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Consequences and management of hyperphosphatemia in patients with renal insufficiency

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Consequences and management of hyperphosphatemia in patients with renal insufficiency. Progressive renal insufficiency leads to hyperphosphatemia, hypocalcemia, and secondary hyperparathyroidism. Bone demineralization in secondary hyperparathyroidism may induce fractures, while joint and subcutaneous precipitations of calcium pyrophosphate limit mobility, and may cause crippling. Strategies to preempt bone and joint destruction in chronic kidney disease and end-stage renal disease have focused on limiting dietary phosphorus, intra-gut binding of ingested phosphorous, enhancing calcium absorption, and limiting parathyroid hormone secretion. Deciding which regimen is most effective to meet these treatment objectives challenges nephrologists; they often uncover conflicting evidence about which abnormal metabolite should be the prime treatment objective. Especially vexing is the question of whether hypercalcemia is a cardiotoxic consequence of calcium-based phosphate binders.

Chronic kidney disease inducing progressive decrease in renal function is estimated by an expert committee of the National Kidney Foundation [1] to occur in about 20 million individuals in the United States. Chronic renal failure results in reduced synthesis of vitamin D by the kidneys and increased retention of phosphorus. Disturbances in calcium and phosphorous metabolism in patients with chronic kidney disease (CKD) can result in secondary hyperparathyroidism, along with ensuing bone disease, soft tissue and vascular calcification, as well as arterial stiffness and artherosclerosis [2]. This review will focus on the consequences of secondary hyperparathyroidism in the context of CKD. The challenges in treating altered mineral metabolism and the resulting renal and cardiac complications will also be discussed.

CKD and secondary hyperparathyroidism

In patients with end-stage renal disease (ESRD), kidney failure results in decreased secretion and increased retention of phosphate. This causes hyperphosphatemia, a condition that results in the development of secondary hyperparathyroidism and renal osteodystrophy. Secondary hyperparathyroidism is characterized by parathyroid gland hyperplasia and increased synthesis of parathyroid hormone (PTH) [3]. Secondary hyperparathyroidism is usually quadraglandular, and results from the combined effect of altered calcium phosphate metabolism and vitamin D production. In addition to increased phosphate retention, patients with ESRD have reduced production of active vitamin D, resulting in hypocalcemia and increased PTH. Over time, these factors result in parathyroid gland hyperplasia, autonomous production of PTH, and tertiary hyperparathyroidism [4]. Figure 1 outlines multiple factors involved in the pathogenesis of secondary hyperparathyroidism, including low levels of vitamin D, hypocalcemia, altered parathyroid gland function, and skeletal resistance to PTH. High levels of circulating PTH result in bone loss and other systemic defects, such as cardiovascular complications that increase mortality in patients with renal failure. The metabolism of calcium, phosphorous, and vitamin D plays an important role in secondary hyperparathyroidism.

Impaired renal production of 1,25-dihydroxyvitamin D (calcitriol), the active hormonal form of vitamin D, contributes to the generation and maintenance of secondary hyperparathyroidism in patients with CKD [5]. Calcitriol represses parathyroid cell proliferation and PTH synthesis. CKD patients have reduced levels of calcitriol, which results in high serum PTH levels [6]. Calcitriol deficiency results in indirect secondary hyperparathyroidism due to decreased intestinal absorption of calcium. The progression of CKD, as determined by glomerular filtration rates, is associated with decreased levels of 1,25-dihydroxyvitamin D and a corresponding increase in PTH levels, as shown in Figure 2 [7]. In this report, PTH levels were compared in 58 diabetic and 268 nondiabetic patients with serum creatinine levels >1.2 mg/dL. Diabetic patients with creatinine clearance <70 mL/min had lower PTH levels than did nondiabetic patients ($P = 0.003$), as well as significant differences in serum phosphorus, magnesium, and tubular resorption of phosphate. Serum glucose concentration in those with diabetes varied inversely with PTH, leading to the inference that poor control of diabetes (hyperglycemia) may contribute to development of hypoparathyroidism in patients

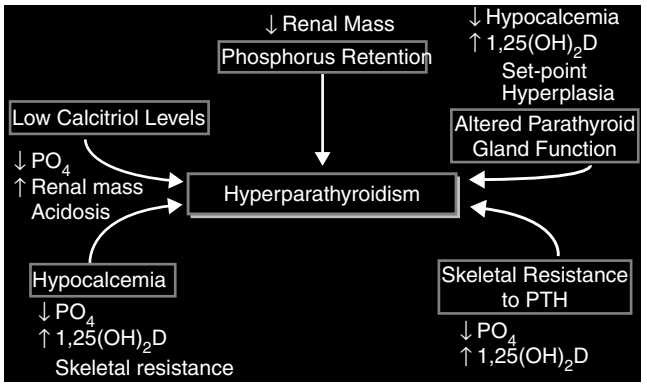

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Fig. 1. Pathogenesis of secondary hyperparathyroidism. Low levels of calcitriol (vitamin D), hypocalcemia, altered PTH gland function, and skeletal resistance to PTH contribute to the pathogenesis of secondary hyperparathyroidism in ESRD patients.

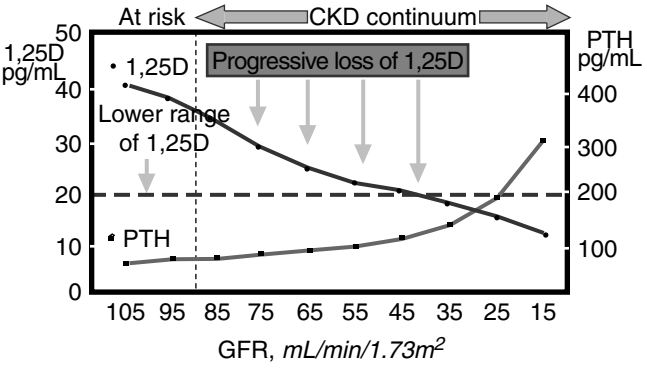

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Fig. 2. Vitamin D levels and the progression of chronic kidney disease (CKD) [6]. Patients with progressive CKD, as determined by glomerular filtration rates (GFR), have decreased levels of vitamin D and a corresponding increase in parathyroid hormone (PTH) levels.

with diabetes and renal insufficiency. Indeed, treatment with 1,25-dihydrovitamin D results in decreased PTH gene transcription and, consequently, decreased PTH production.

Low serum levels of calcium also result in the increased stability of PTH mRNA, which increases the secretion of PTH and parathyroid cell proliferation [8]. The effects of calcium on the parathyroid gland are mediated by a membrane-bound calcium-sensing receptor. Increased levels of serum phosphorus have similar effects in regulating PTH levels. The effects of low calcium levels and high phosphorus levels regulate PTH levels post-transcriptionally via the altered binding of cytosolic proteins to the 3′-untranslated region of the PTH mRNA [9].

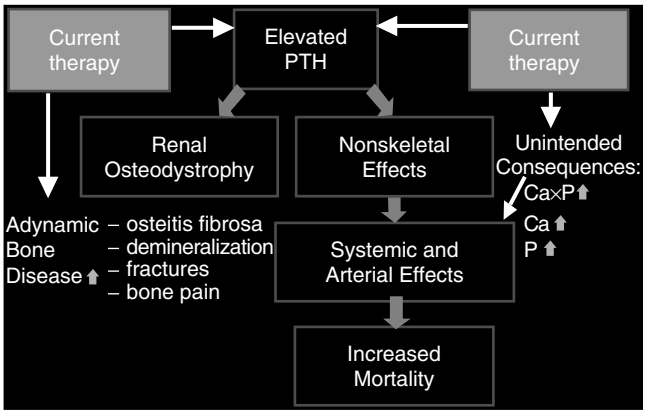

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Fig. 3. Clinical consequences of secondary hyperparathyroidism. Increased risk of cardiovascular and bone disease arises as a result of elevated PTH levels.

EFFECTS OF SECONDARY HYPERPARATHYROIDISM

Secondary hyperparathyroidism occurs in patients with CKD due to a combined effect of hyperphosphatemia, hypocalcemia, increased calcium phosphate (Ca × P) product, and reduced synthesis of vitamin D. Alterations in the metabolism of these minerals is a part of an interrelated cascade that contributes to bone and joint destruction [10]. Additional potential devastating effects on the cardiovascular system, such as cardiovascular calcification, are often seen in patients with ESRD [3]. Figure 3 summarizes the clinical consequences of increased PTH in renal bone disease (osteitis fibrosa, bone pain, demineralization, and fractures) and increased cardiovascular risk.

Bone and joint destruction

The altered calcium and phosphorous metabolism in secondary hyperparathryroidism leads to bone demineralization resulting in fractures of the joint [11]. Additionally, subcutaneous deposits of calcium pyrophosphate limit mobility in patients with CKD. PTH is normally anabolic for bone, but excess levels result in catabolism of bone [12]. In most patients with CKD, a functional and usually actual excess of PTH destroys bone by stimulating the action of osteoclasts, which act to dissolve bone and cause pathologic fractures. Calcium pyrophosphate deposits in the joints of patients with CKD cause arthropathy, crippling joint pain, and swelling accompanied by osteoclast-induced erosion of bone. In children and young adults with slowly progressive renal osteodystrophy, terminal distal phalangeal osteolysis and clubbing are typical. Progressive bone dissolution may be clinically silent until a minor injury produces a pathologic fracture of the wrist, arm, or hip.

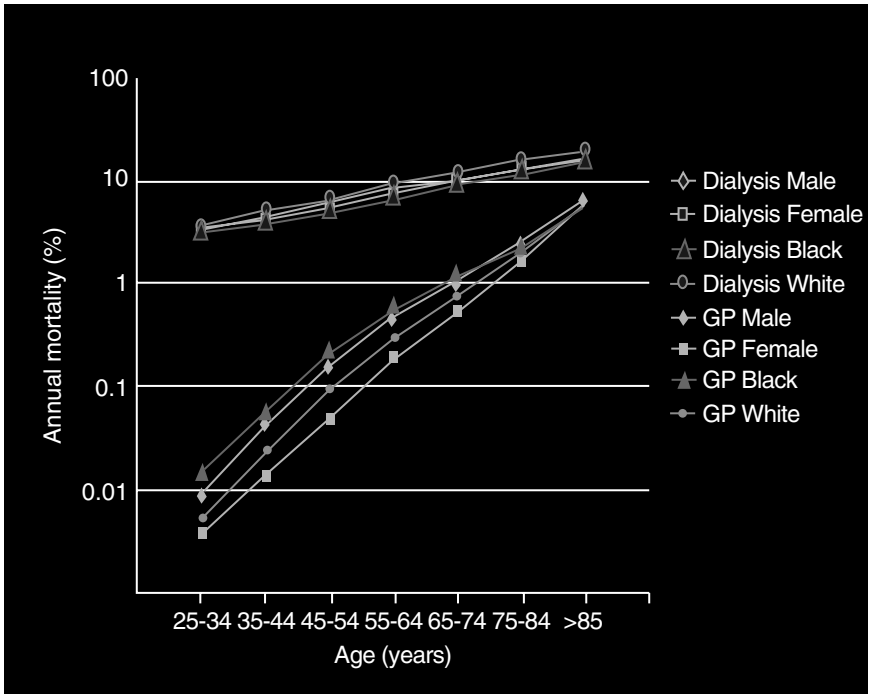

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Fig. 4. Cardiovascular mortality in CKD patients compared with their counterparts in the general population (GP). Increased percent annual mortality is seen in dialysis patients regardless of age, sex, or ethnicity [12].

Cardiovascular calcification

Vascular calcification, a marker of atherosclerosis and arterial stiffness, is commonly seen in dialysis patients, and is a risk factor for mortality. A proposed mechanism for accelerated coronary artery calcification is based on the observation that ESRD patients with more coronary calcification had reduced skeletal mass due to calcium mobilization from the bone.

An epidemiologic report indicated increased cardiovascular mortality in dialysis patients compared with that of the general population [13]. Among patients treated by hemodialysis or peritoneal dialysis, the prevalence of coronary artery disease is approximately 40%, and the prevalence of left ventricular hypertrophy is approximately 75%. According to an earlier report by the same group [14], approximately 9% per year die of cardiovascular disease. Adjusting for age, gender, race, and the presence or absence of diabetes, indicates that cardiovascular mortality in dialysis patients is 10 to 20 times higher than in the general population. Also, cardiac failure is more common in chronic renal disease patients than in the general population, and is an independent predictor of death in chronic renal disease. The prevalence of cardiac failure in hemodialysis and peritoneal dialysis patients is approximately 40%. Often it is difficult to determine whether cardiac failure reflects left ventricular dysfunction or extracellular fluid volume overload. Figure 4 summarizes the results of this group's experience, and shows increased annual mortality in subgroups of patients with renal failure and on dialysis, compared with their counterparts in the general population, regardless of age, gender, or ethnicity. Indeed, after stratification for age, gender, race, and diabetes, cardiovascular morbidity and mortality in dialysis patients were 10 to 20 times higher compared with the general population. Cardiac failure was also higher and seen in approximately 40% of patients on hemodialysis and peritoneal dialysis. Coronary artery calcification is thought to be a contributing factor to this increased mortality. Metastatic calcification in the heart and muscles of the lower extremities has been reported in patients with secondary hyperparathyroidism [15].

Using electron beam computed tomography (EBT), Braun et al have suggested that cardiovascular calcification in dialysis patients is a result of lower vertebral bone mass, and not from altered calcium and phosphate metabolism [16]. EBT is a noninvasive, extensively used method to detect cardiac calcification in coronary arteries of dialysis patients. The rate of calcification was studied in 49 chronic hemodialysis patients, compared with 102 nondialysis patients with documented or suspected coronary artery disease (CAD). All individuals in this study had undergone coronary angiography. A total of 30 axial slices with 30 mm distance between the slices was used to measure the number of calcifications. The surface area was measured; average and highest density values obtained were used to calculate a quantitative coronary artery calcium score. Hemodialysis patients had a 2.5- to

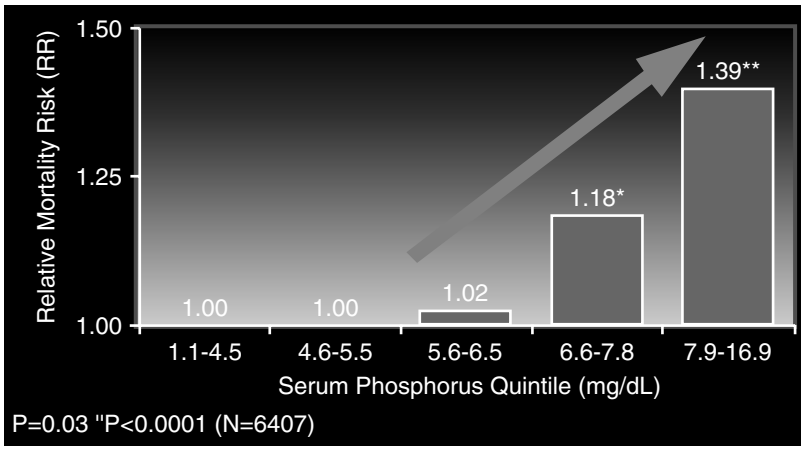

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Fig. 5. Elevated serum phosphorus levels is associated with increased risk of mortality in dialysis patients. Increased serum phosphate (>6.5 mg/dL) in CKD patients is associated with increased risk of mortality.

5-fold higher coronary artery calcium score that correlated with a lower vertebral bone mass compared with nondialysis patients. However, no correlation between serum calcium, phosphate, or PTH levels with the calcium score was seen. Progress in calcification was seen at a 12-month follow-up of these patients. Higher calcium scores correlated with lower vertebral bone mass in dialysis patients.

Due to the prevalence of hyperphosphatemia in ESRD patients, and the associated increased cardiovascular mortality, Ganesh et al studied the mechanism mediating this risk. Data from two large random samples of patients on hemodialysis ($N = 12{,}833$) in the United States were used to test the hypothesis that elevated serum phosphate contributes to cardiac causes of death [17]. A 2-year follow-up for the relative risk (RR) of CAD, sudden death, and other cardiac causes was determined with respect to serum phosphorus, Ca × P product, and serum PTH levels. High cardiovascular mortality was seen in patients with elevated serum phosphate (>6.5 mg/dL), compared with the low phosporus group (≤6.5 mg/dL). Elevated levels of serum P, Ca × P product, and PTH have been implicated in the altered control of phosphate metabolism. Additionally, serum calcium and calcium-based binders were not found to be risk factors for cardiovascular mortality in this report.

TREATMENT GOALS

Because hyperphosphatemia and increased Ca × PO_4 products are associated with increased mortality in dialysis patients, it is important to effectively manage and treat hyperphosphatemia and the resulting hyperparathyroidism in patients with CKD. The aim of the strategy for prevention and treatment should be 3-fold: to reduce hyperphosphatemia and the pathogenesis of phosphate retention, restore synthesis of active vitamin D, and bring the calcium concentration back to normal levels.

Management of hyperphosphatemia

Increased risk of mortality and secondary hyperparathyroidism in dialysis patients occurs when the serum phosphorous levels exceed 6.5 mg/dL and the Ca × P product exceeds 72 mg^2/dL^2. Because of the morbidity and mortality associated with patients with ESRD, data available for serum phosphate were analyzed from two large, random, cross-sectional studies of patients on hemodialysis for at least 1 year. Data were analyzed for patients in the United States Renal Data System, the Case Mix Adequacy Study, and the Dialysis Morbidity and Mortality Study Wave [18]. The relative risk (RR) of death for patients with serum phosphorus greater than 6.5 mg/dL was 1.27 compared with those with serum phosphorus levels between 2.4 and 6.5 mg/dL. The link between higher risk of death and serum phosphorous concentration, however, was not uniform across all the quintiles of serum phosphate analyzed. Figure 5 is a graphic depiction of these data. Patients in the highest 2 quintiles of serum phosphorus are at the greatest risk for mortality. For example, patients in the serum phosphorus quintiles of 6.6 to 7.8 mg/dL and 7.9 to 16.9 mg/dL are predicted to have a mortality risk of 1.18 and 1.39, respectively. The Ca × P product showed a mortality risk trend similar to that seen with serum phosphorus. However, the analysis of serum calcium in this study showed no correlation with the relative risk of death. These observations have resulted in recommendations that serum phosphorous be controlled between 2.5 and 6.5 mg/dL, and the Ca × P be maintained at less than 52 mg^2/dL^2 [18].

The most effective means of controlling hyperphosphatemia is managing dietary phosphorous intake. A typical American diet provides approximately 1300 mg of phosphorous daily from a protein-rich meal. The

recommended dietary allowance for phosphorus is 700 mg/day. Increased dietary intake of phosphorus, combined with elevated serum phosphorous levels resulting from altered mineral metabolism in dialysis patients, are associated with vascular and visceral calcification. A recent study involving 63 dialysis patients showed the effectiveness of dietary education in controlling hyperphosphatemia [19]. At the onset of the study, patients had mean serum phosphorous levels >6 mg/dL. A significant difference ($P < 0.01$) in serum phosphorus (6.8 ± 0.72 mg/dL and 5.2 ± 1.2 mg/dL before and after 6 months of education, respectively) and in the Ca × P product levels (61 ± 7.7 mg^2/dL^2 and 47 ± 11 mg^2/dL^2 before and after 6 months of counseling, respectively) was observed in the group of patients who had received dietary counseling and educational tools, compared with a control group of patients (phosphorus: 7.2 ± 1.3 mg/dL and 6.7 ± 1.7 mg/dL before and after 6 months education, respectively; Ca × P product: 62 ± 9.6 mg^2/dL^2 and 60 ± 14.3 mg^2/dL^2 before and after 6 months of education, respectively).

However, dietary phosphorous restriction and hemodialysis are often not effective in adequately controlling serum phosphorous, and phosphate binders have been routinely prescribed to reduce the intestinal absorption of phosphorous. Various estimates of patient compliance indicate that the side effects of constipation and nausea may cause as many as one half of a dialysis population to discontinue regular use of phosphate binders. Although aluminum-based phosphate binders have been effectively used in reducing levels of serum phosphorus, the risk of toxicity due to aluminum absorption is high. Increased incidence of aluminum-induced bone disease, osteomalacia, encephalopathy, and microcytic anemia seen in CKD patients has resulted in abandoning the use of aluminum-based phosphate binders [20].

Calcium-based phosphate binders have been effective in combination with vitamin D, and have replaced aluminum-binders worldwide; calcium acetate is the binder of choice in the United States, and calcium carbonate is used extensively in Europe [21]. The efficacy and cost effectiveness of calcium-based binders have been outweighed by concern for the long-term safety of these agents. These agents have a risk of metastatic calcification, particularly if taken with vitamin D analogues, and are prescribed when a high dialysate calcium concentration is employed. The major advantage of calcium-based phosphate binders is their low cost, and long experience in their use for "hyperacidity" with minimal toxicity to those who have been treated daily with proprietary antacids for a decade or longer.

However, the debate about the safety of calcium-based phosphate binders continues. Treating dialysis patients with these agents results in a higher oral calcium intake, conferring an additional risk of coronary calcification and death. Goodman et al used EBCT to screen for coronary-artery calcification in 39 young patients with ESRD (mean age 19 years) compared with 60 normal individuals [22]. This study reports an increase in the mean serum phosphorus concentration and the Ca × P product in serum of ESRD patients with coronary calcification. The daily intake of calcium-containing phosphate binders was nearly twice as great in ESRD patients with cardiac calcification as in those patients without calcification. These observations suggest that the long-term exposure to alterations in mineral metabolism seen in ESRD patients, and the subsequent efforts to treat and correct these alterations may contribute to coronary artery calcification in young adults.

An alternative phosphate binder that is not aluminum- or calcium-based is sevelmer hydrochloride, a quaternary amine anion exchange resin that binds phosphate ions and releases hydrochloric acid [23]. A randomized 52-week "Treat-to-Goal " trial compared sevelamer hydrochloride to two calcium-containing phosphate binders in a group of 200 hemodialysis patients [24]. The primary end point of this trial was to achieve Ca × P product target levels, and to estimate calcification of the coronary arteries using a calcification score from EBCT measurements. Both sevelamer hydrochloride and the calcium-based phosphate binders provided equivalent control of serum phosphorus. However, serum calcium concentration, hypercalcemia, and an increased absolute calcium score in coronary arteries were seen in patients treated with calcium, but not with sevelamer.

These data contrasted with those reported in the Calcium Acetate Renagel® Evaluation (CARE) study (discussed by Dr. Nolan in this supplement). The CARE study compared the efficacy and safety of calcium acetate and sevelamer hydrochloride in the treatment of hyperphosphatemia in CKD patients [25]. In this 8-week trial, treatment with calcium acetate was found to be more effective in controlling serum phosphorous and Ca × P product levels than treatment with sevelamer hydrochloride. Side effects were similar for patients treated with calcium acetate or sevelamer hydrochloride.

In a recent review, Coladonato et al suggest that the warnings of putative dangers associated with calcium-containing phosphate binders appear to be premature in the context of risk versus benefits of calcium-containing phosphate binders [26]. The need for prospective, randomized control trials to examine the pathobiology of coronary calcification in CKD and ESRD patients is essential. Studies that examine differences in the rates of calcification in calcium-containing and calcium-free phosphate binders, when controlling hyperphosphatemia and hyperparathyroidism, would help resolve some of these issues. A recommendation is made on the importance of having outcome-based trials, using clinical cardiac events as primary outcomes—along with

thorough scientific research—before abandoning the use of calcium-containing phosphate binders.

Restoring vitamin D and calcium levels

In an attempt to restore vitamin D levels, patients with CKD are also treated with vitamin D derivatives. Until recently, high doses of oral calcium supplements and/or 1-α-hydroxylated vitamin D derivatives were the mainstay of treatment of secondary hyperparathyroidism in CKD. However, these treatments may not be well tolerated due to the associated vascular and soft tissue calcification. An association between vascular calcification and the use of vitamin D therapy has been reported [27]. To circumvent the adverse effects observed with vitamin D therapy, calcimimetic agents are under development.

Calcimimetics

Calcimimetic agents modulate the activity of the calcium-sensing receptor, and result in profound reductions in levels of circulating PTH. Additionally, these agents result in decreases in serum calcium, phosphorus, and Ca × P product [28]. A recent study with the second generation calcimimetic agent, cinacalcet HCl, confirms that this agent represents a safe and effective novel therapy with the potential to dramatically alter the treatment and complications associated with secondary hyperparathyroidism in patients on dialysis. Block et al report the observations from two randomized double-blind placebo trails evaluating the safety and effectiveness of cinacalcet in hemodialysis patients who were unable to control the secondary hyperparathyroidism despite standard treatment [29]. Patients received cinacalcet ($N = 371$) or placebo ($N = 370$) for a period of 26 weeks. The once-daily dosage was increased from 30 mg to 180 mg to achieve intact PTH levels of 250 pg/mL or less. The primary end point was percent of patients with PTH levels in this range during a 14-week efficacy assessment. Mean PTH levels decreased 43% in patients receiving cinacalcet compared with controls ($P < 0.001$). The Ca × P product decreased 15% in the cinacalcet treated group compared with the placebo control group ($P < 0.001$) [29]. The development of calcimimetic agents may dispel the controversy that has prevailed over the use of calcium-based phosphate binders in conjunction with vitamin D therapy.

CONCLUSION

Hypocalcemia, hyperphosphatemia, and reduced vitamin D seen in patients with CKD are associated with elevated levels of PTH and secondary hyperparathyroidism. The clinical consequences of increased PTH levels include renal osteodstrophy, systemic and arterial effects that increase mortality. It is important to control serum phosphorus levels in dialysis patients because hyperphosphatemia and the elevated Ca × P correlate with cardiovascular mortality and bone disease. Currently, both sevelamer and calcium-containing phosphate binders (calcium acetate and calcium carbonate) are acceptable first-line therapeutic agents in the treatment of ESRD patients with hyperphosphatemia. Cost-benefit analysis, and the superior efficacy of calcium acetate in controlling serum phosphorous, make it a treatment choice for initial treatment of ESRD patients. Sevelamer hydrochloride, the noncalcium-, nonaluminum-containing phosphate binder is the preferred treatment choice for patients who develop persistent hypercalcemia during treatment with the calcium-based phosphate binders. This treatment, however, has the potential risk of acid loading in ESRD patients.

Sevelamer hydrochloride and calcium acetate are the only two drugs approved by the FDA in the treatment of hyperphosphatemia in dialysis patients. Ongoing studies with calcimimetic agents will offer alternate therapeutic choices for patients with CKD.

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