Cardiovascular disease (CVD) remains the major mortality risk in dialysis patients, accounting for almost 50 percent of deaths among these patients. Although increased risk of cardiovascular death may be related to increased prevalence of traditional risk factors for CVD, the contribution of uremia-related risk factors, particularly abnormalities in mineral metabolism, recently have been emphasized. Hyperphosphatemia and elevated calcium-phosphorus (Ca x P) product are associated with cardiovascular calcification (CVC), including the aorta, carotid and coronary arteries, the cardiac valves, and the myocardial muscle.

Extraosseous calcification

CVC has been linked to an increased risk of cardiovascular events, including myocardial infarction, fatal arrhythmia, congestive heart failure, and valvular heart disease. Coronary artery calcification (CAC) is absent in normal vessels, but usually occurs when atherosclerosis is present and is considered an integral part of the atherosclerotic plaque. Detection and quantification of arterial calcification now can be easily achieved by the use of newer imaging techniques such as electron-beam computed tomography (EBCT) and multislice computed tomography (MSCT). Recent studies clearly have shown that patients with end-stage renal disease (ESRD) on dialysis have a higher prevalence and severity of CAC than healthy subjects of the same age and gender. Braun and colleagues reported that CAC scores were 2.5 to 5-fold higher in dialysis patients than in nondialysis patients with documented or suspected history of coronary artery disease (CAD), all of whom underwent coronary angiography. More importantly, CVC is common even in younger dialysis patients.

There are four types of extraosseous calcification in patients with chronic kidney disease (CKD): Intimal calcification, which occurs in association with atherosclerotic plaques; medial calcification of arteries, so called Monckeberg’s sclerosis, which may be found in the absence of atherosclerosis and is characterized by diffuse calcification of the media, particularly at the level of the internal elastic lamina; and cardiac valve calcification.
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calcification, which is 8-fold more frequent in patients with ESRD than in an age-matched control population. Additionally, a subgroup of patients with ESRD may develop a specific form of medial calcification known as calciphylaxis or uremic arteriolopathy where calcification affects cutaneous and subcutaneous arteries and arterioles and leads to occlusive intimal proliferation. The resulting tissue ischemia leads to painful ulcers on the trunk and extremities and is associated with high mortality.

Pathogenesis of vascular calcification

CVC is not passive, but rather an active and highly regulated process similar to bone formation. This observation is supported by reports describing ectopic bone elements, which may even contain bone marrow, in calcified blood vessels, advanced atherosclerotic lesions, and in calcified cardiac valves. These findings suggest that vascular cells have the capacity to transform into osteoblast-like cells capable of producing ectopic bone in the vessel wall.

The pathogenesis of CVC is complex and includes factors that promote calcification and that inhibit calcification. In dialysis patients, cross-sectional studies have shown a correlation between CAC and a number of uremia-related factors, such as dialysis vintage, hyperphosphatemia, high Ca x P product, vitamin D therapy, and the prescribed daily dose of calcium-based phosphate binders (CBPB).

Disturbances in serum phosphorus, calcium, and Ca x P product also are frequently seen and have been implicated in promoting CVC as well as an increased risk of death. High phosphorus level, and to a lower extent calcium, stimulates osteoblastic differentiation of vascular smooth muscle cells and directly enhances extracellular calcification by these cells. Given that hyperphosphatemia is common in dialysis patients, and that it plays a key role in the increased risk of CVC, then control of serum phosphorus may result in reduced burden of CVC in these patients and improve their outcomes. The National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative (K/DOQI) “Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease” now recommends stringent levels for controlling serum phosphorus, calcium, and Ca x P product.

Because dietary restriction of phosphorus and intermittent dialysis are not usually effective in controlling serum phosphorus, most dialysis patients require dietary phosphate binders. The ideal phosphate binder should bind most dietary phosphate in the intestine without producing significant adverse effects; it also should be relatively inexpensive because most dialysis patients usually consume relatively large daily doses of the binder. Unfortunately, none of the currently used phosphate binders fulfill all these requirements. Aluminum hydroxide, for instance — which is probably the most cost-effective phosphate binder — has been largely abandoned because of the risk of aluminum intoxication with encephalopathy and osteomalacia. As a result, calcium acetate and calcium carbonate have replaced aluminum hydroxide as the most widely prescribed phosphate binders. More recently, noncalcium, non-aluminum phosphate binders, such as sevelamer hydrochloride (Renagel) and lanthanum carbonate (Fosrenol), have been introduced.

The CARE study

In clinical practice, calcium acetate and sevelamer hydrochloride are currently the two most commonly used phosphate binders. Previous studies comparing these two binders showed superior phosphorus control with CBPB. Others reported that they are equally effective in controlling serum phosphorus.

The Calcium Acetate Renagel Evaluation (CARE) study is the only prospective, randomized, double-blind study that directly compares the efficacy of calcium acetate and sevelamer hydrochloride in controlling serum phosphorus in patients on maintenance hemodialysis. In this study, calcium acetate was found to be more effective than sevelamer hydrochloride in controlling serum phosphorus. In the calcium acetate-treated patients, mean serum phosphorus decreased to the K/DOQI treatment goal of ≤5.5 mg/dL after 3 weeks of titration, while in the sevelamer-treated group, this goal was never achieved despite weekly dose escalation over the 8-week study (Figure 1). Importantly, the prescribed daily dose of sevelamer hydrochloride at week 8 in the study (6.9 ± 3.5 g per day) was comparable with that used in the Treat to Goal (TTG) study (6.5 ± 2.9 g per day). Results are in agreement with three recent cross-sectional studies. Ciampi and colleagues showed in their long-term study of hemodialysis patients that the mean serum phosphorus was significantly lower in calcium acetate-treated patients compared with those treated with sevelamer hydrochloride. Block and colleagues reported similar findings in their study of hemodialysis patients on long-term phosphate binder therapy. More recently, Young and colleagues reported that among 9,016 dialysis patients, the mean serum phosphorus in patients treated with CBPB was 5.37 mg/dL, while that in sevelamer-treated patients was 6.11 mg/dL.

Also in the CARE study, the serum calcium level was significantly higher in calcium acetate-treated patients compared with patients treated with sevelamer hydrochloride. Overall, transient hypercalcemia developed in 8 of 48 (16.7 percent) calcium acetate-treated patients. Hypercalcemia occurred only in calcium acetate-treated patients con-
comitantly treated with intravenous vitamin D preparations. Interestingly, the serum calcium level in sevelamer-treated patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS) was significantly higher (9.60 vs. 9.39, P < 0.01 mg/dL, respectively) than that in patients treated with CBPB, likely due to higher doses of vitamin D.12 Also interesting is that in the CARE study, despite higher mean serum calcium levels, calcium acetate-treated patients consistently had lower mean Ca x P product and more often achieved the K/DOQI treatment goal (≤55 mg²/dL²) than sevelamer-treated patients (Figure 2).

The results of the CARE study and other studies, including DOPPS, have definitively established the superiority of calcium acetate over sevelamer hydrochloride for achieving target levels of serum phosphorus and Ca x P product recommended by the K/DOQI guidelines. Moreover, calcium acetate appears to be the more cost-effective choice as the first-line treatment for hyperphosphatemia in patients with ESRD on maintenance dialysis. Several studies have shown that the doses of calcium acetate required for control of serum phosphorus fall within the 1,500 mg limit of elemental calcium intake per day recommended by the K/DOQI guidelines. Nevertheless, in the occasional patient who develops persistent hypercalcemia during treatment with calcium acetate despite appropriate reduction in vitamin D dosage and adjustment of dialysate calcium level, it may be prudent to reduce the dose of calcium acetate and add a noncalcium-containing binder such as sevelamer hydrochloride.

Over the 8-week course of the study, sevelamer hydrochloride-treated patients had significantly lower serum bicarbonate levels than patients treated with calcium acetate. These results confirmed the results of several short-term and long-term studies that demonstrated that maintenance hemodialysis patients treated with sevelamer hydrochloride have significantly lower predialysis serum bicarbonate levels than patients treated with CBPB. Sevelamer hydrochloride is a quaternary amine anion exchange resin, an anion exchanger whereby monovalent phosphate is bound (via ionic and hydrogen bonding) in exchange for release of the anion chloride. In this model, one molecule of hydrochloric acid is liberated for each molecule of phosphate bound in the gut. Sevelamer hydrochloride also may exchange chloride for any other anion available in the gastrointestinal tract such as bicarbonate and bile acids. Given that sevelamer hydrochloride contains 17 percent chloride by weight, and assuming complete exchange of
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The CARE study has definitively established the superiority of calcium acetate over sevelamer hydrochloride for achieving target levels of serum phosphorus and Ca x P product.

chloride for phosphate, bicarbonate, or bile acids, each 800 mg tablet of sevelamer hydrochloride could theoretically lead to an acid load equivalent to 4 mEq hydrochloride acid. Thus, dialysis patients treated with four 800 mg tablets of sevelamer hydrochloride thrice daily with meals as a phosphate binder might receive an additional dietary acid load approaching 46 mEq/day. These considerations suggest that a widespread shift from use of CBPB to sevelamer hydrochloride might result in an increase in the prevalence and severity of chronic metabolic acidosis in the hemodialysis population.

Chronic metabolic acidosis in maintenance dialysis patients is associated with major systemic effects, including worsening of secondary hyperparathyroidism, net negative nitrogen and total body protein balance, and increased risk of death. For that reason, the long-term risks of worsening metabolic acidosis in hemodialysis patients treated with sevelamer hydrochloride clearly deserve further study. The recently published K/DOQI guidelines recommend keeping predialysis levels of total CO₂ above 22 mM both to promote improvement in bone histology and to ameliorate excess protein catabolism.

Does calcium kill?

Although CBPB is cost-effective, recent concern over the possible role of calcium loading from CBPB in progression of CVC has led to more frequent use of the considerably more expensive noncalcium, nonaluminum phosphate binder, sevelamer hydrochloride. Goodman and colleagues, using EBCT, in comparing the prevalence of CAC in 39 young hemodialysis patients with 60 normal subjects, initially raised this concern. They found that factors associated with a higher incidence of CAC include increased mean serum phosphorus concentration, mean Ca x P product, and daily calcium intake.

These results were strengthened after the publication of the TTG and Renagel in New Dialysis (RIND) Studies. In these trials, CBPB-treated patients had more progression of CAC than sevelamer-treated patients. The mechanism of the beneficial effect of sevelamer on progression of calcification, however, was controversial. The authors of these trials maintained that the mechanism reduced calcium loading during treatment with sevelamer. An important consideration here, however, is the well-documented effect of sevelamer on LDL cholesterol levels. In the TTG study, patients treated with sevelamer had a significant decrease in serum LDL cholesterol levels from 100 to 65 mg/dL, an effect that has been previously reported to be associated with amelioration of CVC. This reduction in the level of LDL provides a plausible explanation for the difference in the rate of CVC progression observed in the two treatment groups.

Unfortunately, the TTG study design did not allow for comparable lowering of LDL levels in both treatment groups. Interestingly, two studies evaluating the effects of lipid lowering agents in the general population, using EBCT-derived coronary calcium scores, revealed similar results to the TTG study, thus supporting the role of oxidized lipids in the development and progression of endothelial calcification. Moreover, it is unclear if the calcium load significantly differed between the two treatment groups. Patients randomized to sevelamer hydrochloride were allowed to receive oral calcium load from calcium supplement at bedtime and higher dialysate calcium concentration and higher vitamin D doses compared with patients randomized to CBPB. Typically, calcium carbonate was given on an empty stomach at nighttime, which results in a significant amount of calcium systemically absorbed. This additional “occult” calcium load in sevelamer-treated patients was not taken into consideration, however, in the analysis of the TTG data. Based on these findings, I believe that results of the TTG and RIND studies do not provide meaningful insight into the role of oral calcium ingestion in the pathogenesis of CVC.

A number of other reasons to question the role of calcium loading from CBPB in progression of CAC can be cited. First, previously evidence had been shown that a noncalcium containing phosphate binder, such as aluminum hydroxide usage, is also associated with an equally high incidence of vascular calcification. Second, McCullough and colleagues found that only 3 of 30 studies reported that oral calcium load was independently associated with progression of CAC. Third, cardiovascular calcification has been documented in nondialyzed patients with CKD, particularly those with diabetic nephropathy. Fourth, in the RIND study, no correlation between the dose of elemental calcium prescribed and episodes of hypercalcemia and CAC scores was found. Significant correlation was shown between, on treatment average, LDL and total cholesterol and change in CAC scores. In addition, patients who had no CAC at baseline did not develop CAC on follow-up despite calcium loading from CBPB. Finally, results of the DCOR study showed no mortality or morbidity benefit associated with sevelamer compared with CBPB.

To circumvent these limitations, the CARE-2 study is designed to test the hypothesis that if LDL levels are lowered to a similar level in calcium acetate and sevelamer-treated patients, there will be no difference in progression of CVC. Patients with ESRD and serum phosphorus >5.5 mg/dL, LDL >80 mg/dL, and EBCT CAC scores of 30 to 5,000 Agatston units were randomized to calcium acetate or sevelamer. Atorvastatin was added to achieve LDL <70 mg/dL in both treatment groups. The primary endpoint is change in CACs at 1 year. Secondary endpoints include serum
phosphorus, calcium, Ca x P product, PTH level, bicarbonate level, and time-to-target phosphorus and Ca x P. Results of this study will be available by the end of 2006.

A final consideration
Although CVC is very common in CKD patients, it is conspicuously absent in approximately 17 percent of patients despite similar exposure to factors promoting calcification. Moreover, subjects who do not have detectable vascular calcification rarely develop calcification in follow-up studies. Because the physiologic concentrations of calcium and phosphorus in human serum, particularly in ESRD patients, are far above their solubility product and, therefore, they should precipitate immediately, then inhibitors of precipitation of these ions must be playing a major role in preventing extraosseous calcification.19

References

Controversies in the Management of Hyperphosphatemia In Patients with End-Stage Renal Disease
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In current discussions about treating hyperphosphatemia in patients with end-stage renal disease (ESRD), a pointed question is being asked about an essential mineral: Is there an association between the ingestion of calcium from calcium-based phosphate binders (CBPB) and the development of cardiovascular calcification (CVC)?

The calcification myth
Attempts have been made to link calcium intake to the development and progression of CVC and, subsequently, a negative impact on outcomes such as all-cause and cardiovascular mortality. Epidemiologic and observational studies have indicated a link between increased serum phosphorus and total calcium phosphorus (Ca x P) product with increased mortality in patients with ESRD. To date, however, no prospective clinical studies have successfully demonstrated that calcium intake from CBPB is linked to increased mortality in uremic patient.1,2,3

CBPB are among the most widely prescribed treatments for reducing elevated serum phosphorus levels. Chronic kidney disease (CKD) patients with hyperphosphatemia have increased mortality risk compared with patients that have levels at or below those recommended by the National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative (K/DOQI) “Clinical Practice Guidelines for Bone Metabolism and Disease.”1–4

At least one study has questioned whether the use of CBPB in hemodialysis patients is related to an increased incidence of CVC.5,6 Moreover, evidence-based literature clearly supports the premise that cardiovascular calcification in chronic kidney disease

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patients has a multifactorial pathogenesis.6–7

Despite an approximately 4-fold cost differential compared with calcium acetate (PhosLo), Genzyme’s sevelamer hydrochloride (Renagel) is widely prescribed and enjoys a significant market share. The launch of sevelamer was accompanied by an aggressive marketing campaign that supported a simple, yet false, premise — that calcium ingestion from CBPB (calcium carbonate and calcium acetate) was linked to vascular deposition, increasing the risk of death (all-cause and cardiovascular) in ESRD patients. This campaign prompted many nephrologists to prescribe sevelamer with the hope of avoiding complications of hypercalcemia in these patients. Additionally, commercial and federal payer groups positioned sevelamer as a first-line treatment option in their formulations for the management of hyperphosphatemia in ESRD patients. To date, there is no credible scientific evidence to support the notion that calcium ingestion from CBPB is associated with an increased risk of death in ESRD patients. Implicit in this notion is that CVC is a passive, degenerative process in which excess calcium is deposited in the vasculature. This overly simplistic view ignores the vast body of evidence that indicates that CVC is an active, regulated process (Figure 1).5,6,7,9

**Questionable clinical studies**

In a systematic review of the medical literature published in the past 25 years, 70 percent of studies conducted have failed to demonstrate a link between calcium ingestion and vascular calcifications in ESRD patients.8 Those studies that have demonstrated a link had significant design limitations, including no control group, open label, retrospective, and failed to control for confounding variables (e.g., vitamin D, calcium dialysate concentration, cholesterol levels). Additionally, most of the studies used calcium carbonate as the calcium-based binder of choice. Calcium carbonate preparations contain 40 percent elemental calcium, while calcium acetate contains only 25 percent elemental calcium.4,10

A recent observational study presented at the 2005 American Society of Nephrology (ASN) Renal Week indicates that approximately 40 percent of sevelamer-treated patients received calcium supplementation with calcium-based binders.11 Of note, the amount of elemental calcium absorbed following calcium acetate dosing is similar to sevelamer plus supplemental calcium (to manage hypocalcemia) and significantly lower than calcium carbonate (Figure 2).12 Importantly, the K/DOQI guidelines recommend calcium acetate as a rational first-line treatment option for the management of hyperphosphatemia in ESRD. Further affirmation of calcium acetate as a first-line therapy for managing hyperphosphatemia in stage 5 CKD is documented in the conclusions of an independent, evidence-based review of the literature that appeared in the Nephrology Self-Assessment Program.13 Other studies support the rational, first-line use of calcium acetate for the management of hyperphosphatemia in uremic patients.5,12,14

**Current treatments**

Treatment of hyperphosphatemia typically is with CBPB (calcium acetate and calcium carbonate) and non-calcium-containing phosphate binders, sevelamer hydrochloride, and lanthanum carbonate.

Aluminum-based binders largely have fallen out of favor with clinicians because of the risk of osteomalacia, microcytic anemia, and encephalopathy. Fosrenol is prescribed less frequently due to concerns about the effect of lanthanum accumulation in bones and tissues. Over-the-counter magnesium carbonate and calcium carbonate preparations also are available. Again, it is important to distinguish between calcium carbonate and calcium acetate: calcium acetate binds twice as much dietary phosphorus as calcium carbonate and is associated with 50 percent less elemental calcium being absorbed systemically (calcium carbonate preparations contain 40 percent elemental calcium, and

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* The U.S. Food and Drug Administration has approved three medications for the treatment of hyperphosphatemia: calcium acetate (PhosLo, Nabi Biopharmaceuticals), sevelamer hydrochloride (Renagel, Genzyme), and lanthanum carbonate (Fosrenol, Shire Pharmaceuticals).
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Calcium and calcification

Consideration of calcium intake is appropriate when a patient presents with hypercalcemia, defined by the K/DOQI guidelines from an opinion-based recommendation as a corrected serum calcium level exceeding 10.2 mg/dL. Another opinion-based recommendation from the K/DOQI guidelines is the daily intake of elemental calcium (approximately 2,000 mg/day from both dietary and pharmacologic sources). The guidelines fail to distinguish between intake and net amount of elemental calcium systemically absorbed. This omission may contribute to confusion among nephrologists and dieticians regarding the safe use of CBPB for the management of hyperphosphatemia in uremic patients.

Of additional relevance, Genzyme’s well-publicized 2005 Dialysis Clinical Outcomes Revisited (DCOR) trial, a three-year trial involving more than 2,100 patients, failed to meet both its primary and secondary endpoints in attempting to definitively demonstrate a morbidity and mortality benefit with sevelamer in ESRD patients. The investigators placed particular emphasis on the subgroup analysis in patients older than 65 years of age, indicating that these patients may have benefited the most from sevelamer. This was not a prospectively defined endpoint, however. Furthermore, there were 14 percent fewer deaths in patients less than 65 years of age who received CBPB.

Efficacy of calcium acetate: The CARE study

The Calcium Acetate Renagel Evaluation (CARE) study was a multicenter, randomized, double-blind study that compared the efficacy of calcium acetate and sevelamer HCl in stage 5 CKD. The CARE study is the first and, so far, only randomized, double-blind, controlled, head-to-head comparison between calcium acetate and sevelamer and was designed to determine which agent best achieves the recommended K/DOQI treatment goals for serum phosphorus (≤5.5 mg/dL) and Ca x P product (<55 mg²/dL²). The study demonstrated the clinical efficacy of calcium acetate over sevelamer in controlling increased serum phosphorus and total Ca x P — both linked to increased mortality in patients with ESRD — within K/DOQI recommended ranges for stage 5 CKD.

Forty-five percent of the patients who received calcium acetate achieved the goal for serum phosphorus in the first 8 weeks of the CARE study, compared with only 10 percent of sevelamer-treated patients (Figure 3). In addition, compared with sevelamer, calcium acetate demonstrated maintenance of mean serum calcium within normal range, significantly higher mean serum bicarbonate (HCO₃⁻) levels, and superior cost-effectiveness. Upon review of the dosing schedule employed in the CARE study — which mirrored recommended package insert dosing and average wholesale prices in 2003 — treatment with calcium acetate, on an
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annualized basis, is approximately 6 times less expensive than sevelamer — $732 versus $4,283, respectively. \(^{12}\)

Cost-savings opportunity

Recent studies have brought into question two important factors in managing hyperphosphatemia in ESRD — the efficacy of sevelamer as a phosphate binder and the unproven link between calcium intake from calcium-based binders and worsening cardiovascular morbidity and mortality outcomes. Most studies conducted in the past 25 years have failed to demonstrate a link between calcium ingestion and vascular morbidity and mortality outcomes. The DCOR trial failed to meet both its primary and secondary endpoints in attempting to demonstrate a morbidity and mortality benefit with sevelamer in ESRD patients. The CARE study showed that 45 percent of patients taking calcium acetate achieved the goal for serum phosphorus in the first eight weeks of the study compared with only 10 percent of sevelamer-treated patients. The cost differential between sevelamer and calcium acetate has clinicians and payers re-examining the additional costs borne by patients, health care providers, and payer organizations. Clinicians, and more importantly patients with ESRD, should have access to safe and effective treatment options for managing hyperphosphatemia, especially when credible scientific data indicate that the less expensive alternative is significantly more effective for the prescribed use.

References


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