitamin D deficiency, and impaired mineral metabolism.⁷ SHPT arises in most patients during the progression of CKD and is associated with several comorbidities,

TABLE 1 Stages of Chronic Kidney Disease

Stage	Description	GFR (mL/min/1.73m ²)
1	Kidney damage and normal/elevated GFR	≥90
2	Kidney damage and mild reduction in GFR	60-89
3	Moderate reduction in GFR	30-59
4	Severe reduction in GFR	15-29
5	Kidney failure	15 (or dialysis)

GFR=glomerular filtration rate.

FIGURE PTH-Vitamin D-Mineral Feedback System—Parathyroid Hormone Regulation



The relationship between the circulating serum calcium concentrations and physiological feedback with the parathyroid glands, bone, intestine, and kidney is depicted. The physiological response to hypocalcemia is to enhance bone resorption and calcium reabsorption from the renal tubules and gastrointestinal tract in order to normalize the serum calcium concentration, while minimizing the potential increases in serum phosphorus concentrations.

including renal osteodystrophy (ROD), extraskeletal calcification, and cardiovascular disease (CVD), resulting in increased mortality.⁷

These complications associated with CKD result in elevated rates of hospitalization and increased health care expenditures. In a retrospective cohort study group of 109,321 elderly patients, Mix et al. found that hospitalization rates increased markedly with the progression of CKD, peaking at 487 hospitalizations/1,000 patient months at risk after initiation of dialysis.⁸ The majority of these hospitalizations, both before and after dialysis, were due to CKD comorbidities, particularly CVD diagnoses and events. Moreover, the economic burden of CKD and its complications is

staggering. The cost to treat CVD, infections, and related hospitalizations associated with CKD is estimated at \$90 billion,⁹ and treating CKD is projected to cost the Medicare system more than \$28 billion in 2010, an increase from \$12 billion in 1998.¹⁰

Several treatment options are available to slow the progression of CKD. A component of CKD care often overlooked and under-treated by both the primary care physician and the nephrologist is the management of SHPT, which can lead to CVD and ROD if untreated. Since kidney disease is often diagnosed comparatively late in many patients, the staging at diagnosis is often stage 3 or 4, the same time that these extrarenal complications begin to appear.¹¹⁻¹⁴ Thus, many patients who acquire the CKD diagnosis often have had chronic exposure to reductions in vitamin D and serum calcium, and elevations in PTH and phosphorus, and may manifest significant skeletal and/or cardiovascular sequelae.

This review focuses on the complications of elevated parathyroid hormone level and their prevalence, evaluates current avenues of treatment, and introduces the subject of the economic impact of different treatments.

Parathyroid Hormone Regulation

The parathyroid glands are responsible for maintaining calcium homeostasis through the actions of PTH, a polypeptide hormone. Fluctuations in serum calcium concentration are detected by calcium receptors (CaRs)—G-protein-coupled receptors located on the chief cells of the parathyroid gland that mediate the secretion of PTH.¹⁵ Stimulated by low serum calcium levels, PTH secretion increases and up-regulates the expression of 1 α -hydroxylase in the kidney. This enzyme is responsible for the production of vitamin D (1,25-dihydroxyvitamin D₃ or calcitriol).¹⁶ Under hypocalcemic conditions, PTH stimulates the synthesis of calcitriol, correcting the calcium imbalance by (1) increasing absorption of calcium from the gastrointestinal tract, (2) conserving calcium that would ordinarily be excreted by the kidneys, and (3) releasing calcium from bone (see Figure).¹⁷

It has been suggested that PTH levels and the serum phosphorus equilibrium are also linked. Patients with advanced CKD who were administered a low-phosphorus diet showed reductions in serum PTH levels independent of calcium and calcitriol concentrations.¹⁸ Recent studies have elaborated on the role of phosphorus in PTH regulation. Animal models have shown that dietary phosphorus can alter PTH mRNA expression and, moreover, phosphorus has been shown to directly stimulate PTH secretion from parathyroid cells.¹⁹⁻²¹

Calcitriol and PTH are both capable of directly regulating serum mineral levels, as shown in the Figure. The effects of PTH on the intestine are accomplished indirectly through the actions of calcitriol. Acting to increase calcium absorption, calcitriol has been shown to up-regulate the expression of calcium channel and transporter proteins, correcting hypocalcemia at the transcriptional level.²² The effects of elevated PTH levels on the skeleton include the stimulation of calcium mobilization from bone and the direct

TABLE 2 Complications of Secondary Hyperparathyroidism.^{7,51}

Renal Osteodystrophy	Cardiovascular Disease
Osteitis fibrosa Adynamic bone disease Osteomalacia	Left ventricular hypertrophy Vascular calcification Visceral calcification Peripheral artery disease Hypertension Congestive heart failure

regulation of osteoblast apoptosis to correct hypocalcemia.²³

Completing the feedback loop, both elevated calcium and calcitriol levels can suppress PTH secretion but via different mechanisms. Sela-Brown et al. have shown that calcitriol suppresses PTH synthesis at the transcriptional level whereas calcium regulation is posttranscriptional.²⁴ Abnormalities in mineral homeostasis usually originate from the failure to maintain this critical feedback loop, often leading to hyperparathyroidism.

Secondary Hyperparathyroidism

SHPT is a major complication of CKD, resulting from disturbances in the regulation of PTH, calcium, phosphorus, and vitamin D (see Figure). Although hyperphosphatemia appears to be particularly important in the development of SHPT, the complication often occurs early in stage 3 of kidney failure, before the development of hyperphosphatemia.^{25,26} A majority, if not all, of untreated CKD patients will develop SHPT as a result of the kidney's inability to maintain mineral homeostasis.

In patients with stage 2 CKD (GFR 60-89 mL/min), levels of vitamin D are often depressed in conjunction with rising serum PTH levels.^{27,28} This decline in vitamin D level can be attributed to decreased expression of 1 α -hydroxylase, the kidney-localized enzyme responsible for converting 25-hydroxyvitamin D₃ to biologically active vitamin D (1,25-dihydroxyvitamin D₃).²⁹ Alternatively, reduced 25-hydroxyvitamin D₃ concentrations have also been found in CKD patients, resulting in less substrate available for the 1 α -hydroxylase.³⁰⁻³³ A recent observational study by González et al. established a negative correlation between active vitamin D levels and intact PTH levels in predialysis patients. Overall, this study demonstrated that the majority of predialysis and dialysis patients are vitamin D insufficient or deficient, severing the vitamin D-PTH feedback loop.³⁴ A further consequence of SHPT arises through the growth of the nodular tissue that accompanies parathyroid gland hyperplasia. This nodular tissue has been shown to be less sensitive to elevated calcium levels, severing the calcium-level feedback loop.³⁵

The Dialysis Outcomes and Practice Patterns Survey, a large international observational study, found clinically unacceptable elevations in PTH (>300 pg/mL) in 25% of end-stage renal disease (ESRD) patients (range: 19%-31% for Japan and the United

Kingdom, respectively).³⁶ Determining mean measures of SHPT prevalence are challenging, however, as risk has been shown to vary widely among patient populations. For example, African American CKD patients are more than twice as likely to develop SHPT as are white CKD patients.³⁷ This finding is thought to be due to the decreased synthesis of 25-dihydroxyvitamin D₃ in response to sunlight among African Americans, perhaps due to skin pigmentation.³⁸ In contrast, diabetic CKD patients have markedly lower PTH levels and a decreased risk of SHPT, perhaps due to PTH suppression by hyperglycemia.³⁸

Chronic SHPT is associated with several complications (Table 2). Two major concerns for patients with SHPT are ROD and progressive CVD.^{39,40} CVD is particularly important, accounting for more than 50% of all stage-5 CKD patient deaths.⁴¹ A retrospective analysis of the United States Renal Data System Waves 1, 3, and 4 Study suggested that disorders of calcium homeostasis are often associated with higher incidences of fatal and nonfatal cardiovascular events and all-cause mortality in hemodialysis patients.⁴²

Despite the lack of a definitive link between PTH and increased CVD risk, there are observational data that illustrate a strong association between cardiac mortality and serum phosphate and calcium-phosphate (Ca x P) product levels. Hyperphosphatemia is often closely associated with SHPT in the context of increased mortality in dialysis patients.⁴³ The adjusted relative risk of death was found to be higher with serum phosphate levels greater than 6.5 mg/dL and Ca x P product levels greater than 72 mg²/dL². This translates into a 1.27 and 1.34 relative mortality risk for elevated serum phosphorus and Ca x P product levels, respectively.⁴⁴

In addition to hyperphosphatemia and an elevated Ca x P product, other widespread observational findings in CKD patients are considered to be independent risk factors for CVD, including hypertension, left ventricular hypertrophy (LVH), increased serum creatinine levels, and microalbuminuria.⁴⁵ Traditional risk factors such as smoking, diabetes, hypertension, dyslipidemia, and obesity can be present at all stages of CKD and may also increase the risk of CVD.⁴⁶ The prominent role that ROD and CVD comorbidities play in the increased mortality and treatment cost of CKD warrant further discussion of these conditions.

Renal Osteodystrophy

The processes of bone absorption and resorption are closely regulated in healthy individuals. ROD arises as a consequence of bone remodeling dysregulation. While the pathogenesis of ESRD is similar across patients, the pathogenesis of ROD varies from high- to low-bone turnover. Elevated levels of PTH stimulate bone demineralization and lead to high-bone turnover, a condition characterized by accelerated rates of bone absorption and resorption. The new bone is structurally inferior and fragile, and carries an increased risk of fractures.⁴⁷ The classic histological form of ROD is osteitis fibrosa, which arises from increased bone

TABLE 3 Prevalence of Renal Osteodystrophy in Chronic Kidney Disease⁵³⁻⁵⁶

	Stage 3	Stage 4	Stage 5 (ESRD)
High bone turnover	90%	90%	25%-40%
Low bone turnover	10%	10%	60% (20%-40% ADB; 4%-12% OM)*

ADB=adynamic bone disease; ESRD=end-stage renal disease; OM=osteomalacia.

remodeling and fibrosis of the marrow.^{48,49} Presentation of reduced bone mass, increased nonlamellar bone via biopsy, osteopenia, and fractures accompany osteitis fibrosa.⁵⁰

Conversely, depressed PTH levels as a consequence of parathyroidectomy or overtreatment with vitamin D can lead to low-bone turnover disease, characterized by lower rates of bone absorption and resorption. Osteomalacia arises through decreased remodeling coupled to a mineralization defect causing accumulation of unmineralized osteoid.⁵¹ Adynamic bone disease is another manifestation of low-bone turnover ROD, characterized by reduced bone volume, mineralization, and collagen synthesis due, in part, to decreased cellular activity.⁵² As this generalized dormancy leads to fewer active bone remodeling sites, adynamic bone disease is associated with a decreased ability of the skeleton to buffer serum calcium fluctuations.⁵¹

As shown in Table 3, prevalence of high- versus low-bone turnover ROD depends strongly on CKD staging. High-bone turnover dominates in CKD stages 3-4 with 90% of the ROD case-load as determined by bone biopsy.⁵³ In ESRD patients, low-bone turnover disease becomes increasingly prevalent, due, in part, to PTH oversuppression, aluminum intoxication, and high calcium dialysate concentrations.⁵¹ Osteitis fibrosa represents 25% to 40% of ROD seen in ESRD patients, compared with 60% low-bone turnover.⁵⁴ Of that percentage, adynamic bone accounts for 20% to 40% of the low-bone turnover ROD, and osteomalacia, 4% to 12%, along with some mixed osteodystrophy histology.^{55,56}

Cardiovascular Disease

The elevated risk of cardiovascular mortality in CKD patients is responsible, in part, for the steep decline in the numbers of late-stage CKD patients. Studies show that more than 40% of all deaths in ESRD patients are linked to CVD and that CVD mortality is 10 to 70 times greater in the dialysis population than in the general age-matched cohort.⁵⁷ The soft-tissue and vascular calcification that accompanies SHPT in advanced CKD is associated with a high risk of cardiac events among dialysis patients.

LVH is the most prevalent cardiac complication observed in CKD patients and is often associated with myocardial fibrosis, poor perfusion, and cell death.⁵⁷⁻⁶¹ Increased cardiac afterload, a potential consequence of increased arterial resistance due to vascular calci-

fication, induces formation of the pathophysiology.⁶¹ In a cross-sectional study, Saleh et al. found PTH to be an independent predictor of LVH among patients in the upper PTH percentiles (>3.3 pmol/L for men and >3.1 pmol/L for women).⁶² Nasri et al. analyzed the influence of PTH on myocardial function. In their cross-sectional study in hemodialysis patients, they determined that excess PTH played a significant role in the development of LVH and reduced left ventricular ejection fraction.⁶³

In a decade-long retrospective study, Dai et al. found a 52% prevalence of severe LVH among ESRD patients.⁶⁴ Ha et al. further extended the links between LVH and CKD, finding an 87% prevalence of concentric and eccentric LVH among predialysis patients.⁶⁵ Foley et al. corroborated the results in a decade-long prospective study, finding that 80% of the 433 patients initiating dialysis presented with LVH on echocardiography.⁶⁶

The relationship between elevated PTH and LVH was further explored in a retrospective study by Goto et al., who determined that parathyroidectomy in CKD patients with advanced SHPT led to a significant improvement of left ventricular ejection fraction and function.⁶⁷ A prospective study of 15 patients by Park et al. confirmed the association with SHPT, finding that PTH-suppressive calcitriol therapy led to a regression in myocardial hypertrophy in dialysis patients.⁶⁸

Hyperphosphatemia and hypercalcemia have been shown to promote calcification of the vasculature, myocardium, and cardiac valves.⁶⁹⁻⁷¹ Vascular calcification, manifested in reduced vessel wall elasticity, increased intima-media layer thickness and enhanced pulse-wave velocity, has been linked to LVH, and occurs with increased severity in dialysis patients versus non-CKD patients.⁷² One observational study demonstrated as many as 92% of young adult dialysis patients had evidence of coronary arterial calcifications.⁷³ Furthermore, vascular and soft-tissue calcifications are strong predictors of cardiovascular mortality among CKD patients.^{40,74} Retrospective studies by Block et al. and Ganesh et al. suggest that hyperphosphatemia (>6.5 mg/dL) and increased Ca x P product (>72 mg²/dL²) are factors that contribute to the high mortality rate in dialysis patients.^{44,75,76}

Peripheral artery disease (PAD) has recently surfaced as a CKD-related disorder. Manifested commonly as claudication, resting pain, or numbness of the lower extremities, PAD is a consequence of the atherosclerosis of the arteries that serve those regions. One observational study demonstrated a high prevalence of PAD in nondialyzed CKD patients upon first-time referral to a nephrology clinic. A higher prevalence was also seen in those patients with a greater severity of SHPT (PTH 228 ± 267 pg/mL).⁷⁷

Shane et al. postulated that SHPT might be a contributing factor in congestive heart failure (CHF). The authors analyzed 101 patients (79 men and 22 women, aged 25 to 70 years) with severe CHF who were referred for evaluation for cardiac transplantation. Osteoporosis and osteopenia were observed in approximately half these patients, as well as SHPT (30%) and vitamin D deficiency (26%).⁷⁸

Current Treatment Options for Secondary Hyperparathyroidism

In recent years, clinical research has demonstrated that along with PTH regulation, controlling mineral homeostasis (calcium, phosphorus, and Ca x P product) may reduce morbidity and mortality in patients with SHPT.⁷⁹ While oral phosphate-binding agents (calcium, sevelamer, lanthanum, magnesium, and aluminum) are used to reduce blood concentrations of phosphorus and are often taken concurrently with vitamin D (when SHPT is present), the focus of this article is on SHPT and its treatments. Vitamin D therapy is the standard medical treatment for predialysis and ESRD patients with vitamin D deficiency due to progressive kidney failure and associated elevations in PTH levels that exceed the K/DOQI-targeted ranges for the CKD stage.⁸⁰ Calcimimetic therapy is also approved for SHPT treatment in ESRD patients. The overall goal of treatment is to restore the PTH-calcium-vitamin D endocrine feedback loop, reestablish mineral homeostasis, and reduce the associated complications.⁸¹ Important clinical trial data that report efficacy and safety for SHPT therapies are compiled in Table 4. Costs associated with current pharmacological treatments of SHPT in CKD are reported in Table 5.

Ergocalciferol

Ergocalciferol (Drisdol and generics, vitamin D₂), available as an oral capsule, is indicated for use in CKD stages 3-4 patients with vitamin D deficiency and concomitant elevation in PTH. It is U.S. Food and Drug Administration (FDA)-approved for the treatment of vitamin D deficiency, etiology unspecified. A prohormone, ergocalciferol, must be activated in the liver and kidney to biologically active forms of vitamin D.⁸² While recommended by the K/DOQI guidelines for treating 25-hydroxyvitamin D deficiency, ergocalciferol's effectiveness in PTH inhibition is not well defined.^{83,84}

Calcitriol

Calcitriol (Rocaltrol, Calcijex, and generic 1,25 dihydroxyvitamin D₃) is available as an oral solution, oral capsule, and injectable formulation. The oral formulations are approved in CKD stages 3-5 patients for the treatment of SHPT and in dialysis patients for the treatment of hypocalcemia and metabolic bone disease. The intravenous formulation is approved for the treatment of hypocalcemia and SHPT in hemodialysis patients. Administration of biologically active vitamin D (calcitriol) has been shown effective in treating the underlying deficiency in SHPT. In fact, the use of either oral or intravenous calcitriol has been shown to inhibit PTH synthesis and secretion and prevent parathyroid gland hyperplasia in CKD patients.⁸⁵ Furthermore, calcitriol has been approved for the pediatric dialysis population.

However, calcitriol efficacy is limited by the development of hypercalcemia and the aggravation of hyperphosphatemia prevalent in CKD patients.⁸⁶ Both conditions have been linked to visceral and vascular calcification; furthermore, calcium loading has been associated with bone loss in dialysis patients.⁸⁷ A detailed under-

standing of calcitriol and vitamin D receptor interactions has led to the development of 3 generations of vitamin D analogs that attenuate PTH levels with fewer adverse mineral homeostatic effects. Two vitamin D analogs approved for use in the United States are doxercalciferol (Hectorol) and paricalcitol (Zemplar).

Doxercalciferol

Doxercalciferol (Hectorol, 1 α -hydroxyvitamin D₂) is a second-generation prohormone analog, biologically activated in the liver mainly to 1,25-dihydroxyvitamin D₂.⁸⁸ Doxercalciferol has been approved for use in CKD stages 3-5, including dialysis, and is administered as an oral capsule for CKD stages 3-4 and as an intravenous solution for dialysis patients.⁸⁸ In a recent double-blinded, multicenter randomized controlled trial (RCT) of 55 predialysis patients, Coburn et al. found that, at study's end, 74% of patients showed a $\geq 30\%$ reduction in PTH levels and that 56% of patients had met their K/DOQI PTH target.⁸⁹ Evaluating doxercalciferol in dialysis patients in an open-label study, Maung et al. found that 95% of patients (94% and 95%, intravenous and oral doxercalciferol formulations, respectively) had $\geq 30\%$ reductions in PTH levels, and 77% of patients on the oral doxercalciferol regimen achieved their K/DOQI recommendations for PTH control.⁹⁰ While PTH suppressive in the adult CKD population, doxercalciferol awaits prospective study and FDA approval in the pediatric CKD population.

Although less calcemic and phosphatemic than calcitriol, preclinical studies raised concern over the calcemic and phosphatemic potential of doxercalciferol.^{91,92} Despite clinically important PTH suppression, Tan et al. found doxercalciferol therapy unacceptably raised serum mineral levels by 13 times in half the ESRD patients in the observational study, totaling 4.9 hypercalcemic episodes and 10.1 hyperphosphatemic episodes per 100 weeks of treatment.⁹³ In a double-blind RCT investigating doxercalciferol therapy in dialysis patients suffering from moderate-to-severe SHPT, Frazao et al. found that 82 of the 99 patients (83%) studied achieved PTH targets but with concomitant mild hypercalcemia and hyperphosphatemia.⁹⁴ A crossover study comparing doxercalciferol and paricalcitol found equipotent PTH suppression but a higher incidence of hyperphosphatemia among doxercalciferol recipients, twice that seen with paricalcitol therapy.⁹⁵ A paucity of comparative data exists between doxercalciferol versus calcitriol, highlighting the need for future prospective study.

Paricalcitol

Paricalcitol (Zemplar, 19-nor-1,25-dihydroxyvitamin D₂) is a third-generation vitamin D analog that is bioactive upon administration, mimicking the actions of calcitriol on the vitamin D receptor.⁸² Similarly to doxercalciferol, paricalcitol has been approved for CKD stages 3-5, administered as an oral capsule for predialysis patients and intravenously in dialysis patients.⁹⁶ Paricalcitol was proven safe and effective versus placebo in both short-term and

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TABLE 4 Summary of Literature for SHPT Therapy

Treatment	Citation	Study Design	Outcomes	Adverse Effects
Doxercalciferol vs. placebo	Coburn et al. (2004) ⁸⁹	Double-blind, RCT n=55 predialysis patients 24-week study	Mean plasma PTH level decreased by 46% from baseline after 24 weeks of doxercalciferol treatment but was unchanged with placebo. After 6 weeks, PTH level reductions with doxercalciferol treatment exceeded those with placebo at all subsequent intervals ($P < 0.001$).	Adverse effect rates and changes in GFR did not differ between study groups.
Doxercalciferol	Maung et al. (2001) ⁹⁰	Open-label study n=64 dialysis patients 12-week study	95% of patients showed $\geq 30\%$ reduction in PTH levels, and 77% of patients met their K/DOQI PTH targets.	Prevalence of $[Ca] \geq 11.2$ mg/dL during oral and IV treatment was 3.62% and 0.86%. Hypercalcemia was less frequent, and serum phosphorus levels increased less during IV versus oral therapy.
Doxercalciferol	Tan et al. (1997) ⁹³	Observational study n=24 dialysis patients 12-week study	Pretreatment serum PTH fell from 672 ± 70 pg/mL to 289 ± 36 pg/mL after treatment; 87.5% patients met the study's PTH targets.	There were an average of 4.9 hypercalcemic and 10.1 hyperphosphatemic episodes per 100 weeks of treatment. Hypercalcemia necessitated stopping therapy in 1 patient.
Doxercalciferol vs. placebo	Frazao et al. (2000) ⁹⁴	Double-blind, RCT n=99 dialysis patients 8-week study	80% of doxercalciferol patients showed a 70% reduction in PTH levels from baseline, and 83% of the doxercalciferol patients met the study's PTH targets.	During double-blinded treatment, 3.26% and 0.46% of $[Ca]$ measurements exceeded 11.2 mg/dL with doxercalciferol and placebo, respectively.
Doxercalciferol vs. paricalcitol	Martin et al. (2006) ⁹⁵ [Poster]	Crossover study n=9 dialysis patients 20-week study	At comparable dosing, effective suppression of PTH was not different between treatment arms.	Twice as many hyperphosphatemia episodes for doxercalciferol occurred in comparison to paricalcitol (28 vs. 13 episodes).
Paricalcitol vs. placebo	Coyne et al. (2006) ⁹⁷	3 double-blind RCTs n=220 predialysis patients 24-week study	At least 2 consecutive decreases in PTH levels of 30% or greater from baseline occurred in 91% of paricalcitol versus 13% of placebo patients ($P < 0.001$).	Incidences of hypercalcemia, hyperphosphatemia, and elevated $Ca \times P$ were not significantly different between groups. No significant differences in urinary Ca and PO_4 excretion or decrease in kidney function detected between study groups
Paricalcitol vs. placebo	Martin et al. (1998) ⁹⁸	3 double-blind RCTs n=78 dialysis patients 12-week study	Of 40 patients receiving paricalcitol, 27 (68%) had at least a 30% decrease in serum PTH for 4 consecutive weeks, compared with 3 of 38 patients (8%) receiving placebo ($P < 0.001$).	Hypercalcemia did not occur before achieving target serum PTH levels in any of the paricalcitol-treated patients. There was no significant difference in the change from baseline in serum $[PO_4]$ within or between treatment groups. There was no significant difference in adverse events between the paricalcitol and placebo-treated groups.
Paricalcitol vs. placebo	Lindberg et al. (2001) ⁹⁹	Open-label study n=164 dialysis patients 13-month study	Mean PTH levels fell into target range (100-300 pg/ml) by month 5. Importantly, among 35 hyperphosphatemic patients $[PO_4]$ fell by an average 0.57 ± 0.52 mg/dL. Mean $[Ca]$ and mean $[PO_4]$ was kept within the normal range throughout the study.	Adverse events that were considered by the investigator to have a possible relationship to the study drug occurred in 26% of patients, namely nausea/vomiting and metallic taste.

(continued on next page)

long-term studies. Double-blind RCTs in predialysis patients demonstrated the clinical efficacy of oral paricalcitol, finding 91% of patients reached the primary endpoint of 2 consecutive reductions of $\geq 30\%$ in PTH levels.⁹⁷ Martin et al. found 68% of paricalcitol recipients showed $\geq 30\%$ reduction in PTH levels in 3 short-term

double-blind RCTs among dialysis patients.⁹⁸ An open-label 13-month study conducted by Lindberg et al. found IV paricalcitol provided clinically relevant 60% reductions in serum PTH from baseline and that targeted mean PTH levels were reached by 5 months.⁹⁹

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TABLE 4 Summary of Literature for SHPT Therapy (continued)

Treatment	Citation	Study Design	Outcomes	Adverse Effects
Paricalcitol vs. placebo	Sprague et al. (2003) ¹⁰⁰	Multicenter, double-blind RCT n = 263 dialysis patients 32-week study	Paricalcitol patients showed a $\geq 50\%$ reduction in baseline PTH, significantly faster vs. calcitriol patients (87 days vs. 107 days). Paricalcitol patients reached a determined therapeutic PTH range in 18 weeks, whereas calcitriol patients never reached the target range. Calcitriol recipients suffered from significantly more prolonged hypercalcemic episodes (18% for paricalcitol vs. 33% for calcitriol).	No meaningful differences were observed between treatment groups in the incidence, severity, or relationship of adverse effects occurring during treatment. Other laboratory values and vital sign assessments were similar between treatment arms.
Paricalcitol vs. calcitriol	Mittman et al. (2004) ¹⁰² (Poster)	Retrospective study n = 101 dialysis patients 24-month study	Mean PTH levels were significantly lower for paricalcitol vs. calcitriol (247 vs. 190 pg/mL). Additionally, 79% of participants were African American, a population with elevated risk of SHPT.	Calcitriol showed almost double the number of hypercalcemic episodes versus paricalcitol (111 versus 69) and more episodes of hyperphosphatemia (225 versus 186)
Paricalcitol vs. calcitriol	Coyne et al. (2002) ¹⁰³	Crossover study n = 10 dialysis patients 36-hour study	Suppression of PTH at 36 hours was similar after administration of calcitriol ($54.1\% \pm 6.0\%$) and 120 μg of paricalcitol ($54.4\% \pm 3.4\%$) and significantly greater after administration of 160 μg of paricalcitol ($63.6\% \pm 2.3\%$).	Ca x P product increased more after calcitriol administration than after a 6- or 8-fold greater dose of paricalcitol and was significantly greater at 6, 12, and 24 hours.
Paricalcitol vs. doxercalciferol	Joist et al. (2006) ¹⁰⁴	Crossover study n = 13 dialysis patients 36-hour study	Clinical suppression of PTH (defined by Nichols immunoradiometric assay) at 36 hours was comparable between treatment arms (63% following paricalcitol therapy and 65% following doxercalciferol therapy).	Serum [PO ₄] peaked significantly higher during administration of doxercalciferol (2.12 ± 0.11 mmol/L vs. 1.85 ± 0.07 mmol/L). Ca x P also peaked higher at 36 hours following doxercalciferol than paricalcitol, (5.02 ± 0.26 mmol/L vs. 4.54 ± 0.21 mmol/L)
Cinacalcet vs. placebo	Block et al. (2004) ¹¹⁶	Double-blind RCT n = 741 dialysis patients 26-week study	43% of patients reached the study's primary endpoint (≤ 250 pg/mL PTH) vs. 5% of placebo patients. Ca x P decreased 15% over placebo by study's end and moderate reductions in [Ca] and [PO ₄] (6.8%, 8.4%, respectively).	91% of cinacalcet patients experienced at least 1 adverse event. Adverse effects included hypocalcemia (5%), nausea (32%), and vomiting (30%).
Cinacalcet vs. placebo	Lindberg et al (2003) ¹¹⁷	Double-blind RCT n = 78 dialysis patients 18-week study	A mean 26% decrease in PTH level, compared with 22% increase in placebo group; Serum [Ca] decreased by 4.7% and Ca x P by 11.9% in the cinacalcet treatment arm.	Adverse effects included nausea (21%), dyspnea (18%), and hypocalcemia (recurred in 3/38 subjects)
Cinacalcet vs. placebo	Quarles et al. (2003) ¹¹⁹	Double-blind RCT n = 71 dialysis patients 18-week study	Mean PTH decreased by 33% in the cinacalcet patients compared with an increase of 3% in placebo patients. Ca x P decreased by 7.9% in cinacalcet patients compared with an increase of 11.3% in placebo patients.	Vomiting (not quantified) occurred more often in cinacalcet patients than in placebo patients.

(continued on next page)

Comparing paricalcitol with calcitriol in a head-to-head, multicenter RCT in dialysis patients, Sprague et al. found that paricalcitol-treated patients reached a $\geq 50\%$ reduction in baseline PTH significantly faster than did calcitriol patients (87 days vs. 107 days, respectively).¹⁰⁰ Furthermore, paricalcitol patients reached a

determined therapeutic PTH range in 18 weeks, whereas calcitriol patients never reached the target range. Most important, however, calcitriol recipients suffered from significantly more episodes of prolonged hypercalcemia (33% vs. 18%, [$P=0.008$], incidence of hypercalcemia at 2 consecutive laboratory draws).¹⁰⁰

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TABLE 4 Summary of Literature for SHPT Therapy (continued)

Treatment	Citation	Study Design	Outcomes	Adverse Effects
Cinacalcet	Strippoli et al. (Cochrane Review, CD006254, 2007) ¹²¹	Literature review, 8 RCTs n = 1,429 patients	Calcimimetic treatment of SHPT leads to significant improvements in biochemical assessments that observational studies have shown to be associated with increased mortality, CVD risk, and ROD. However, patient-level benefits have not yet been demonstrated other than reduced risk of hypotension for the calcimimetics compared with placebo (RR, 0.53; 95% CI, 0.36- 0.79). For patients with SHPT, the advantages of calcimimetics over standard therapy are uncertain until RCTs further examine those outcomes.	There was no statistically significant increase in the risk of hypocalcemia, nausea, dyspnea, asthenia, paresthesia, headache, or parathyroidectomy with calcimimetics compared with placebo. No statistically significant reduction in the risk of mixed uremic osteodystrophy was seen with calcimimetics versus placebo. In general, the trials reported transient and mild to moderate toxicity with only few participants withdrawing from therapy due to adverse events. However, rates of withdrawal and valid, precise estimates of adverse effects such as hypotension and nausea were often not available.
Cinacalcet vs. placebo	Goodman et al. (2002) ¹³¹	Double-blind RCT n = 52 dialysis patients 2-week study	In patients treated with daily doses of 25 mg or 50 mg of cinacalcet for 8 days, plasma PTH levels declined for the first 3 to 4 days and remained below baseline values after 8 days of treatment. Serum [Ca] decreased by 5% to 10% from baseline in patients given 50 mg of cinacalcet for 8 days, but values were unchanged in those who received lower doses. Serum phosphorus levels and values for the calcium-phosphorus ion product both decreased after treatment with cinacalcet.	The most commonly reported adverse effects for both placebo and cinacalcet included nausea, headache, and hypertension, none of which were quantified.
Cinacalcet vs. placebo	Lindberg et al. (2005) ¹¹⁸	Double-blind RCT n = 395 dialysis patients 26-week study	46% of cinacalcet recipients had >30% decrease in PTH level relative to 9% on placebo. Cinacalcet had similar efficacy in peritoneal and hemodialysis patients.	Adverse effects included nausea (30%), vomiting (23%), and diarrhea (24%).

CVD = cardiovascular disease; GFR = glomerular filtration rate; K/DOQI ; PTH = parathyroid hormone; RCT = randomized controlled trial; ROD = renal osteodystrophy; RR = relative risk [?]; SHPT = secondary hyperparathyroidism.

The efficacy of paricalcitol was extended successfully to difficult-to-treat hyperphosphatemic patients in an open-label study.⁹⁹ Lindberg et al. showed that among 35 initially hyperphosphatemic patients (mean phosphorus levels 8.0 mg/dL), phosphorus levels fell with a mean decrease of 0.57 ± 0.52 mg/dL.⁹⁹ Based on the results in adult patients, a placebo-controlled study was performed in pediatric and adolescent SHPT patients (aged 5-19 years), finding positive PTH suppression without concomitant elevations in serum calcium and phosphorus levels.¹⁰¹ Paricalcitol was subsequently approved for the pediatric population and is the only vitamin D analog approved for these CKD patients.

Several comparative studies suggest clinical superiority of paricalcitol over calcitriol and doxercalciferol. A large 2-year retrospective study evaluating paricalcitol and calcitriol was undertaken by Mittman et al., demonstrating paricalcitol superiority in PTH suppression, mineral metabolism, and adverse events reduction.¹⁰² Mean PTH levels were significantly higher

for calcitriol in comparison with paricalcitol (247 pg/mL vs. 190 pg/mL) as was corrected calcium (9.71 ± 0.55 vs. 9.53 ± 0.67) and phosphorus levels (4.98 ± 0.93 vs. 4.79 ± 0.90). The majority (79%) of study participants were African American, a cohort with elevated risk of SHPT.³⁶ Comparing paricalcitol with doxercalciferol in a small crossover study, Martin et al. found doxercalciferol produced twice as many hyperphosphatemic episodes at similar levels of PTH suppression.⁹⁵

To better address the concerns of hypercalcemia and hyperphosphatemia, 2 prospective crossover studies were performed with dialysis patients. Patients were placed on low calcium and phosphorus diets and were randomly assigned to 1 of 2 drugs at the start of the study. After being administered a single high dose of the drug, serum calcium and phosphorus levels were measured. The protocol was subsequently repeated with the alternate drug. Comparing calcitriol and paricalcitol, Coyne et al. found greater PTH suppression (63.4 % vs. 54.4% of patients) and lower calcium-phosphorus product (4.91 ± 0.27 mmol²/L² vs. 4.29 ± 0.22

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TABLE 5 Medications to Manage SHPT in Chronic Kidney Disease Patients¹³²
(AWP Prices in April 2007, Sorted Ascending by Cost per Year)

Drug	Class	Maintenance Dose	Cost per Week (\$)†	Cost per Year (\$)†
Ergocalciferol oral (generic)	Vitamin D ₂ analog	50,000 U, 3x weekly (3 caps)	3.24	168.48
Calcitriol oral (generic)	Vitamin D ₃	0.5 mcg daily (2 x 0.25 mcg tabs)	8.40	436.80
Calcitriol oral	Vitamin D ₃	0.5 mcg daily (2 x 0.25 mcg tabs)	16.66	866.32
Doxercalciferol oral	Vitamin D ₂ analog	1.0 mcg daily (2 x 0.50 mcg tabs)	47.88	2,489.76
Calcitriol IV* (generic)	Vitamin D ₃	3.0 mcg, 3x weekly (5 vials)	80.20	4,170.40
Paricalcitol oral	Vitamin D ₃ analog	2.0 mcg daily (1 x 2.0 mcg tabs)	88.90	4,622.80
Calcitriol IV*	Vitamin D ₃	3.0 mcg, 3x weekly (5 vials)	111.25	5,785.00
Paricalcitol IV*	Vitamin D ₃ analog	8.0 mcg, 3x weekly (5 vials)	124.10	6,453.20
Doxercalciferol IV*	Vitamin D ₂ analog	8.0 mcg, 3x weekly (6 ampoules)	147.12	7,650.24
Cinacalcet HCl oral*	Calcimimetic	120 mg daily (3 x 60 mcg tabs)	278.46	14,479.92

* Stage 5 (hemodialysis) CKD therapy.

† 85% AWP for brand, 70% AWP for generic-April 2007 from AmerisourceBergen Pharmaceutical Supply. Available at: www.amerisourcebergen.com. Accessed April 20, 2007.¹³²
AWP = average wholesale price; CKD = chronic kidney disease; IV = intravenous; SHPT = secondary hyperparathyroidism.

mmol²/L²) with paricalcitol therapy.¹⁰³ Joist et al. found paricalcitol and doxercalciferol showed equipotent PTH suppression but serum phosphorus levels rose significantly higher during doxercalciferol therapy (2.12 ± 0.11 mmol/L vs. 1.85 ± 0.07 mmol/L, doxercalciferol and paricalcitol, respectively).¹⁰⁴

Comparing mortality between calcitriol and paricalcitol recipients over a 3-year period, an uncontrolled historical cohort analyzed from the databases of the U.S.-based Fresenius Medical Care North America provided tantalizing findings when published in 2003. Teng et al. found dialysis patients receiving paricalcitol achieved a 16% survival advantage over calcitriol recipients that was apparent at 12 months.¹⁰⁵ The authors speculated the survival advantage seen with paricalcitol therapy was due to the nonclassical targets of paricalcitol.^{105,106} However, this advantage of paricalcitol may be explained by considering small differences between the study groups; namely, a longer duration of dialysis before enrollment (90 days) and a higher population of African Americans in the paricalcitol arm (39% vs. 36%). Since African American dialysis patients are known to be at higher risk for SHPT and CVD, the observational data may only be showing that the greater the degree of hyperparathyroidism, the greater the benefit from paricalcitol treatment.

In a recent 2-year retrospective study, Kalantar-Zadeh et al. found that dialysis patients treated with paricalcitol demonstrated a survival benefit, up to a maximum 40% survival advantage.¹⁰⁷ Most recently, however, Tentori et al. studied mortality over a 5-year period in dialysis patients from a not-for-profit group, which over-represented African American patients (44.5%).¹⁰⁸ In all models of mortality rate (deaths/100 patient-years), paricalcitol and doxercalciferol performed similarly (13.6-17.1 for doxercalciferol vs.

13.6-16.9 for paricalcitol). Although unadjusted results showed a survival advantage of both doxercalciferol and paricalcitol versus calcitriol, when models were adjusted for laboratory values and clinic standardized mortality, the hazard ratios for doxercalciferol and paricalcitol versus calcitriol both increased and were no longer statistically significant.

Molecular Mechanisms Differentiating Vitamin D-Based Therapies

The reduced calcemic and phosphatemic potential seen in paricalcitol versus calcitriol and doxercalciferol appears to be due, in part, to differences in intestinal absorption.²² In a preclinical murine model, Slatopolsky et al. demonstrated that paricalcitol treatment causes reduced intestinal absorption of calcium and phosphorus versus equipotent doses of calcitriol.¹⁰⁹ The cause of this clinical advantage has been investigated on the molecular level and appears to be mediated by transcription of genes in enterocytes. Vitamin D compounds are believed to increase intestinal calcium absorption by up-regulating calcium-transporter-1 (CaT1) on the luminal membrane, calbindin in the cytosol, and plasma membrane calcium ATPase-1 (PMCA1) on the basolateral membrane of enterocytes.²² Northern blot analysis in an experimental rat model revealed paricalcitol to be less potent than calcitriol in stimulating expression of CaT1, calbindin, and PMCA1.²²

The differentiation of vitamin D therapies regarding ROD was further studied in vitro, revealing more molecular-level evidence in support of clinical data. The stimulation of collagen synthesis, a marker of bone growth, was investigated in mouse calvariae culture as a function of vitamin D therapy.¹¹⁰ Nakane et al. found paricalcitol more potent than either calcitriol or doxercalciferol in the increased expression of collagen. The rate of osteoclastic bone

resorption was also investigated as a function of drug therapy in mouse calvariae culture. The same group found paricalcitol to be at least 10-fold less active in mobilizing skeletal calcium than either calcitriol or doxercalciferol.¹¹⁰

A similar study found calcitriol-treated osteoclasts resorbed a 63% greater area than paricalcitol-treated cells, a result only partially explained by a higher rate of paricalcitol chemical degradation.¹¹¹ Moreover, a recent preclinical study by Davies et al. demonstrated a favorable bone metabolism effect with paricalcitol therapy in an animal model of adynamic bone disease.¹¹² In comparison to calcitriol, paricalcitol was found to increase distal femur trabecular bone volume, demonstrating anabolic growth in a low-bone turnover model.¹¹² Together, these studies suggest that paricalcitol therapy results in less bone demineralization while maintaining similar or greater bone growth, as evidenced by collagen synthesis.

Cinacalcet

Calcimimetics are novel agents that increase the sensitivity of the CaR in the parathyroid gland.¹¹³ Binding to the transmembrane domain of the CaR, type II calcimimetic agents induce a conformation change in the CaR that lowers the activation threshold for serum calcium.¹¹⁴ Thus, these drugs suppress PTH secretion at calcium levels below the normal physiological concentration.¹¹⁵ Cinacalcet HCl (Sensipar), a type II calcimimetic agent, is the only FDA-approved calcimimetic.¹¹⁴ Cinacalcet is available as a once-daily oral formulation for the treatment of SHPT in adult CKD stage 5 patients on dialysis and for the treatment of hypercalcemia in patients with parathyroid carcinoma.¹¹⁴

Proven safe and effective in clinical trials, cinacalcet has been shown to substantially suppress PTH levels without concomitant elevations in calcium, phosphorus, or Ca x P. A randomized controlled trial undertaken by Block et al. evaluated cinacalcet therapy over a 26-week study period, finding a 43% reduction in mean PTH levels among recipients.¹¹⁶ In a short 18-week RCT, Lindberg et al. found an average decrease of 26% in PTH level in cinacalcet patients, compared with a 22% increase in the placebo group. Serum calcium levels decreased by 4.7% and Ca x P decreased by 11.9% in cinacalcet recipients.¹¹⁷ These results were later corroborated in a multicenter RCT performed by Lindberg et al. over a 26-week study period.¹¹⁸ The investigators found cinacalcet therapy was effective in reducing PTH levels $\geq 30\%$ from baseline versus control (65% of patients vs. 13% of patients) and in reaching target PTH levels ≤ 300 pg/mL versus control (46% of patients vs. 9% of controls).

In a multicenter RCT to evaluate higher dosages, Quarles et al. found a maximum reduction of 60% in PTH level from baseline accompanied by a 4.6% decrease in serum calcium.¹¹⁹ Serum phosphorus levels, however, were comparable between cinacalcet and placebo groups. The most common adverse effects as reported by the package insert include nausea (31%) and vomiting (27%) in patients with baseline calcium levels below 8.4 mg/dL.¹²⁰

While clinical trials have reported significant improvements in Ca x P, PTH, and calcium and phosphorus levels, data demonstrating the impact of cinacalcet on all-cause mortality, bone histomorphometry, fracture rate, cardiovascular event rate, and other hard patient-based outcomes is lacking.^{106,121} Furthermore, all studies except one have reported treatment outcomes only up to 6 months, seriously limiting the data on long-term effects of treatment.²¹ While showing promise, there is a lack of comparative data between cinacalcet and vitamin D therapies, highlighting the need for future head-to-head trials.

Parathyroidectomy

Surgical parathyroidectomy is the oldest treatment option for hyperparathyroidism and is reserved for patients refractory to other therapies. Surgery carries risks, including anesthetic risks, preoperative and postoperative complications, and, importantly, injury to the recurrent laryngeal nerve. Furthermore, because of the varied number of parathyroid glands (4 is normal, but the range is 3-7), failure to remove or locate all the glands may require additional surgery. Even total parathyroidectomy has proven ineffectual in certain patients, as reported by Stracke et al., possibly because of ectopic parathyroid tissue.¹²² Removal of too much parathyroid gland, however, can result in permanent hypoparathyroidism and severe hypocalcemia, requiring patients to be prescribed daily calcium supplementation.^{123,124} Thus, although parathyroidectomy is often necessary in patients with severe recalcitrant SHPT, the surgical option remains a suboptimal treatment option for CKD patients.

Direct Costs of Treating Secondary Hyperparathyroidism

In order to better understand the economic burden associated with CKD, Smith et al. recently performed a large observational study (n = 13,796 predialysis CKD patients) investigating direct medical costs and resource utilization in the predialysis population.¹²⁵ Dividing the control group into 2 cohorts, 1 presenting with several CKD-related comorbidities (n = 12,459) and 1 without any comorbidities (n = 1,337), the authors were able to separate the per-patient-per-year costs of CKD from the CKD-related comorbidities within the case population. They determined that the cost to treat CKD-related comorbidities was almost twice that of treating CKD alone, \$14,000 vs. \$8,000, respectively. Of perhaps greater concern was the finding that the cumulative cost of CKD plus comorbidities was greater than their simple sum, \$26,000 vs. \$22,000, respectively. Taken together, these findings underscore the importance of actively treating the etiology of the comorbidities and not passively waiting for the comorbidities to develop.

Unfortunately, despite such findings, SHPT remains consistently underrecognized, underdiagnosed, and undertreated by clinicians. This problem is evidenced in the lack of large-cohort epidemiological studies of SHPT among predialysis patients, making thorough determinations of prevalence challenging. Two studies, to date, have attempted to estimate the prevalence of SHPT in the

CKD population. The first estimate made by De Boer et al. found that up to 24% of CKD stages 3-4 patients suffered from mild-to-moderate SHPT, compared with the 19% to 31% of ESRD patients who presented with moderate-to-severe SHPT.^{126,36} The second study by Levin et al. found that 56% of predialysis patients with an eGFR <60 ml/min/1.73 m² (CKD stages 3-5) had elevated PTH levels.¹²⁷

While these 2 studies found significantly different frequencies of hyperparathyroidism, these differences can be attributed to the reference values used for a cutoff point. Abnormal PTH levels were considered to be >195 pg/ml by De Boer et al., whereas Levin et al. considered >65 pg/ml to be abnormal. Despite their significantly different findings, these 2 studies reinforce the fact that abnormal PTH levels are prevalent among the CKD population. The K/DOQI guidelines define target PTH values according to CKD stage: stage 3, 35 to 70 pmol/L; stage 4, 70 to 110 pmol/L; and stage 5, 150 to 300 pmol/L. Data regarding CKD stage-related estimates of the percentage of patients compliant with PTH targets are lacking.

According to the K/DOQI guidelines, the prevalence of stages 3, 4, and 5 CKD in the United States is 7.6, 0.4, and 0.3 million, respectively.¹ Therefore, using the SHPT prevalence findings from De Boer et al. and Levin et al., respectively, we can assume that between 2.0 million and 4.7 million individuals with CKD have elevated PTH levels and therefore would be candidates for the above-mentioned treatment options. These findings, together with the findings from Smith et al.,¹²⁵ show that the cost to treat these individuals and the comorbidities that are predicted to develop are in the range of \$52 billion to \$122 billion. However, if the comorbidities could be prevented or significantly delayed, the costs would range from \$16 billion to \$37 billion, a cost savings of between \$36 billion and \$85 billion.

Conclusions

There is an increasing body of evidence, largely observational, that shows that elevated PTH levels cause deleterious physiological effects across a variety of organ systems, including the cardiovascular manifestation of LVH, a common cause of morbidity and mortality in CKD. Mild-to-moderate LVH affects 87% of predialysis patients and occurs with severe pathophysiology in 52% of dialysis patients.^{64,65} In the skeletal system, osteodystrophy occurs with a prevalence of more than 90% in chronic hemodialysis patients as a consequence of progressive mineral depletion from bone, resulting in fractures and other complications.¹²⁸

Medical management of PTH and mineral imbalances in CKD focuses on controlling SHPT with vitamin D therapy. New vitamin D analogs have the benefit of reducing PTH levels with fewer hyperphosphatemic and hypercalcemic episodes, a problem often associated with calcitriol therapy. In addition, a paucity of comparative clinical data for doxercalciferol indicates the superiority of paricalcitol but supports doxercalciferol as a therapeutic alternative for patients refractory to other vitamin D therapies.¹²⁹ Alternatively, calcimimetics represent another avenue of medical

management of SHPT but their value (on hard endpoint outcomes versus biochemical outcomes) has not been established in clinical trials. The therapeutic landscape at present relies in large part on observational data, motivating future controlled trials to clarify several questions that remain to be answered in a convincing manner. In particular, studies should focus on determining optimal PTH levels, particularly regarding bone disease, evaluating proper staging to initiate treatment, collecting important prevalence data, and calculating costs for the treatment of SHPT.

The K/DOQI guidelines established by the National Kidney Foundation have altered the treatment paradigm of CKD, expanding clinical focus past dialysis to view the disease as a progressive illness capable of maintenance.¹³⁰ Recent studies have reinforced this perspective, recognizing that the bulk of the morbidity, mortality, and economic burden of CKD lies in the comorbidities that accompany the development of SHPT very early in CKD.^{8,9,41,44,57,74,75,76,126}

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