Control of Hyperphosphatemia among Patients with ESRD

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Derangements of mineral metabolism occur during the early stages of chronic kidney disease (CKD). Hyperphosphatemia develops in the majority of patients with ESRD and has long been associated with progression of secondary hyperparathyroidism and renal osteodystrophy. More recent observational data have associated hyperphosphatemia with increased cardiovascular mortality among dialysis patients. Adequate control of serum phosphorus remains a cornerstone in the clinical management of patients with CKD not only to attenuate the progression of secondary hyperparathyroidism but also possibly to reduce the risk for vascular calcification and cardiovascular mortality. These measures include dietary phosphorus restriction, dialysis, and oral phosphate binders. Dietary restriction is limited in advanced stages of CKD. Phosphate binders are necessary to limit dietary absorption of phosphorus. Aluminum hydroxide is an efficient binder; however, its use has been nearly eliminated because of concerns of toxicity. Calcium salts are inexpensive and have been used effectively worldwide as an alternative to aluminum. Concerns of calcium overload have led to the investigation of alternatives. Currently, only two Food and Drug Administration–approved noncalcium, nonaluminum binders are available. Sevelamer hydrochloride is an exchange resin and was not as effective as calcium acetate in meeting new guideline recommendations in one double-blind clinical trial. Lanthanum carbonate is a rare earth element and has been studied less extensively. Concerns of long-term administration and toxicity exist. Furthermore, these agents are significantly more expensive than calcium salts, which may contribute to patient noncompliance.

Dietary Restriction

Dietary phosphate restriction has been shown to prevent the development of HPTH early in the course of disease, as well as increase plasma calcitriol levels and inhibit parathyroid cell proliferation (9,10). Furthermore, phosphorus restriction may be instrumental in preventing progressive renal failure and soft tissue calcification (11,12).

The average diet in North America and Europe contains approximately 1000 to 1500 mg of phosphorus per day (13). Patients with ESRD absorb approximately 50 to 60% of dietary phosphorus, and as GFR declines, urinary phosphorus excretion is inadequate to maintain normal homeostasis, resulting in a positive phosphorus balance (14). Vitamin D administration aggravates this problem by increasing intestinal absorption of dietary phosphorus and calcium (15).

Aggressive dietary phosphate restriction among patients with CKD is impractical and could compromise overall nutrition, particularly protein intake (16). For preventing malnutrition among patients with CKD, the NKF–K/DOQI guidelines recommend a minimum protein intake of 1.2 g/kg per d (approximately 800 to 1000 mg/d phosphorus). As renal function
Dialysis

The clearance of phosphorus varies among the different modalities of dialysis. Ideally, adequate dialysis in any form would remove adequate amounts of all uremic toxins, including phosphorus. Unfortunately, conventional, thrice-weekly hemodialysis (4 h duration) removes approximately 900 mg of phosphorus each treatment (an average of only 300 mg/d) (18). Conventional, intermittent hemodiafiltration improves phosphorus removal modestly (1030 to 1700 mg/treatment) (19), but overall, conventional, intermittent hemodialysis provides inadequate removal of phosphorus. This seems to be due to the high postdialysis rebound from mobilization of phosphorus from the intracellular space and/or bone induced by intradialytic removal of this solute. Moreover, the clearance of phosphorus during peritoneal dialysis is comparable or inferior to that of conventional hemodialysis, especially when intradialytic protein loss is taken into consideration (20). Hence, the need for phosphate binders for the majority of patients with ESRD is predictable.

One approach to overcome this rebound is quotidian hemodialysis. Short, daily hemodialysis utilizes blood flow rates (Qb) of 450 ml/min, dialysate flow rates (Qd) of 800 ml/min, a duration of 1.5 to 2.5 h, and a frequency of six to seven treatments per week. Alternatively, slow nocturnal hemodialysis (NH) entails Qb of 150 to 300 ml/min, Qd of 300 ml/min, duration of 6 to 8 h, and a frequency of six to seven nights per week. During a 4-yr observational study that compared patients who received conventional, intermittent hemodialysis; short, daily hemodialysis; and NH, the only modality of dialysis to show a significant reduction in the serum phosphorus levels and eliminate the need for phosphate binders was NH (21–23). Some patients actually required phosphorus supplementation during the study (22), as well as adjustments to dialysate calcium levels as a result of significant reductions in serum calcium levels (23). NH has also been associated with improved solute clearance, quality of life, BP control, and reduction in medication requirements. However, obstacles to its use on a larger scale include unfamiliarity with home hemodialysis, as well as issues with reimbursement and cost of equipment and nonreusable materials.

Phosphate Binders

Aluminum Hydroxide

The use of phosphate binders began in the early 1970s, when the importance of phosphorus control was first emphasized. Use of aluminum-containing phosphate binders was the standard of care among patients with ESRD. Aluminum hydroxide was a very efficient phosphate binder (24). Unfortunately, long-term use was associated with aluminum accumulation and toxicity, manifesting itself as encephalopathy, osteomalacia, microcytic anemia, and myopathy (25–27). Subsequently, the use of aluminum hydroxide has been limited to salvage, short-term therapy or abandoned entirely.

Calcium Carbonate

Calcium salts then emerged as an alternative to aluminum as a phosphate binder. It was well established that calcium salts bound dietary phosphorus, although less efficiently than aluminum (28). Calcium carbonate has been used extensively worldwide since the early 1980s because of its efficacy, tolerability, and affordability (29–31).

One prospective, randomized, open-label trial suggested that high-dose calcium carbonate was effective as monotherapy to control mild to moderate secondary HPTH (PTH 150 to 600 pg/ml) among hemodialysis patients (32). Indridason et al. (32) randomly assigned 52 patients to receive escalating doses of calcium carbonate alone, daily oral calcitriol, or intermittent intravenous (IV) calcitriol. The calcitriol groups received calcium carbonate in fixed doses. The mean serum phosphorus was significantly lower in the calcium carbonate group throughout the study and was 3.5 mg/dl at the treatment end of 36 wk. However, this required a mean dose of 7 g/d elemental calcium. The oral and IV calcitriol groups required aluminum hydroxide to help control hyperphosphatemia. PTH levels were significantly decreased in all groups but most notable in the IV calcitriol group (240 ± 37.7 to 65 ± 10 pg/ml). Although not statistically significant, there was a trend toward fewer hypercalcemic episodes in the calcium carbonate group. No adverse effect on surrogate markers of bone metabolism was noted with the administration of calcium carbonate.

Overall, calcium carbonate adequately controls phosphorus; however, its effectiveness may be limited by hypercalcemia. Calcium carbonate contains a high proportion of elemental calcium (40%), and hypercalcemia can occur when given at escalating doses (33), when administered concomitantly with vitamin D (which increases gastrointestinal [GI] absorption of calcium), or with use of higher dialysate calcium concentrations (31,34). Furthermore, the proportion of calcium absorbed from phosphate-binder intake dramatically increases when there is unsynchronized administration in relation to meals. Significantly more elemental calcium is absorbed when calcium carbonate is given on an empty stomach or 2 h after meals compared with administration before or directly after meals (35).

Calcium Acetate

Calcium acetate (PhosLo, Nabi Pharmaceuticals, Boca Raton, FL) is an alternative to calcium carbonate as a phosphate binder and contains less elemental calcium (25%) than calcium carbonate. GI washout studies have shown that the amount of phosphorus bound per amount of calcium absorbed was almost twice as great with calcium acetate compared with calcium carbonate (36). Moreover, Mai et al. (37) showed that phosphorus absorption decreased to 40% of the ingested load with calcium carbonate compared with 21.7% with an equivalent amount of calcium acetate. Thus, among patients with ESRD, calcium acetate binds approximately twice the amount of phosphorus per amount of calcium absorbed (38,39). This is believed to be attributable to the increased solubility of calcium acetate in both acid and alkaline solutions in vitro.

Calcium acetate is well tolerated and has been shown to significantly reduce and maintain serum phosphorus and cal-
cium × phosphorus product levels during a long-term clinical trial (40). This prospective, randomized, controlled trial was undertaken to prove that sevelamer hydrochloride was more effective in lowering the Ca × PO₄ product compared with calcium-containing phosphate binders. During the 52-wk treatment phase, study patients experienced significant reductions in serum phosphorus and Ca × PO₄ product, and no significant difference was noted between treatment arms.

Hypercalcemia, however, has been associated with both calcium carbonate and calcium acetate ingestion. Growing concerns have been voiced regarding calcium loading and its putative role in the progression of cardiovascular calcifications and the increased cardiovascular mortality among patients with ESRD. Although associations have been drawn from cross-sectional observational studies and one prospective, randomized trial (40), the burden of proof for causation remains unmet given the limitations of study design, failure to account for confounders such as established risk factors for cardiovascular disease (dyslipidemia, smoking, oxidative stress, hyperhomocysteinemia, inflammation [C-reactive protein]), and a flawed causal pathway linking calcium ingestion in the form of phosphate binders with coronary calcification (41). Nonetheless, alternatives to calcium-containing binders are necessary and wisely have been explored in greater magnitude.

Noncalcium, Nonaluminum Phosphate Binders

Magnesium Salts
Magnesium hydroxide and carbonate have been studied as adjuncts or alternatives to calcium-based binders over the years. However, these agents are not particularly effective as phosphate binders, and adjustments in dialysate magnesium are necessary (42). Given the lower efficacy of phosphorus binding of magnesium salts, larger doses are required and adverse GI effects such as diarrhea, hyperkalemia, and hypermagnesemia are often treatment limiting (43–45). MagnEBind (Nephro-Tech Inc., Shawnee, KS) is a commercially available binding agent that contains varying amounts of magnesium chloride. It is considered a dietary supplement; therefore, the safety and efficacy of this agent as a phosphate binder has not been evaluated by the Food and Drug Administration (FDA).

Sevelamer Hydrochloride
Sevelamer hydrochloride (RenaGel, Genzyme Corp., Cambridge, MA) is a novel nonaluminum, noncalcium phosphate-binding polymer. Sevelamer is a hydrogel of cross-linked poly(allylamine) and is completely resistant to digestive degradation and, therefore, not absorbed from the GI tract. It is an exchange resin that binds dietary phosphorus and releases chloride (46). Multiple clinical studies have demonstrated that sevelamer lowers serum phosphorus levels among patients with ESRD and is generally well tolerated (40,47,48). Furthermore, sevelamer binds bile acids and thereby reduces fecal bile acid excretion and lowers LDL cholesterol (49).

Use of sevelamer has gained support in light of growing concerns of calcium loading and hypercalcemia. In fact, sevelamer therapy has been associated with hypocalcemia, and study subjects often required the administration of 1 g of elemental calcium at bedtime during clinical studies (40,47–50).

Several open-label studies that compared sevelamer and calcium salts have suggested similar abilities to lower and maintain serum phosphorus levels (40,46–50). However, sevelamer has not consistently reduced serum phosphorus levels to the newly recommended NKF–K/DOQI targets in these previous studies.

To date, one prospective, double-blind, randomized, controlled trial has determined whether calcium acetate or sevelamer hydrochloride best achieves recently recommended treatment goals of phosphorus and Ca × PO₄ product (51). During the 8-wk study, patients were randomly assigned to either calcium acetate or sevelamer. Initial doses were determined by postwashout phosphorus levels consistent with package inserts of both agents. After 3 wk of therapy, the calcium acetate recipients reached the NKF–K/DOQI target serum phosphorus level of ≤5.5 mg/dl; however, this goal was never achieved in the sevelamer group. Serum calcium level was significantly higher in the calcium acetate group; the goal Ca × PO₄ product was achieved within 2 wk and was maintained throughout the study period. This study was the first to show that calcium acetate more effectively lowered serum phosphorus and Ca × PO₄ product compared with sevelamer hydrochloride.

These results conflict with a previous, open-label clinical trial that compared sevelamer with calcium salts (both carbonate and acetate) (40). In that study, there was no difference in the primary end point, control of Ca × PO₄ product, but there was an attenuation of coronary and aortic calcification as measured by electron-beam computed tomography. The exact mechanism(s) and implication(s) remain uncertain given the current state of scientific evidence. Some would argue that sevelamer was underdosed during the CARE Study (51). However, the achieved dose of sevelamer (17.2 capsules, or 6.9 g/d) was higher than those administered in the Treat-to-Goal Study (6 g/d). One reason for the discrepancy may be the bias associated with open-label trials. Alternatively, the investigators postulated that better control of phosphorus in the calcium acetate group was related to a decreased phosphorus release from bone as a result of better correction of metabolic acidosis (52).

Aside from efficacy, other concerns regarding the use of sevelamer exist. Because phosphate is bound in exchange for hydrochloric acid, lower levels of serum bicarbonate have been noted with long-term administration compared with calcium salts (40,51). In at least one clinical trial, the serum bicarbonate levels fell below the NKF–K/DOQI targets (52), and further investigation on the effects of metabolic acidosis may be necessary. Also, sevelamer remains one of the most expensive phosphate binders currently available. Nevertheless, sevelamer remains an important therapy in the control of hyperphosphatemia among patients with ESRD.

Lanthanum Carbonate
Lanthanum carbonate (Fosrenol, Shire US Inc., Wayne, PA) is a rare earth element that was approved recently by the FDA for the treatment of hyperphosphatemia among patients with
ESRD. Lanthanum belongs to a group known as the “lanthanides” and has a low solubility. In the acid environment of the stomach and upper small intestine, lanthanum dissociates sufficiently to become available for phosphate binding. In laboratory experiments, lanthanum was found to be as effective as aluminum hydroxide and more effective than calcium carbonate or sevelamer hydrochloride at binding dietary phosphate at equivalent doses (53). Several clinical trials have shown that lanthanum is effective and well tolerated among healthy volunteers as well as hemodialysis patients (54,55). In short-term studies, lanthanum significantly reduced serum phosphorus levels and Ca × PO₄ product compared with placebo among patients with ESRD (56–59). Lanthanum carbonate therapy in doses ranging from 1500 to 3000 mg/d, however, was unable to lower the serum phosphorus below 5.5 mg/dl in any of these trials.

Lanthanum is not metabolized and has a low GI absorption. Its main route of elimination is biliary. However, in long-term clinical studies, patients who were administered lanthanum carbonate at various doses developed increased serum levels (60). In light of past experiences with chronic aluminum ingestion and toxicity, long-term safety with lanthanum carbonate remains a great concern. In two different rat models of CKD, the oral administration of lanthanum led to more than a 10-fold increase of tissue content in the liver, lung, and kidney (61). Furthermore, rats that were administered large doses of lanthanum for 12 wk showed a dose-dependent decrease in bone formation rate and osteomalacia (62). However, this may have been related to phosphorus depletion rather than lanthanum toxicity (63).

Given the toxic effects of mineral and metal accumulation reported in the past, the long-term effects of lanthanum on bone have been an area of speculation. Before FDA approval, long-term outcomes on bone morphology were required. In a prospective, randomized, parallel study, 197 patients were randomly assigned to receive either lanthanum carbonate or the standard phosphate binder. Bone biopsies were obtained at either 1 or 2 yr of treatment (64,65). During these trials, treatment with lanthanum carbonate was not associated with any significant shift on the classification of bone disease, and there was no incidence of osteomalacia as seen on bone biopsies in either group. Moreover, 11 patients who had been receiving lanthanum for >4 yr underwent bone biopsies, which did not reveal any evidence of aluminum-like effects (66).

Overall, lanthanum carbonate was well tolerated, and the most common adverse events were GI, such as nausea and vomiting, which abated over time. Lanthanum was supplied as a chewable tablet in two dosage strengths, 250 and 500 mg. The total daily dose ranged between 1500 and 3000 mg. Despite encouraging results and need for alternative phosphate binders, the widespread use of lanthanum may be limited by concerns of long-term exposure and cost.

**Polynuclear Iron Preparations**

The use of trivalent iron has increased since the observation that the solubility product of these agents and phosphate is extremely low. Several animal studies and small-scale human trials have suggested their efficacy and tolerability (67–69). Although these agents are promising and potentially will become a low-cost alternative to current therapies, they remain in the early stages of clinical development at this time.

**Emerging Therapies**

Although not indicated for the treatment of hyperphosphatemia, calcimimetics are a new class of agents in the armamentarium available to treat secondary HPTH and may have a significant impact on the choice of phosphate binders in the future (70). Cinacalcet (Sensipar, Amgen, Thousand Oaks, CA) is a first-in-class agent that binds to and allosterically modifies the calcium-sensing receptor (CSR), increasing its sensitivity to extracellular calcium (71). The CSR located on the chief cell of the parathyroid gland is the principal regulator of PTH secretion, and activation by serum calcium leads to the activation of secondary messenger pathways and a cascade of intracellular events resulting in decreased PTH secretion (72). Cinacalcet is the only FDA-approved calcimimetic for use in the United States for the treatment of HPTH. In three large, prospective, randomized, double-blind, controlled trials, cinacalcet significantly reduced PTH levels compared with placebo (73–75). Moreover, cinacalcet significantly reduced serum phosphorus, calcium, and intuitively the Ca × PO₄ product in all three studies over the 26-wk study period. The exact mechanism by which cinacalcet lowers calcium, phosphorus, and Ca × PO₄ product is unclear but may be related to the attenuated release of PTH and subsequent mineralization of bone similar to that seen in the period after surgical parathyroidectomy (i.e., hungry bone syndrome). Alternatively, cinacalcet has also been shown to downregulate mRNA expression levels encoding proteins that are involved in active transcellular calcium reabsorption in the intestine (76).

Cinacalcet was well tolerated but did have a higher incidence of GI intolerance (nausea and vomiting) compared with placebo. These symptoms were reduced when the drug was administered with food. Cinacalcet was also associated with a 5 to 8% incidence of hypocalcemia as defined by a serum calcium <7.5 mg/dl that necessitated modification of calcium-containing phosphate binders, vitamin D sterols, or both (73,74). Despite the absence of a significant difference in the dose of either phosphate binders or vitamin D sterols between the groups during the relatively short study period, the incidence of hypocalcemia cannot be overlooked because it has also been associated with increased mortality among patients with ESRD (77). These findings warrant further investigation; however, the chain of logic suggests the potential need for calcium supplementation of some form by increasing dialysate calcium concentration, nightly calcium salt ingestion, or calcium-containing phosphate binders. The potential benefit of the last is apparent.

**Barriers to Success**

Despite the growing diversity of therapeutic options available, achievement and maintenance of the NKF–K/DOQI targets for hyperphosphatemia and HPTH remain poor. Fewer than 50% of prevalent dialysis patients met guideline recommendations for phosphorus control during the first 6 mo of the
Dialysis Outcomes and Practice Patterns Study and fell to 25% for the entire 12 mo of the study (78). Several reasons may account for failure to adequately treat hyperphosphatemia, such as compliance, cost of therapies, binder inefficiency as a result of inappropriate administration or prescription, and refractory disease states at time of initiation of renal replacement therapy.

Compliance
Unfortunately, poor compliance with diet and phosphate binders is common among adult chronic hemodialysis patients (79,80). It is believed that aggressive patient education programs and positive reinforcement by the nursing staff, renal dieticians, and nephrologists may be beneficial (81). Effective dietary counseling requires a team effort, and restricted diets should be personalized. Patients also need to be instructed on how to read food labels so that they can identify products with phosphate additives. Although the most common reason given by patients is that they forgot to take their binders, it is important to note that noncompliance is often multifactorial. A web-based survey revealed that 64% of patients did not comply with regularly prescribed drugs because they “forgot.” It is interesting that 35% did not take their medications because they wanted to save money.

Cost
Financial limitations rather than psychologic/cultural issues may play an even bigger role among patients with ESRD. More affordable fare including processed meats and cheeses, dried fruits and beans, peanut butter, and eggs are foodstuffs that are very high in phosphorus. These are often the only sources of protein available to dialysis patients with limited resources (82).

Social workers are also vital team members to help identify and enroll patients into pharmacologically sponsored patient-assistance programs, because newer noncalcium, nonaluminum phosphate binders are expensive. For example, RenaGel costs approximately $1.48/pill (83). Assuming the mean RenaGel dose required in long-term clinical trials (8 tablets/d), the yearly cost would be roughly $4200 for this medication alone. In contrast, PhosLo costs approximately $0.20/pill, with a yearly cost of approximately $500/yr (based on 7 tablets/d per the Treat-to-Goal Study). This substantial discrepancy in cost could have even farther reaching consequences with the implementation of the NKF–K/DOQI guidelines for the use of RenaGel. Manns et al. (85) performed a systematic review to analyze the potential economic impact of RenaGel prescription on the basis of these guidelines. According to their data, 51% of Canadian and 64% of American cohorts would respectively meet the NKF–K/DOQI criteria for use of RenaGel. For the US hemodialysis population, this would result in expenditures of approximately $781 million for RenaGel alone. This is a substantial burden to assume without the benefit of any outcomes data to support these recommendations. Moreover, Fosrenol, the other alternative to calcium salts, costs approximately $2/pill (83). According to current studies, the yearly cost would range from approximately $2400/yr (using the minimum dose of 1500 mg/d) to $4800/yr (using 3000 mg/d). These figures are disconcerting in light of the current budgetary concerns and rising cost of medical care.

Binder Performance
Calcium carbonate dissolves best in an acidic environment; however, its binding to phosphorus is best at higher pH and falls significantly at a pH below 5, which may be one reason that it is less effective than aluminum for phosphorus reduction (36). Furthermore, variability in dissolution rates exists among different manufacturers of calcium carbonate (86), mainly because the FDA does not view it as a drug. Therefore, calcium carbonate is not subjected to the rigorous standards of the FDA, similar to other “nutritional supplements.”

Prescription Error
Dietary habits of our patients are variable in not only the number of meals per day but also in the proportion of phosphorus in each meal and/or snack. Therefore, a careful dietary history is essential to prescribe phosphate binders properly to match quantity of phosphorus ingestion with appropriate binder dosage. Moreover, the temporal relationship with meals is crucial to bind dietary phosphate adequately. It is well-established that unsynchronized administration of binders significantly increases the proportion of dietary phosphorus absorbed compared with concomitant administration of binder with meals (24,35,36,46,87).

Refractory Disease State
Control of serum phosphorus becomes more difficult with the worsening severity of secondary HPTH over time. The reasons are multifactorial and include increased circulating PTH (which stimulates further release of phosphorus and calcium from bone), reduced production of active vitamin D metabolites, vitamin D receptor downregulation, and decreased CSR expression and autonomous parathyroid cell proliferation (88,89). Vitamin D and its analogs suppress PTH; however, with increased parathyroid tissue, the required doses are higher and subsequently increase intestinal absorption of calcium and phosphorus (90). This can further exacerbate the problem by worsening hyperphosphatemia and also limit further use of vitamin D and its analogs as a result of elevations of Ca × PO₄ product. The resultant metabolic abnormalities, as well as parathyroid hyperplasia, are not easily reversed; therefore, early interventions to prevent the development and/or progression of secondary HPTH and its sequelae are crucial.

Future Study Directions
Major advances in the understanding of mineral metabolism disturbances in CKD have been made in recent years. However, there remains a need for prospective, randomized, controlled trials to evaluate the effects of phosphorus control via various modalities on hard clinical outcomes such as cardiovascular events. These will need to account for other processes that are known to contribute to intimal injury and propagate atherosclerosis such as dyslipidemia, inflammation, and hyperhomocysteinemia. Subsequently, cost-effective analyses for different
therapies are necessary given the considerable financial burden for as of yet unproved therapies. Likewise, outcomes related to the implementation of these therapies during earlier stages of CKD require further exploration.

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