CHRONIC KIDNEY DISEASE

Chronic kidney disease (CKD) is defined as dysfunction of the kidney lasting longer than 3 months, with or without reduced glomerular filtration rate (GFR) [National Kidney Foundation (NKF), 2003]. GFR is the volume of fluid filtered from the renal glomerular capillaries into Bowman’s capsule per unit time and provides an estimate of the filtering capacity of the functioning nephrons. While GFR can be measured directly, it is often estimated (eGFR) from the serum creatinine level using the patient’s age, weight, gender, and body size in the calculation. CKD is also defined by the presence of urinary albumin with an excretion rate higher than 300 mg per 24 hours or in a ratio of greater than 200 mg of albumin to 1 g of creatinine (NKF, 2003). Staging of CKD is categorized by kidney damage and the level of GFR (see Table 1).

Secondary hyperparathyroidism (SHPT) is an early and major complication of CKD that progresses as GFR decreases (De Boer, Gorodetskaya, Young, Hsu & Chertow, 2002). Stage 5 CKD is characterized by kidney damage and the level of GFR (see Table 1).

Secondary hyperparathyroidism is an early complication of chronic kidney disease (CKD). Vitamin D deficiency and reduced synthesis of 1,25-dihydroxyvitamin D (calcitriol) early in the progression of CKD leads to abnormal mineral metabolism. Vitamin D deficiency leads to increased parathyroid hormone and remodeling of bone that releases calcium and phosphorus, resulting in vascular calcification. Vitamin D deficiency is associated with cardiovascular disease and contributes to the high morbidity and mortality in patients with CKD.

Goal
To increase understanding for causes and treatment of secondary hyperparathyroidism.

Objectives
1. Relate the pathophysiology of CKD to the development of secondary hyperparathyroidism (SHPT).
2. Describe the ultimate effects SHPT has on body systems.
3. Summarize the current treatment options for SHPT.

Secondary hyperparathyroidism is an early complication of chronic kidney disease (CKD). Vitamin D deficiency and reduced synthesis of 1,25-dihydroxyvitamin D (calcitriol) early in the progression of CKD leads to abnormal mineral metabolism. Vitamin D deficiency leads to increased parathyroid hormone and remodeling of bone that releases calcium and phosphorus, resulting in vascular calcification. Vitamin D deficiency is associated with cardiovascular disease and contributes to the high morbidity and mortality in patients with CKD.

This offering for 2.5 contact hours is being provided by the American Nephrology Nurses’ Association (ANNA). ANNA is accredited as a provider of continuing nursing education (CNE) by the American Nurses Credentialing Center’s Commission on Accreditation. ANNA is a provider approved by the California Board of Registered Nursing, provider number CEP 00910. This CNE article meets the Nephrology Nursing Certification Commission’s (NNCC’s) continuing nursing education requirements for certification and recertification.

Note: The authors reported no actual or potential conflict of interest in relation to this continuing nursing education article.

Note: This article is supported by an unrestricted educational grant from Abbott. The manuscript has undergone peer review. The information does not necessarily reflect the opinions of ANNA or the sponsor.
with CVD in patients with CKD and may contribute to the high morbidity and mortality observed in this population. Treatment of SHPT remains an important consideration in CKD, as prolonged elevation of PTH results in bone resorption and loss of bone density and structural integrity. Bone resorption leads to increased release of calcium and phosphorus from bone and increases the risk for vascular calcification [Block, Hulbert-Shearon, Levin & Port, 1998; Ganesh, Stack, Levin, Hulbert-Shearon & Port, 2001]. Since CKD is often diagnosed comparatively late in many patients (often Stage 3 or 4), the extrarenal complications have already been initiated [Valderrabano, Golper, Muirhead, Ritz & Levin, 2001]. Patients with CKD often exhibit elevated serum PTH and phosphorus levels and may already be predisposed to cardiovascular sequelae. This article focuses on the complications of SHPT, the use of vitamin D and other agents for therapy, and how therapy improves survival. The economic impact of CKD and different treatments will be discussed.

### Table 1

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (ml/min/1.73m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage and normal/elevated GFR</td>
<td>more than 90</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage and mild reduction in GFR</td>
<td>60-89</td>
</tr>
<tr>
<td>3</td>
<td>Moderate reduction in GFR</td>
<td>30-59</td>
</tr>
<tr>
<td>4</td>
<td>Severe reduction in GFR</td>
<td>15-29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure</td>
<td>less than 15 (or dialysis)</td>
</tr>
</tbody>
</table>

**Note:** GFR = glomerular filtration rate  
**Source:** National Kidney Foundation, 2002. Used with permission.

### Figure 1

**Model for the Effects of Elevated Serum Calcium and Phosphorus on Vascular Smooth Muscle Cell Matrix Mineralization**

Increases of serum calcium and phosphorus stimulate the activity of Pit-1, a transporter located on vascular smooth muscle cells. Elevated calcium also induces expression of Pit-1 mRNA. Activation of these mechanisms are proposed to enhance calcium and phosphate uptake into vesicles of smooth muscle cells as well as matrix vesicles. The vesicles combine with collagen and stiffen the vascular wall, leading to loss of elasticity.

### Regulation of PTH and Initiation of SHPT

The parathyroid glands secrete PTH, the polypeptide hormone that is responsible for maintaining calcium homeostasis. Serum calcium concentrations are detected by G-protein coupled calcium receptors or “calcium sensors,” located on the chief cells of the parathyroid gland [Llach & Yudd, 1998]. Low serum calcium levels detected through the calcium sensor result in PTH secretion. In turn, PTH up-regulates the expression of 1α-hydroxylase in the kidney, the enzyme that catalyzes the formation of the active form of vitamin D (1,25-dihydroxyvitamin D₃, or calcitriol) [Hewison, Zehnder, Bland, & Stewart, 2000]. When serum calcium levels are low, PTH stimulates the synthesis of calcitriol in an effort to correct the calcium imbalance through several mechanisms: 1) increasing absorption of calcium from the gastrointestinal tract; 2) conserving calcium that would be excreted by the kidneys, and 3) mobilizing calcium from bone (see Figure 1).

In patients with Stage 2 CKD, levels of vitamin D are often inadequate in lieu of increasing serum PTH levels (Levey et al., 2007). Reduced levels of vitamin D result in less substrate for the 1α-hydroxylase
enzyme to convert to active vitamin D (Jones, 2007). A recent report shows a negative correlation between active vitamin D levels and PTH levels in patients not yet on dialysis, with the majority who are predialysis and patients on dialysis being vitamin D insufficient or deficient (Gonzalez, Sachdeva, Oliver & Martin, 2004).

Phosphorus also has major effects on parathyroid gland growth. Several studies show that phosphorus restriction, independent of serum calcium and calcitriol levels, may prevent parathyroid gland growth and the development of SHPT in both animals and patients with CKD (Cizman, 2003; Denda, Finch & Slatopolsky, 1996; Naveh-Many, Rahamimov, Livni & Silver, 1995; Slatopolsky et al., 1996). In animals that are on a high-phosphorus diet, there is an acceleration of parathyroid gland growth, whereas a low-phosphorus diet prevents parathyroid gland hyperplasia; in experimental animals this effect of dietary phosphorus on parathyroid gland growth occurs extremely rapidly, within days after the induction of kidney failure (see Figure 2) (Denda et al., 1996).

**Vascular Calcification and CKD**

Cardiovascular complications are the leading cause of death in patients with CKD (Foley, Parfrey & Sarnak, 1998). The elevated risk of cardiovascular mortality in patients with CKD is responsible, in part, for the steep decline in the numbers of patients with late stage CKD. Studies show that more than 40% of all deaths in patients with end stage renal disease (ESRD) are linked to CVD, and mortality is 3 to 7 times greater in the dialysis population than in the general age-matched cohort (Foley & Collins, 2007). Vascular calcification is common in patients with CKD and the progression of the calcification is directly related to mortality (London et al., 2003). The factors that lead to the initiation and enhance the progression of vascular calcification in patients with CKD is not fully understood but indicate the involvement of altered calcium and phosphorus metabolism.

There are a myriad of cardiovascular disease risk factors observed in patients with CKD (see Table 2) (Mitsnefes, 2005). The relationship between blood pressure and cardiovascular disease is continuous and independent of other risks, i.e., the higher the blood pressure the greater the chance of myocardial infarction,

---

**Table 2**

<table>
<thead>
<tr>
<th>Cardiovascular Risk Factors in Adults with CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Traditional Risk Factors</strong></td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Race</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Increased LDL cholesterol</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Use of tobacco</td>
</tr>
<tr>
<td>Physical inactivity</td>
</tr>
<tr>
<td>Obesity</td>
</tr>
<tr>
<td>Positive family history of CVD</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
</tr>
<tr>
<td><strong>CKD-Related Risk Factors</strong></td>
</tr>
<tr>
<td>Decreased GFR</td>
</tr>
<tr>
<td>Proteinuria</td>
</tr>
<tr>
<td>Renin-angiotensin-aldosterone activity</td>
</tr>
<tr>
<td>Anemia</td>
</tr>
<tr>
<td>Abnormal serum calcium and phosphorus</td>
</tr>
<tr>
<td>Hypoalbuminuria</td>
</tr>
<tr>
<td>Hemodynamic overload</td>
</tr>
<tr>
<td>Thrombogenic factors</td>
</tr>
<tr>
<td>Chronic inflammation</td>
</tr>
</tbody>
</table>

Source: Adapted from Mitsnefes, 2005. Used with permission.
heart failure, stroke, and kidney disease (Chobanian et al., 2003). Chobanian and colleagues have suggested that achieving a sustained reduction of only 12 mmHg in the systolic blood pressure for 10 years will prevent 1 death in every 9 patients with CKD. Poorly controlled hypertension is also associated with the development of CKD.

Hypertension can contribute to changes in the structure and function of the heart, specifically the left ventricle. Left ventricular hypertrophy (LVH) refers to the adaptation of the myocardium to increased cardiac load. In the initial stages, LVH is an adaptive process; however, when sustained, it results in increased wall thickness. Recent studies show that less than 15% of patients with CKD have normal left ventricular function (Pendse & Singh, 2005).

Increased arterial stiffness in patients with CKD may be a consequence of vascular calcification and chronic overload, along with other factors (Gusbeth-Tatomir & Covic, 2007). The increased arterial stiffness, in turn, generates additional increases in blood pressure. Reduced vascular compliance due to calcification results can be detected as a widened pulse pressure (Hujairi, Afzali, & Goldsmith, 2004). Medial lesions (also referred to as Monckeberg’s medial sclerosis) contribute to the stiffness of the vessels and reduce vascular compliance (Giachelli, 2004). Stiff arteries exhibit a reciprocal relationship with hypertension; medial lesions accelerate blood pressure changes. Systolic blood pressure increases, whereas diastolic pressure remains unchanged or may even decrease, leading to an increased pulse pressure (Goodman et al., 2004).

Pathogenesis of vascular calcification in patients with CKD is not fully understood but postulated to be multifactorial. Early studies postulated that calcification of the vascular wall was a passive process that resulted in deposition of hydroxyapatite due to elevated serum calcium and phosphorus levels (Alfrey, 2004; Cannata-Andia & Rodriguez-Garcia, 2002). However, recent data suggest vascular calcification is an active process that resembles bone mineralization (Cozzolino, Gallieni, & Brancaccio, 2006; Moe, 2006). The process involves alterations of vascular smooth muscle cells and the expression of proteins normally involved in bone metabolism. Vascular calcification shares many of the same proteins and processes that often transform vascular smooth muscle cells into osteoblast-like cells (Fukagawa & Kazama, 2007; Huybers & Bindels, 2007). When human vascular smooth muscle cells are cultured in media containing high phosphorus or calcium levels, there is an increased mineralization of vascular smooth muscle cells and upregulation of markers for osteoblastic differentiation (Jono et al., 2000; Yang, Curinga, & Giachelli, 2004). Hyperphosphatemia and hypercalcemia promote calcification of the vasculature, myocardium, and cardiac valves (Raggi et al., 2002). Vascular calcification results in reduced vessel wall elasticity and increased intima-media layer thickness, with increased severity in patients on dialysis versus patients who did not have CKD (see Figure 3) (London et al., 2003). One study indicates that as many as 92% of adult patients on dialysis demonstrate coronary arterial calcification (Oh et al., 2002). Further, vascular calcification is a strong predictor of cardiovascular mortality among patients with CKD (Moe & Drueke, 2003). Elevated phosphorus levels (greater than 6.5 mg/dL) and increased calcium-phosphorus product (greater than 72 mg²/dL²) are factors that promote vascular calcification and lead to the high mortality rate in patients on dialysis (Ganesh et al., 2001).

**NKF KDOQI Treatment Guidelines**

In 2003, the National Kidney Foundation (NKF) published the Kidney Disease Outcomes Quality Initiative (KDOQI) treatment guidelines for bone metabolism and disease in CKD (NKF, 2003). Re-
commendations included measuring serum levels of intact PTH (iPTH), calcium, and phosphorus in all patients with eGFR less than 60 mL/min/1.73 m². The specific recommendations for Stage 5 CKD are shown in Table 3. More recent analyses of the associations among serum calcium, phosphorus, and iPTH levels with survival suggest that changes in therapeutic targets may be needed since the 2003 NKF-KDOQI guidelines were issued (Andress et al., 2008).

### Table 3
Measurement Frequency and Target Ranges of Parathyroid Hormone (PTH), Calcium, and Phosphorus

<table>
<thead>
<tr>
<th>CKD Stage</th>
<th>GFR Range (mL/min/1.73 m²)</th>
<th>Measure PTH</th>
<th>Measure Calcium and Phosphorus Levels</th>
<th>Target Phosphorus Levels (mg/dL)</th>
<th>Target Calcium Levels (mg/dL)</th>
<th>Target PTH (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>less than 15 or dialysis</td>
<td>every 3 months</td>
<td>every month</td>
<td>3.5–5.5</td>
<td>8.4–9.5</td>
<td>150–300, based on evidence</td>
</tr>
</tbody>
</table>

**Note:** GFR = glomerular filtration rate.  
**Source:** Adapted from National Kidney Foundation, 2003. Used with permission.

Diagnosis and Treatment Of Vitamin D Deficiency

In addition to its well-known actions on mineral metabolism, vitamin D also acts as a cell-differentiating factor and antiproliferative agent with actions on a variety of tissues. Vitamin D influences gene expression, cell differentiation, insulin secretion, blood pressure regulation, and the immune response (Jones, 2007). Health care practitioners must start to manage vitamin D insufficiency with administration of vitamin D supplements throughout Stages 1-5 CKD and continue to provide active vitamin D replacement therapy in Stages 3-5 CKD (Jones, 2007). Several recent studies have noted a high prevalence of vitamin D deficiency among patients with CKD and on dialysis. The largest of these studies is the recently published SEEK study (Levin et al., 2007). This study demonstrated that among patients in Stages 3 and 4 CKD, 12% had 25-hydroxyvitamin D levels less than 15 ng/mL, indicating overt vitamin D deficiency, while the majority had levels between 15 and 30 ng/mL.

### Current Treatment Options For SHPT

**Vitamin D Therapy**

Treatment of SHPT includes the administration of active vitamin D therapies to suppress PTH levels and prevent skeletal complications (NKF, 2003). Vitamin D compounds currently available in the United States are listed in Table 4. Structural and functional differences among vitamin D therapies relate to their ability to directly activate vitamin D receptors (see Figure 4). Active vitamin D therapies include calcitriol and paricalcitol. Paricalcitol differs structurally from calcitriol, and, as a result, exhibits reduced calcemic and phosphatemic effects compared with calcitriol (Slatopolsky et al., 1995). Inactive vitamin D therapies require activation by the kidney or liver before they can bind with high affinity to vitamin D receptors and include ergocalciferol, cholecalciferol, calcifidiol, and doxercalciferol. Ergocalciferol and cholecalciferol are used to treat nutritional vitamin D deficiency, whereas doxercalciferol, which requires activation by the liver, is used in patients with kidney disease who have normal hepatic function (Coburn et al., 2004).

**Ergocalciferol**

Ergocalciferol is indicated for use in patients with CKD Stages 3-4 with vitamin D deficiency and elevated PTH levels. It is available in an oral capsule and is FDA-approved for the treatment of vitamin D deficiency. Ergocalciferol is a prohormone that must be converted in the liver and kidney to the biologically active
forms of vitamin D (Hudson, 2006). Although the NKF-KDOQI guidelines (NKF, 2003) indicate ergocalciferol for treating vitamin D deficiency, the effectiveness of ergocalciferol for reducing PTH levels has not been established (Andress, 2005). Doses of ergocalciferol recommended by the NKF-KDOQI guidelines to treat deficiency in Stages 3 and 4 CKD may be inadequate and higher doses are required (Zisman, Hristova, Ho, & Sprague, 2007).

The 2003 NKF-KDOQI recommendations for treating vitamin D deficiency with ergocalciferol are shown in Table 5. One study showed that a single 50,000 IU capsule of ergocalciferol given once per month to patients on dialysis virtually eliminated vitamin D deficiency after 6 months (Saab et al., 2007). Ergocalciferol is a reasonable initial therapy for vitamin D deficiency associated with elevated PTH levels in patients with Stage 3 CKD but may not have equivalent benefits in Stage 4 CKD (Zisman et al., 2007).

Calcitriol
Calcitriol (1,25 dihydroxyvitamin D₃) is approved for patients with Stages 3-5 CKD for the treatment of SHPT and in patients on dialysis for the treatment of hypocalcemia and metabolic bone disease. Calcitriol is available in oral solution, oral capsule, and injectable forms. The injectable formulation is approved for hypocalcemia in patients undergoing hemodialysis. Administration of calcitriol is effective for correcting the underlying vitamin D deficiency observed with SHPT. Both oral and injectable forms of calcitriol inhibit PTH secretion and prevent parathyroid gland hyperplasia in patients with CKD (Brown, Dusso, & Slatopolsky, 1999). A major problem associated with calcitriol therapy is hypercalcemia and increased hyperphosphatemia in patients with CKD (Slatopolsky, Finch, & Brown, 2003). Calcium-based phosphate binders further increase the risk of hypercalcemia from calcitriol therapy (Friedman, 2005).

### Table 5

**Recommended Supplementation for Vitamin D Deficiency in Patients with Stages 3 and 4 CKD**

<table>
<thead>
<tr>
<th>Serum 25 (OH) - Vitamin D (ng/mL)</th>
<th>Definition</th>
<th>Ergocalciferol Dose (IU = International Units)</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 5</td>
<td>Severe vitamin D deficiency</td>
<td>50,000 IU/week orally for 12 weeks; then monthly</td>
<td>6 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>500,000 IU as single IM dose</td>
<td></td>
</tr>
<tr>
<td>5–15</td>
<td>Mild vitamin D deficiency</td>
<td>50,000 IU/week for 4 weeks, then 50,000 IU/month orally</td>
<td>6 months</td>
</tr>
<tr>
<td>16–30</td>
<td>Vitamin D deficiency</td>
<td>50,000 IU/month orally</td>
<td>6 months</td>
</tr>
</tbody>
</table>

Doxercalciferol

Doxercalciferol (Hectorol, 1-hydroxyvitamin D₃) is a second-generation analog that requires biological activation in the liver (Coburn et al., 2004; Slatopolsky, Cozzolino, & Finch, 2002). Doxercalciferol is approved for CKD patients with Stages 3-5, including patients on dialysis. Doxercalciferol is available as oral capsules for CKD patients Stages 3-5 and an injectable for patients on dialysis. Doxercalciferol also effectively suppresses PTH levels in patients on hemodialysis (Slatopolsky et al., 2002). However, statistically significant elevations in serum calcium and phosphorus have been noted with doxercalciferol (Coburn et al., 2004). In a recent study, 74% of patients demonstrated a 30% or greater reduction in PTH levels and, in addition, 56% of patients with CKD had achieved the recommended KDOQI target levels for PTH (Slatopolsky et al., 2002). In another study, greater than 94% of patients on both oral and injectable doxercalciferol had 30% or greater reductions in PTH levels; 77% of patients on the oral formulation of doxercalciferol achieved the NKF-KDOQI recommended iPTH levels (Maung et al., 2001). Maung et al. also reported that intermittent doxercalciferol intravenous therapy resulted in less frequent episodes of hypercalcemia and hyperphosphatemia compared with oral therapy, suggesting that intravenous doxercalciferol may be advantageous in patients prone to hypercalcemia or hyperphosphatemia. By comparison, Frazao and colleagues (2000) found that in 83% of the patients they studied (82 of 99 patients) target PTH levels were achieved but the patients showed mild hypercalcemia and hyperphosphatemia.

Paricalcitol

Paricalcitol (Zemplar, 19-nor-1,25-dihydroxyvitamin D₃) is a third generation vitamin D analog that is active when administered, i.e., it does not have to be metabolized to an active form. Paricalcitol mimics the actions of calcitriol when it binds the vitamin D receptor (Hudson, 2006). Paricalcitol Capsules has been approved for CKD Stages 3 and 4, and is available in an oral form for patients not yet on dialysis and as an injectable for use in patients with CKD Stage 5.

Paricalcitol effectively and significantly suppresses PTH levels with much less impact on serum calcium and phosphorus levels in patients on hemodialysis (Lindberg et al., 2001). In clinical studies, 91% of patients receiving paricalcitol achieved 2 consecutive reductions of 30% or greater in PTH levels (Coyne et al., 2006). It was also reported that 68% of patients treated with paricalcitol showed 30% or greater reduction in PTH levels in 3 short-term double-blind studies among patients on dialysis (Martin et al., 1998). In an open-label study (Lindberg et al., 2001), paricalcitol injectable resulted in an average 60% reduction in serum PTH from baseline and allowed targeted PTH levels to be reached within 5 months. Paricalcitol also was found to have minimal effects on serum and urinary calcium, with increases of only 1% and 6%, respectively; phosphorus levels did not differ significantly between paricalcitol and placebo (Coyne et al., 2006). Patients treated with paricalcitol also show a significant reduction in proteinuria (Agarwal et al., 2005). Comparing paricalcitol with calcitriol in a head-to-head, multicenter studies in patients on dialysis, patients treated with paricalcitol reached a 50% or greater reduction in baseline PTH significantly faster than did patients treated with calcitriol (87 days vs. 107 days, respectively) (Sprague, Llach, Amdahl, Taccetta, & Batlle, 2003). In addition, patients treated with paricalcitol reached a therapeutic range for PTH in 18 weeks, whereas patients treated with calcitriol never achieved the targeted range. Calcitriol recipients also had significantly more episodes of prolonged hypercalcemia (33% vs. 18%; P = 0.008) (Sprague et al., 2003).

In a study to examine the efficacy of paricalcitol with 35 patients who were hyperphosphatemic (mean phosphorus levels 8.0 mg/dL), phosphorus levels decreased an average of 0.57 ± 0.52 mg/dL (Lindberg et al., 2001). Paricalcitol is approved for pediatric patients and is the only vitamin D analog approved for pediatric and adolescent patients with CKD. A comparison of calcitriol and paricalcitol effects on PTH reduction, showed there was greater PTH suppression (63.4% vs. 54.4% of patients) and lower calcium-phosphorus product (4.91 ± 0.27 mmol/L² vs. 4.29 ± 0.22 mmol/L²) with paricalcitol therapy (Coyne et al., 2002). When comparing paricalcitol to doxercalciferol in patients with CKD, similar degrees of PTH suppression were observed but serum phosphorus levels were significantly higher with doxercalciferol therapy (2.12 ± 0.11 mmol/L with doxercalciferol versus 1.85 ± 0.07 mmol/L with paricalcitol) (see Figure 5) (Joist et al., 2006). The results of a mortality study by Teng et al. (2003) comparing the effects of calcitriol and paricalcitol in patients over a 3-year period showed that patients on dialysis receiving paricalcitol had a 16% survival advantage over calcitriol recipients at the 1-year time point. The survival benefit observed with paricalcitol therapy and not calcitriol therapy was postulated to be due to the “nonclassical” target action of paricalcitol since it is an active vitamin D receptor agonist (Teng et al., 2003). A recent study by Kalantar-Zadeh et al. (2006) demonstrated that patients on dialysis who were treated with paricalcitol exhibited up to a maximum 40% survival advantage.

Adjunct Therapy: Calcimimetics

Cinacalcet is a calcimimetic agent that binds the calcium-sensing receptor of the parathyroid gland, resulting in diminished secretion of parathyroid hormone (Nemeth et al., 2004). Several studies have demonstrated the efficacy of cinacalcet in lowering PTH concentrations in patients on dialysis with SHPT (Lindberg et al., 2003; Lindberg et al., 2005). Regular monitoring of serum calcium is nec-
Figure 5
Differential Effect of Paricalcitol and Doxercalciferol on Phosphorus and Intact Parathyroid Hormone (iPTH)

Comparison of two vitamin D analogs, second generation doxercalciferol, and third generation paricalcitol on serum phosphorus and iPTH. Serum phosphorus rose faster and peaked significantly higher at 6, 12, and 36 hours following doxercalciferol treatment compared with patients receiving paricalcitol. PTH suppression was significantly greater at 6 hours with paricalcitol treatment, but subsequently both analogs caused similar reductions in iPTH.

*P<.05 by paired t-test; † P,.01 by paired t-test; PTH=parathyroid hormone.

Source: Adapted from Joist et al., 2006. Used with permission.
range, allowing it to bind phosphorus throughout the gastrointestinal tract. The range of pH values for binding of phosphorus with lanthanum carbonate is similar to that seen with aluminum-based therapies (pH 3–7), whereas calcium-based therapies are only effective in a more restricted range (pH 5.5–7) (Emmett & Hootkins, 1993). Lanthanum carbonate has demonstrated potency similar to aluminum, but does not cause aluminum-like toxicity in the bone (Behets et al., 2004). Studies have demonstrated that lanthanum carbonate is well-tolerated and effective in controlling phosphate levels (Finn, Joy, & Hladik, 2004; Hutchison et al., 2005; Joy & Finn, 2003).

Survival Benefit with Vitamin D Receptor Activator (VDRA) Therapy

Administration of vitamin D supplements is associated with decreases in mortality rates (Autier & Gandini, 2007). However, the relationship between baseline vitamin D status, dose of vitamin D supplements, and total mortality rates require further investigation. Although several studies implicate altered mineral metabolism in the excessive risk of cardiovascular mortality that occurs in patients with CKD, few studies have examined the role of vitamin D and its contribution to outcomes (Wolf & Thadhani, 2007).

A recent study by Wolf et al. (2007) examined outcomes in an analysis of 825 patients on hemodialysis. Low vitamin D levels were associated with increased mortality, but mortality could be reduced with VDRA therapy. Similar results were observed by Teng et al. (2005) when they examined 2-year survival in a historical cohort study of 51,037 patients on chronic hemodialysis. Two-year survival was significantly improved among patients with VDRA therapy compared with patients who did not receive vitamin D therapy (75.6% vs 58.7%, respectively; P < .001). At 2 years, the mortality rate was 13.8/100 person-years in the group that received VDRA therapy versus 28.6/100 person-years in the group that did not receive vitamin D therapy (P < .001). The incidence of cardiovascular-related mortality was 7.6/100 person-years in the vitamin D group compared with 14.6/100 person-years in the untreated group (P < .001) (see Figure 6). The benefit of vitamin D was evident in 48 of 49 strata examined. After adjusting for potential confounders and accounting for the time-dependency of initiating therapy, patients who received any form of VDRA therapy had a 20% lower risk of mortality (hazard ratio 0.80; 95% CI, 0.76-0.83) compared with patients who never received VDRA therapy. This study data showed that the use of injectable vitamin D in patients on chronic hemodialysis, conferred a significant survival advantage over patients who did not receive vitamin D.

In the 2-year period, 37,173 patients received a VDRA (paricalcitol or calcitriol) and 13,864 patients did not receive VDRA therapy. The analysis of the data was unique in that it was among the first to adjust for time-varying levels of calcium, phosphorus, and parathyroid hormone in dialysis studies; all these known risk factors for mortality also influenced the decision of whether to initiate, continue, or stop VDRA therapy (see Figure 7). Baseline characteristics were similar between the 2 groups except for PTH levels, which, as expected, were significantly greater among patients who were ultimately treated with VDRA therapy.

Wolf and Thadhani (2007) studied the survival of patients in a historical cohort study of 67,399 patients who received treatment with injectable paricalcitol or calcitriol. During the 36-month study period, the survival difference was 59% in the paricalcitol group (n = 29,021) compared with 51% in the calcitriol group (n = 38,378), an absolute difference of 8% in survival. After adjusting for age, gender, race, etiology of renal failure, dialysis duration,
etc, there was a 16% survival advantage associated with paricalcitol treatment (95% confidence interval, 10 to 21%; \(P < .001\)). When 14,862 patients were switched from calcitriol to paricalcitol, there was a significant survival advantage compared to the 1,621 patients switched from paricalcitol to calcitriol (2-year survival 73% versus 64%; \(P = .04\)). The results of this study suggested that treatment with paricalcitol appears to be associated with a significant survival advantage compared to treatment with calcitriol.

Teng et al. (2003) also compared the long term survival rate of patients on long-term hemodialysis receiving paracalcitol or calcitriol. They conducted a historical cohort to compare 36-month survival in patients that received paricalcitol \(n = 29,021\) or calcitriol \(n = 38,738\). A subgroup of 16,483 patients who switched therapy was also evaluated. The mortality rate among patients receiving paricalcitol was 18.0/100 person-years compared with 22.3/100 person-years in the calcitriol group \(P < .001\). The difference in survival was significant at 12 months and increased with time \(P < .001\). In the adjusted analysis, the mortality rate was 16% lower among patients treated with paricalcitol compared to patients treated with calcitriol. A significant survival benefit was observed in 28 of 42 strata examined, and in no stratum was calcitriol favored. At 12 months, calcium and phosphorus levels had increased by 6.7% and 11.9%, respectively, compared with 8.2% and 13.9% in the calcitriol group \(P < .001\). The 2-year survival rate for patients who switched from calcitriol to paricalcitol was 73% compared with 64% for patients who switched from paricalcitol to calcitriol \(P = .04\). The authors concluded that patients on long-term hemodialysis who receive paricalcitol have a significant survival advantage over patients who receive calcitriol.

Further evidence was reported in a 2-year cohort of survival in 58,058 patients on hemodialysis (Lee, Benner, Regidor, & Kalantar-Zadeh, 2007). They concluded that adminis-

---

**Figure 7**

**Hazard Ratios for Mortality According to Baseline Quintiles of Serum Calcium, Phosphorus, and Parathyroid Hormone**

In a multivariate model using a multivariable adjusted stratified analysis, levels of calcium, phosphorus, and parathyroid hormone (PTH) were associated with survival to compare patients who received parenteral vitamin D versus patients who did not receive vitamin D. When the analyses were divided into quintiles, it is evident that elevated serum calcium, phosphorus, and PTH were associated with increased mortality. Importantly, the mortality risk was significantly lower in patients who received parenteral vitamin D therapy.

---

Source: Adapted from Teng et al., 2005. Used with permission.
The analysis examined whether changes over time may influence survival. Reductions in serum calcium, phosphorus, and calcium-phosphorus product during the first 6 months of treatment that started within KDOQI-recommended levels, indicate a worsening in survival. For patients with an excessive fall or rise in serum calcium and phosphorus, there is an associated higher death risk. An incremental rise in calcium-phosphorus product was also associated with progressively increasing death risk.

**Figure 8**

Changes in Albumin-adjusted Serum Calcium, Phosphorus, and Calcium X Phosphorus Product During First 6 Months of All-Cause Death

The analysis examined whether changes over time may influence survival. Reductions in serum calcium, phosphorus, and calcium-phosphorus product during the first 6 months of treatment that started within KDOQI-recommended levels, indicate a worsening in survival. For patients with an excessive fall or rise in serum calcium and phosphorus, there is an associated higher death risk. An incremental rise in calcium-phosphorus product was also associated with progressively increasing death risk.

**Source:** Adapted from Kalantar-Zadeh et al., 2006. Used with permission.
threshold for significantly increased mortality when the serum calcium was greater than 8.5 mg/dL. Similarly, hypophosphatemia correlated with higher mortality risks. These results support previously observed associations between hypophosphatemia and increased mortality, an association suggestive of poor nutritional intake (Marinella, 2003). Hyperphosphatemia has also been correlated strongly with an increased risk of death - with a threshold for significantly increased mortality when the phosphorous exceeded 7 mg/dL (Rodriguez-Benot, Martin-Malo, Alvarez-Lara, Rodriguez, & Aljama, 2005). This threshold is significantly higher than that which previous studies observed as well as the current NKF-KDOQI target range for serum phosphorus (3.5–5.5 mg/dL) (NKF, 2003). These data represent important findings as they suggest that therapeutic interventions that specifically target lowering of serum calcium and phosphorus may not contribute to improved outcomes, as would normally be expected. Small reductions of calcium by as little as 0.6 mg/dL in a patient with baseline serum calcium of 9.5 mg/dL may have a negative impact on mortality.

**Mortality Risks Associated with Altered Calcium, Phosphorus, and Calcium-Phosphorus Product**

In addition to examining the time-dependent associations between measured serum concentrations of the minerals and mortality, Kalantar-Zadeh et al. (2006) found that changes over time in these measures might influence survival. Cox regression modeling was examined in patients whose baseline values were within NKF-KDOQI recommended ranges (serum calcium, 8.4–9.5 mg/dL; serum phosphorus, 3.5–5.5 mg/dL; and calcium-phosphorus product, less than 5.5 mg²/dL²) (see Figure 8) (NKF, 2003). Reductions in serum calcium, phosphorus, and calcium-phosphorus product during the first 6 months of treatment from baseline levels that started within the normal target KDOQI range were associated with an unexpected decline, rather than improvement, in survival. For those patients whose baseline serum calcium was within the NKF-KDOQI recommended range, an excessive fall or rise greater than 0.6 mg/dL in 6 months was associated with higher death risk (Kalantar-Zadeh et al., 2006). A similar association with mortality was observed for an excessive fall or rise in serum phosphorus greater than 1.5 mg/dL. An incremental rise in serum calcium-phosphorus product greater than 10 mg²/dL² in 6 months was also associated with progressively increasing death risk. This study suggests that pushing calcium and phosphorus as low as possible may not be beneficial, and may in fact be harmful.

**Figure 9**

*Association Between the Time-Varying Parathyroid Hormone Level and the Relative Risk of Death*

Multivariate adjustments disclosed a strong association between incrementally higher parathyroid hormone (PTH) levels and increased death risk. These findings provide support for vitamin D therapies that lower PTH levels associated with improved survival. Lower levels of PTH below the NKF-KDOQI guidelines were also associated with an increased risk of death.

*Source: Adapted from Kalantar-Zadeh et al., 2006. Used with permission.*
Similarly, lower levels of PTH, particularly those below the NKF-KDOQI recommended lower threshold (less than 150 pg/mL) were also associated with increased risk of death, consistent with previous findings (Avram, Mittman, Myint, & Fein, 2001; Panuccio et al., 2002).

In order to examine the association between administration of paricalcitol and survival, Kalantar-Zadeh et al. (2006) classified the patients on hemodialysis into 5 groups according to the average dose of paricalcitol administered (per calendar quarter) (see Table 6). Patients who received no dose or low doses of paricalcitol had the lowest baseline serum PTH, whereas patients who received incrementally higher doses of paricalcitol had correspondingly higher baseline PTH concentrations. After exclusion of 2,342 patients who received calcitriol, receiving any dose of paricalcitol (greater than 95% of cohort) was associated with greater survival compared with receiving no dose of paricalcitol (see Figure 9). These data confirm the previously reported association between the administration of paricalcitol and greater survival in patients on maintenance hemodialysis (Kalantar-Zadeh et al., 2006). However, the optimal dose of paricalcitol providing greater survival in patients maintained on hemodialysis remains unknown.

**What Are the Costs of Treatment?**

Compliance is often a problem in patients with CKD and often the lack of compliance involves copays for medication costs. Due to the cost of treating CKD, compliance usually becomes an issue when patients reach the ‘donut hole’ of their insurance plans where they pay almost entirely the medication cost. To provide information on the economic burden associated with CKD, an observational study was conducted (n = 13,796 predialysis patients) to assess medical costs in the patient population with CKD (Smith, Gullion, Nichols, Keith, & Brown, 2004). The control group was divided into 2 cohorts, 1 group with CKD-related comorbidities (n = 12,459 patients) and another group without any comorbidities (n = 1337 patients). The results of the study indicate that the costs of treating CKD-related comorbidities ($14,000 per patient per year) was almost twice that of treating CKD alone ($8,000 per patient per year). The costs of treating CKD with comorbidities was greater than the simple sum, approximately $26,000 per patient per year. According to recent estimates (Coresh et al., 2007; Foley & Collins, 2007), the prevalence CKD in the United States is approximately 20 million patients with another million more at increased risk. This brings the estimated costs for patients with CKD who have comorbidities in the range of $52 to $122 billion dollars (Smith et al., 2004). Smith et al. compare a population of patients with and without CKD, and with and without comorbidities, and calculate the costs of healthcare based on the increased expenditure required for each comorbidity. The authors estimate that treating associated cardiovascular risk and reducing the comorbidities of CKD patients in turn would result in a cost savings of approximately $36 to $85 billion annually (Smith et al., 2004).

Dobrez et al. (2004) examined the relationship between vitamin D therapies and hospitalizations for 11,443 patients on hemodialysis. Multivariate models were used to evaluate the effects of vitamin D therapy on: 1) total number of hospitalizations; 2) total number of hospital days; and 3) risk of first hospitalization after initiation of vitamin D therapy. The results showed that the paricalcitol-treated group had significantly lower risk of first all-cause hospitalizations (14% less likely, P < .0001), fewer hospitalizations per year (P < .001), and fewer hospital hospitalizations per year (P < .001), and fewer hospital hospitalizations per year (P < .001), and fewer hospital hospitalizations per year (P < .001), and fewer hospital hospitalizations per year (P < .001), and fewer hospital hospitalizations per year (P < .001), and fewer hospital hospitalizations per year (P < .001), and fewer hospital hospitalizations per year (P < .001), and fewer hospital hospitalizations per year (P < .001), and fewer hospital hospitalizations per year (P < .001), and fewer hospital hospitalizations per year (P < .001), and fewer hospital hospitalizations per year (P < .001), and fewer hospital hospitalizations per year (P < .001), and fewer hospital hospitalizations per year (P < .001), and fewer hospital hospitalizations per year (P < .001), and fewer hospital hospitalizations per year (P < .001), and fewer hospital hospitalizations per year (P < .001), and fewer hospital hospitalizations per year (P < .001), and fewer hospital hospitalizations per year (P < .001), and fewer hospital hospitalizations per year (P < .001), and fewer hospital hospitalizations per year (P < .001), and fewer hospital hospitalizations per year (P < .001), and fewer hospital hospitalizations per year (P < .001), and fewer hospital hospitalizations per year (P < .001), and fewer hospital hospitalizations per year (P < .001), and fewer hospital hospitalizations per year (P < .001), and fewer hospital hospitalizations per year (P < .001), and fewer hospital hospitalizations per year (P < .001), and fewer hospital hospitalizations per year (P < .001), and fewer hospital hospitalizations per year (P < .001), and fewer hospital hospitalizations per year (P < .001), and fewer hospital hospitalizations per year (P < .001), and fewer hospital.
Implications for Nephrology Nurses

As the number of patients with CKD rises exponentially, there is an increased demand for nephrology nurses with expertise in all areas of practice. For nephrology nurses, it can be difficult to help patients adhere to a complicated management plan that often involves a multitude of medications, planning and modifying a diet, introducing exercise, and coordinating communication with a number of healthcare providers.

The NKF KDOQI guidelines provide a clinical action plan specific for each stage of chronic kidney disease. The plan is cumulative with actions recommended at earlier stages continuing as new actions are added. For patients with Stage 1 CKD, the initial focus is on identifying the cause of the disease and possible comorbidities, as well as instituting management of diet, exercise, and treatment strategies. Patients should be monitored for risk factors that may progress more rapidly and exacerbate the decline in renal function. Nurses are a critical component in monitoring patient diet and exercise progress and tracking the response to medication regimens. At this point, GFR should be estimated at least annually. Patients with CKD are often at higher risk for cardiovascular disease. Monitoring of weight, blood pressure, cholesterol levels, and control of diabetes is critical to reducing cardiovascular risks and preserving renal function.

The progression of renal function must be carefully tracked in patients with Stage 2 CKD. Associated risk factors that may cause a more rapid deterioration of kidney function include severe proteinuria, uncontrolled high blood pressure, poor glycemic control in patients with diabetes and continued smoking. Nurses play an integral role in educating patients to monitor blood pressure and blood glucose levels at home. As patients with CKD progress to stage 3, symptoms become more pronounced. Complications such as SHPT, anemia, and bone disease may become apparent, and the clinical focus shifts to their evaluation and management strategies.

Nurses are the first step in the health care line for emphasizing to patients the importance of recognizing and reporting symptoms. Nurses explain and stress the benefits of following the treatment regimen to patients, their families and significant others. Ideally, patients at CKD Stage 3 will be referred to a nephrologist for care and monitoring in collaboration with nephrology nurses. Nephrology nurses provide support for these patients in a number of ways:

1. Identify and assist in achieving specific health care goals eg monitoring blood pressure, dietary modifications, exercise programs, etc.;
2. Provide support for patients to foster maintenance of their independence;
3. Invite the participation and education of family members in patient care and well-being;
4. Evaluate the patients’ progress;
5. Facilitate revising the plan of care as needed;
6. Assist in referrals to other disciplines as appropriate;
7. Understand patients’ concerns and identify sources for information or contacts when needed.

The nephrology team must prepare the patient with CKD Stage 4 for renal replacement therapy. If renal function continues to decline, nephrology nurses will need to develop and implement a plan of care for pre-emptive kidney transplant or dialysis therapy, or a coordinated schedule for transplantation at a later date. The nephrology nurse is pivotal in preparing the patient for access placement for peritoneal and/or hemodialysis. The nurse can provide intensive management of cardiovascular complications and symptoms of bone disease. Patients with Stage 4 CKD will need instruction to recognize and manage symptoms that may include altered pattern or loss of sleep, fatigue, itching, and loss of appetite. As CKD progresses, nephrology nurses become the first contact point for patients and serve as educator, facilitator, and communicator between and among patient and health care professionals.

Summary/Conclusions

SHPT is an early and serious complication of CKD and contributes to the significant morbidity and mortality of patients on hemodialysis. Treatment of SHPT involves suppression of PTH and prevention of cardiovascular and metabolic complications. Treatment options for SHPT include vitamin D therapies, phosphate binders, and calcimimetics. Calcitriol is effective in treating SHPT, but has a narrow therapeutic range due to hypercalcemia and hyperphosphatemia associated with its use. Doxercalciferol, a prohormone that requires activation by the liver, is also effective in treating SHPT, but is associated with significant elevations of calcium and phosphorous. Paricalcitol has been shown to effectively suppress PTH with less impact on serum calcium and phosphorous levels in patients on hemodialysis.

Active vitamin D therapy demonstrates a survival advantage for patients on hemodialysis. Future studies are necessary to confirm these data and to optimize active vitamin D therapy utilization in treating SHPT in this population.
Finally, although data is limited, there appears to be considerable costs involved in treatment of CKD and associated SHPT. Active vitamin D therapies provide a cost-effective means for treating SHPT and reducing the associated comorbidities that escalate health care costs for these patients.

References


Improvised Patient Outcomes in Chronic Kidney Disease: Optimizing Vitamin D Therapy


Lindberg, J.S., Cullerton, B., Wong, G., Borah, M.F., Clark, R.V., Shapiro, W.B., et al. (2005). Cinacalcet HCl, an oral calcimimetic agent for the treatment of secondary hyper-


Improving Patient Outcomes in Chronic Kidney Disease:
Optimizing Vitamin D Therapy

Frank A. Gesek, PhD, RPh, and Jennifer S. Desmond, MFA, MSN, BSN, FNP-C

Evaluation Instructions
• Answer the open-ended question(s) below.
• Complete the evaluation.
• Send this evaluation form to the ANNA National Office; East Holly Avenue Box 56; Pitman, NJ 08071-0056; or fax this form to (856) 589-7463.
• Enclose a check or money order payable to ANNA. Fees listed in payment section.
• Upon completion of the answer/evaluation form, a certificate for 2.5 contact hours will be awarded and sent to you.
• Please allow 2-3 weeks for processing. You may submit multiple answer forms in one mailing, however, because of various processing procedures for each answer form, you may not receive all of your certificates returned in one mailing.

2.5 Contact Hours
Expires: April 20, 2010
ANNA Member: $15
Regular Price: $25

Complete the Following:
Name: ____________________________________________________________
Address: ____________________________________________________________
__________________________________________________________________
Telephone: ______________________ Email: _____________________________

Payment:
ANNA Member: ____ Yes   ____ No    Member #___________________________
☐ Check Enclosed  ☐ American Express  ☐ Visa  ☐ MasterCard
Total Amount Submitted: _______________________
Credit Card Number: _______________________________ Exp. Date: _______
Name as it Appears on the Card: ________________________________

Special Note
Your posttest can be processed in 1 week for an additional rush charge of $5.00.
☐ Yes, I would like this posttest rush processed. I have included an additional fee of $5.00 for rush processing.

Online submissions through a partnership with HDCN.com are accepted on this posttest at $20 for ANNA members and $30 regular price. CNE certificates will be available immediately upon successful completion of the posttest.

Note: You may photocopy the answer sheet or access this posttest at www.annanurse.org/journal

1. What would be different in your practice if you applied what you have learned from this activity?
__________________________________________________________________
__________________________________________________________________
__________________________________________________________________
__________________________________________________________________
__________________________________________________________________

2. By completing this offering, I was able to meet the stated objectives
a. Relate the pathophysiology of CKD to the development of secondary hyperparathyroidism (SHPT).
b. Describe the ultimate effects SHPT has on body systems.
c. Summarize the current treatment options for SHPT.
3. The content was current and relevant.
4. This was an effective method to learn this content.
5. Time required to complete reading assignment: _________ minutes.

I verify that I have completed this activity ________________________________________________________________________________
(Signature)

GOAL
To increase understanding of causes and treatment of secondary hyperparathyroidism

New Posttest Format
Please note that this continuing education activity does not contain multiple-choice questions. We have introduced a new type of posttest that substitutes the multiple-choice questions with an open-ended question. Simply answer the open-ended question(s) directly above the evaluation portion of the Answer/Evaluation Form and return the form, with payment, to the National Office as usual.