Slowing the Progression of Vascular Calcification in Hemodialysis

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Abstract. Hyperphosphatemia and secondary hyperparathyroidism are common complications of ESRD (chronic kidney disease stage 5) that, when untreated, may result in increased morbidity and mortality. Hyperphosphatemia and hypercalcemia have been associated with increased coronary artery calcification. Achieving control of serum phosphorus without increasing serum calcium is an important goal for patients with ESRD. Although calcium-based phosphate binders effectively reduce serum phosphorus and parathyroid hormone concentrations, these agents can lead to hypercalcemia and have been associated with increased vascular calcification. The phosphorus binder sevelamer was developed to overcome the limitations associated with the usual management of hyperphosphatemia and secondary hyperparathyroidism (i.e., mineral salts). Sevelamer, a nonabsorbable hydrogel, is as efficacious as calcium-based phosphate binders for reducing serum phosphorus but does not cause hypercalcemia or other adverse metabolic effects. Sevelamer also exhibits beneficial effects on lipid, consistently and significantly decreasing LDL cholesterol and increasing HDL cholesterol in most studies. In a head-to-head randomized clinical trial, sevelamer and calcium-based binders achieved similarly excellent phosphorus control, but the use of calcium-based binders led to significantly higher serum calcium concentrations and an increased incidence of hypercalcemia and unintended suppression of parathyroid hormone. Treatment with calcium-based binders also led to the progression of coronary artery and aortic calcification, whereas sevelamer attenuated or arrested progression. Strategies that use oral calcium and vitamin D in patients with ESRD should be reexamined, and the potential advantages of sevelamer should be considered when selecting a primary agent to reduce serum phosphorus in hemodialysis patients.

Hyperphosphatemia and secondary hyperparathyroidism (HPT) are common complications of end-stage renal disease (ESRD) (1). Untreated secondary HPT can lead to significant morbidity as a result of pain, pruritus, bone loss, increased fracture risk, and anemia (2,3) and can contribute to heart disease and hypertension (4,5). Management of hyperphosphatemia and secondary HPT in patients with ESRD is critical, because cardiovascular disease is the leading cause of death in this patient population (6). Annual cardiovascular mortality rates are several-fold higher in patients with ESRD than in the general population, even when adjusted for age, gender, race, and the presence of diabetes.

In addition to traditional risk factors (age, gender, race, diabetes, hypertension, lifestyle factors, smoking, lipids, hyperhomocysteinemia), inflammation, oxidative stress as a result of uremia and/or dialysis, and disorders of mineral metabolism may contribute to cardiovascular disease in patients with ESRD (7,8). In particular, disorders of mineral metabolism may contribute to cardiac calcification, which may in turn increase the risk of cardiovascular disease and mortality. Individuals who are on dialysis are prone to severe calcification (9,10), and a correlation has been demonstrated between the degree of coronary calcification and the prevalence of overt atherosclerotic vascular disease (11). These results are in agreement with those of Blacher et al. (12), who demonstrated that in hemodialysis patients, the probability of all-cause mortality increased with increasing calcification score using B-mode ultrasound.

Hyperphosphatemia is associated with elevated cardiovascular risk and mortality (13–16). Analysis of data from the United States Renal Data System demonstrated an association between elevated phosphorus and calcium-phosphorus product and mortality (15), and a follow-up analysis indicated that hyperphosphatemia was associated with case-specific cardiovascular death (16). These adverse effects of hyperphosphatemia are thought to be linked to the ability of phosphate to enhance vascular calcification (14,16), although the exact mechanism(s) is unknown. Data from Giachelli in this supplement (17) suggest that the mechanism is more complex than the traditional theory of passive crystallization and tissue deposition.

Hyperphosphatemia and HPT: Treatment Options
Several treatment options, either alone or in combination, are available for the treatment of hyperphosphatemia and secondary HPT in patients with ESRD (Table 1). The duration and
frequency of dialysis may be adjusted to normalize phosphorus levels; nocturnal hemodialysis with long treatment times seems to be most effective (18). Dietary phosphorus restriction can be applied, although the need for adequate dietary protein limits this approach, and with conventional dialysis a phosphate binder is almost always required. Oral or intravenous administration of vitamin D metabolites can correct secondary HPT (19) but leads to enhanced intestinal absorption of calcium and phosphorus and, in doing so, may indirectly contribute to vascular calcification. Aluminum, magnesium, and calcium salts have also been used to bind dietary phosphorus. Aluminum salts can lead to osteomalacia, anemia, and, in rare cases, encephalopathy (20,21). Most physicians advise against the routine use of aluminum because of the side effects associated with its accumulation. Magnesium salts are infrequently used, being dose limited by gastrointestinal side effects (22).

Calcium salts tend to be well tolerated in most individuals and can effectively bind intestinal phosphorus. During the late 1980s and the 1990s, calcium salts became the conventional strategy for controlling hyperphosphatemia. However, a variable fraction of the calcium can be absorbed, depending in part on co-administration of vitamin D and other gastrointestinal factors (e.g., gastric pH, timing of administration, meal content, other medications). Moreover, despite more intensive dialysis, dietary phosphorus restriction, and treatment with calcium- and aluminum-based phosphate binders, more than 60% of hemodialysis patients have suboptimal control of calcium and phosphorus, and others experience persistent elevations of parathyroid hormone (PTH) or require parathyroidectomy to achieve adequate phosphorus control (23).

The phosphate binder sevelamer (Renagel; Genzyme, Cambridge, MA) was developed and introduced in 1998 to overcome the limitations associated with traditional management of hyperphosphatemia and secondary HPT. Sevelamer is a non-calcium-, non-aluminum-containing hydrogel that is resistant to digestive degradation and is not absorbed from the gastrointestinal tract (23).

Table 1. Treatment options for hyperphosphatemia and hyperparathyroidism

| Adjustment of dialysis duration and frequency
| Dietary restriction
| Oral or intravenous administration of vitamin D metabolites
| Oral phosphate binders
| aluminum salts
| calcium salts
| magnesium salts
| sevelamer

Sevelamer Hydrochloride

Short-Term Studies

Several short-term studies have shown sevelamer to be as efficacious as calcium acetate or calcium carbonate in decreasing serum phosphorus concentrations (24–29). Moreover, results indicate that sevelamer is well tolerated and provides adequate control of HPT without increasing serum calcium, even when used in conjunction with vitamin D metabolites. In short-term studies, sevelamer consistently reduced PTH (25,29). Furthermore, maintenance of target PTH concentrations in sevelamer-treated subjects was accomplished, often with the addition of vitamin D metabolites (30). Sevelamer also leads to significant decreases in the calcium-phosphorus product (23). Compared with calcium salts, sevelamer may lead to reductions in serum bicarbonate, on the order of 2 to 3 mEq/L, in part as a result of the withdrawal of acetate or carbonate anions from previous binder usage. In addition, sevelamer has been shown to induce small but statistically significant reductions in serum uric acid concentration (31). Unique among phosphate binders, sevelamer has favorable effects on the lipid profile, consistently decreasing LDL cholesterol by more than 30% and increasing HDL cholesterol by 5 to 15% in most studies (23–27,29).

Long-Term Studies

Recent long-term studies have evaluated the safety and efficacy of sevelamer in hemodialysis patients (23,32). The long-term efficacy of open-label sevelamer was evaluated over a 46-wk period in 192 adult hemodialysis patients (23). Sevelamer significantly decreased serum phosphorus (mean decrease, 2.2 ± 2.4 mg/dl) and calcium-phosphorus product (mean decrease, 18.1 ± 22 mg²/dl²) and overall led to no significant changes in PTH at 1 yr. A small but statistically significant increase in serum calcium was observed with sevelamer treatment that was independent of dose, although the average incidence of hypercalcemia (defined in this study as ≥11 mg/dl) was less than 2%.

A single long-term, randomized, clinical trial (“treat to goal”) compared sevelamer with calcium-based phosphate binders in 200 hemodialysis patients at 15 sites in the United States and Europe (32). The subjects were randomized to 1 yr of open-label treatment with sevelamer or calcium salts (acetate in the United States and carbonate in Europe). Patients were eligible for study participation when they were hyperphosphatemic (≥5.5 mg/dl) after a 1- to 2-wk phosphate binder washout period. Target values for serum phosphorus were more ambitious (3.0 to 5.0 mg/dl) than in other studies. Target values for serum calcium (adjusted for albumin) were 8.5 to 10.5 mg/dl and for PTH were 150 to 300 pg/ml. In addition to evaluating the comparative effects of sevelamer and calcium salts on parameters of mineral metabolism, we tested the hypothesis that sevelamer and calcium salts would have differential effects on vascular calcification. In evaluating coronary and aortic calcification, electron beam tomography (EBT) was performed at baseline, 6 mo, and 1 yr.

Subjects who were treated with sevelamer and calcium achieved excellent phosphorus control (end of treatment serum phosphorus for both groups, 5.1 mg/dl; Figure 1). The use of calcium-based binders led to significantly higher serum calcium concentrations (P = 0.002; Figure 2) and a higher incidence of hypercalcemia (P = 0.04; defined in this study as an adjusted serum calcium ≥10.5 mg/dl; Figure 3). These changes were attenuated during the study by the reduction or discon-
Continuation of vitamin D, reduction in dialysate calcium, and the use of “rescue” aluminum hydroxide in some calcium-treated subjects, all provided for by the study protocol for safety considerations. Subjects who were treated with calcium-based binders experienced significant unintentional suppression of PTH with median values below 150 pg/ml at all on-treatment time points compared with sevelamer-treated subjects, whose median PTH concentrations remained within the target range (Figure 4).

Even transient hypercalcemia with calcium-based phosphate binders may be undesirable. Guérin et al. (33) showed a significant relation between vascular calcification by B-mode ultrasonography and episodes of hypercalcemia (8%, 10%, 18%, 36%, and 42% in patients with 0, 1, 2, 3, or 4 sites of calcification, respectively; \( P = 0.034 \)). Several investigators have shown PTH concentrations below 150 pg/ml to be associated with low bone turnover and an increased rate of fractures and extraskeletal calcification (34,35).

Atherosclerotic vascular disease is significantly associated with the coronary artery calcification score by EBT in the general population (36–38) and in people with uremia (11). In hemodialysis patients, correlates of the extent of coronary calcification were advanced age, male gender, white race, diabetes, and longer vintage; calcium and phosphorus were the only modifiable risk factors. We found a 1.0-mg/dl higher serum phosphorus and a 0.5-mg/dl higher serum calcium to be associated with the same relative increase in vascular calcification as 2.5 yr of dialysis. There were no associations between the extent of coronary artery calcification and serum albumin, hemoglobin, and lipid parameters. Therefore, the favorable metabolic effects of sevelamer might be expected to reduce the extent of coro-
nary artery calcification and potentially reduce the risk of overt coronary heart disease.

In the treat-to-goal study, baseline EBT scores were extremely high (93rd percentile for age- and gender-matched normal subjects) and were nominally higher in the subjects who were randomized to sevelamer (although not significantly different) (32). However, the mean and median nominal change, mean and median percentage change, and mean and median weekly trend scores were significantly higher in calcium-treated subjects. In other words, the difference in vascular calcification was evident regardless of the method of data analysis. Given a median zero nominal change in coronary and aortic calcification in sevelamer-treated subjects, an equal number of subjects experienced regression as progression over the 1-yr study.

Non–Calcium-Based Versus Calcium-Based Phosphate Binders: A Comparative Overview

Evidence suggests that sevelamer would provide considerable benefits over calcium salts as primary therapy for hyperphosphatemia. The treat-to-goal study demonstrated that in achieving satisfactory phosphorus control using calcium salts, a high frequency of unacceptable metabolic side effects can be anticipated. Indeed, the frequency of hypercalcemia and the more pronounced degree of PTH lowering seen in calcium-treated subjects in the treat-to-goal study reflect the ambitious phosphorus targets. Therefore, even in the absence of cardiovascular benefits, sevelamer would be preferred for its metabolic effects on bone. The exact mechanism(s) for progressive vascular calcification in hemodialysis patients is unknown. An increasing incidence of cardiovascular disease and other disorders of calcification (e.g., uremic calcific arteriolopathy) over the past decade has been attributed in part to the widespread use of oral calcium and vitamin D metabolites. Possible reasons for a protective vascular effect of sevelamer include improved metabolic control; differences in calcium load; and differential effects on bone dynamics, lipids, and inflammation.

Calcium-based phosphate binders increase calcium load. Several studies have linked the dose of oral calcium with vascular calcification. Goodman et al. (10) showed that adolescents and young adults who were on dialysis and had evidence of coronary artery calcification were prescribed nearly twice the dose of oral calcium carbonate as patients without calcification (mean, 6456 versus 3325 mg; P = 0.02). Guérin et al. (33) showed a direct correlation between prescribed oral calcium and the number of sites of vascular calcification (1.35, 1.35, 1.50, 1.84, and 2.18 g elemental calcium in patients with 0, 1, 2, 3, and 4 sites of calcification, respectively; P = 0.001).

We cannot determine whether the beneficial effects on lipids induced by sevelamer contributed to the benefit on vascular calcification. In the treat-to-goal study, mean LDL cholesterol (71 versus 108 mg/dl; P < 0.001), mean apolipoprotein B (63 versus 84 mg/dl; P < 0.0001), and median homocysteine (19.3 versus 29.7 ‰; P = 0.04) concentrations were significantly lower in sevelamer-treated subjects than in subjects who received calcium-based phosphate binders. Finally, differential effects of sevelamer and calcium-based phosphate binders on inflammation may contribute to differences in coronary calcification. Chronic inflammation is commonly observed in patients with ESRD (39), and markers of inflammation have been associated with coronary calcification in these patients (33). It has been hypothesized that inflammation may trigger arterial calcium deposition in dialysis patients, particularly at the end of the dialysis session, when back-filtration is most likely to occur and the plasma is maximally alkalized (40). Further studies are needed to investigate the effects of sevelamer and calcium-based phosphate binders on markers of inflammation, such as C-reactive protein and fibrinogen, and to examine the relation between changes in these markers and changes in coronary calcification.

Conclusion

Hyperphosphatemia has been recognized as a key modifiable risk factor in patients who are on hemodialysis. As target values for serum phosphorus and the calcium–phosphorus product have been reduced (e.g., Kidney Disease Outcomes Quality Initiative guidelines of <5.5 mg/dl and <55 mg²/dl², respectively [National Kidney Foundation, unpublished review, 2003]), the need for improved phosphate binders has become even more pronounced. As the dose of calcium-based phosphate binders increases, so does the frequency of hypercalcemia, and excessive calcium intake can lead to adynamic (low turnover) bone disease. In contrast, sevelamer can be titrated safely with no metal absorption. Changes in vascular calcification are provocative. Additional studies are under way to examine the relative effects of sevelamer and calcium-based phosphate binders on mortality and cardiovascular events. For now, practitioners should use calcium-based phosphate binders cautiously. With ongoing evidence, non–calcium-containing phosphate binders may soon evolve into first-line therapies for dialysis-related hyperphosphatemia.

References


