REVIEW

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Cardiovascular mortality in chronic renal failure: Hyperphosphatemia, coronary calcification, and the role of phosphate binders

KEY POINTS

Hyperphosphatemia is a strong and unique risk factor for cardiovascular mortality in patients on dialysis for chronic renal failure.

Overall treatment of hyperphosphatemia should focus on achieving and maintaining a serum phosphate level less than 5.5 mg/dL.

Calcium-containing phosphate binders remain standard therapy, although selected patients may benefit from the addition or substitution of calcium-free phosphate binders.

Reducing cardiovascular risk in patients with chronic renal failure should focus on addressing traditional cardiovascular risk factors.

The incremental risk-assessment value of coronary artery calcium scoring is limited.

Both authors have indicated that they have no affiliation with or financial interest in a commercial organization that poses a potential conflict of interest with their article.

THE CARDIOVASCULAR MORTALITY RATE is 20 to 40 times higher for adults on dialysis than for the general population.[1] In treating patients on dialysis, nephrologists contend with the cumulative effects of the processes that cause renal failure, the generic consequences of globally disordered renal function, and the potential adverse effects of treatment or lack of treatment.

Recent observations implicate hyperphosphatemia and increased calcium-phosphate product (Ca × P) as contributing factors to increased mortality in dialysis patients.[2–4] A major proposed mechanism is accelerated coronary calcification, perhaps related to inadequate or inappropriate treatment of hyperphosphatemia. While this is an attractive hypothesis, it remains unproven.

The interrelationships among chronic renal failure, phosphate, calcium, vascular disease, and the treatment of divalent ion disorders are complex, and the significance of coronary artery calcifications is controversial, especially in patients with chronic renal failure. Moreover, clinical concerns about hyperphosphatemia, calcium, calcium-phosphate product, and vascular calcifications are further clouded by issues raised in the marketing of phosphate binders.[5]

This review summarizes the major reports that relate disordered calcium and phosphate metabolism to mortality in dialysis patients. It then places these findings in the context of what is and is not known about coronary artery calcifications in patients with and without chronic renal failure.

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HYPERPHOSPHATEMIA IN CHRONIC RENAL FAILURE

The kidney is the major organ for maintaining phosphate homeostasis. Intestinal absorption of dietary phosphate is largely unregulated, so phosphate homeostasis is maintained primarily by renal excretion.[6] The kidney also plays an important role in calcium homeostasis by generating calcitriol and clearing calcium. Accordingly, some of the earliest disturbances in homeostasis that occur as chronic renal failure progresses result from the abnormal retention of phosphate and changes in overall calcium metabolism.[7]

Phosphate retention occurs early and inevitably as the glomerular filtration rate declines. This is offset initially by increased secretion of parathyroid hormone (PTH) triggered by decreased ionized calcium. Parathyroid hormone levels tend to maintain serum calcium and phosphate concentrations in the normal range,[8] but without treatment hyperphosphatemia typically ensues as the glomerular filtration rate falls below about 20 to 30 mL/min. Hyperphosphatemia may further affect calcium metabolism by augmenting PTH secretion, reducing calcitriol production, and inducing skeletal resistance to PTH, thereby limiting calcium resorption from bone.[9]

Phosphate retention occurs early and inevitably as glomerular filtration rate declines

In animal models, early reduction in phosphate intake can prevent or delay many of these changes,[8] but dietary restriction of phosphate in humans has limited clinical effectiveness because phosphates are ubiquitous in normal diets, especially with the high protein intake recommended for patients on dialysis. Weekly phosphate intake in patients on hemodialysis exceeds weekly removal by approximately 1,030 mg.[7] Moreover, calcitriol or vitamin D analogues are often given to suppress PTH secretion and prevent or reverse secondary hyperparathyroidism.[10,11] These may increase the intestinal absorption of calcium and phosphate.

HYPERPHOSPHATEMIA AND MORTALITY

Although the concern about disordered phosphate and calcium metabolism in chronic renal failure focuses mainly on bone disease, recent observational studies connect hyperphosphatemia to cardiovascular mortality in patients on dialysis.

USRDS mortality analysis

Using two large random cross-sectional samples of patients on hemodialysis from the United States Renal Data System (N = 6,407), Block et al[2] found that 39% of patients had serum phosphate concentrations above 6.5 mg/dL. These hyperphosphatemic patients had a relative risk (RR) of mortality of 1.27 compared with patients with serum phosphate levels between 2.4 and 6.5 mg/dL. All patients had been on dialysis for at least 1 year (average 4.5 years). About 20% of patients had a calcium-phosphate product greater than 72 mg^2/dL^2, and these patients had a significantly higher risk of death compared with a reference group with calcium-phosphate products between 42 and 52 mg^2/dL^2 (RR = 1.34; $P < .01$). Serum calcium concentration was not an independent risk factor at any level, however, so the association between calcium-phosphate product and mortality was attributed to hyperphosphatemia. Parathyroid hormone levels were weakly associated with mortality risk, and this association was heavily influenced by a small group of patients with very high PTH values (> 1,000 pg/mL). The authors concluded that hyperphosphatemia represents a risk for increased mortality in patients on dialysis for at least 1 year and that serum phosphate levels should be maintained below 6.5 mg/dL.

Analysis of cardiovascular mortality

Ganesh et al[4] extended these findings by assessing cardiovascular-specific deaths as a function of serum phosphate concentrations in a similar cohort of 12,833 patients on hemodialysis. A total of 4,120 deaths occurred over 2 years, of which 27% were sudden deaths and 18% were attributed to coronary artery disease or other cardiac causes. Patients with serum phosphate concentrations greater than 6.5 mg/dL had a relative risk of 1.41 for cardiac death and of 1.20 for sudden death compared with patients whose concentrations were between 2.4 and 6.5 mg/dL. When adjusted for age, duration of end-stage renal disease, race, gender, diabetes, smoking, AIDS, and neoplasm, the relative risk of mortality was a continuous function of serum

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phosphate concentration and calcium-phosphate product. A weak association was found between increased mortality risk and PTH levels between 496 and 9,476 pg/mL.

Correlation, not causality

These two studies draw heightened attention to the potential adverse effects of hyperphosphatemia in the context of hemodialysis. As observational studies, however, they demonstrate correlations rather than causality and cannot provide a mechanism. Notably, each study indicates that the consistent risk factor is hyperphosphatemia, not hypercalcemia or hyperparathyroidism.

PREVENTION OF HYPERPHOSPHATEMIA WITH PHOSPHATE-BINDING AGENTS

Because restriction of dietary phosphate is largely ineffective, the primary way to prevent hyperphosphatemia in patients with chronic renal failure is by inhibiting intestinal phosphate absorption through the use of phosphate binders. There are primarily two types of agents currently used as intestinal phosphate binders:

- **Calcium salts of acetate** (PhosLo, Braintree Laboratories, Braintree, Mass) or **calcium salts of carbonate** (eg, Tums, GlaxoSmithKline, London, UK, and other generic products)
- **Sevelamer hydrochloride** (Renagel, Genzyme, Cambridge, Mass), a calcium-free allylamine polymer.

Both calcium salts are commonly prescribed as phosphate-binding agents, although calcium acetate is more efficient than calcium carbonate and provides less absorbable calcium.[6] Calcium acetate and sevelamer are marketed specifically for use as phosphate binders in chronic renal failure and have been compared in a clinical trial.

Calcium acetate vs sevelamer

Only one randomized comparative trial of calcium acetate and sevelamer has been published to date. It was a crossover study of 80 patients on hemodialysis that found sevelamer and calcium acetate to have similar efficacy in controlling hyperphosphatemia.[12] At the end of the 8-week treatment periods, serum phosphate concentrations were comparable with the two agents, averaging 6.4 ± 1.7 mg/dL with sevelamer and 5.9 ± 1.7 mg/dL with calcium acetate. The calcium-phosphate products also were similar between the treatments (60.0 ± 16.1 mg^2/dL^2 vs 57.1 ± 16.2 mg^2/dL^2, respectively). There was a trend toward higher serum calcium concentrations and lower PTH concentrations during treatment with calcium acetate. Sixty-six percent of all patients received vitamin D analogues during the study, with stable calcium intakes of about 550 mg/d and phosphate intakes of 780 to 800 mg/d. Hypercalcemia, defined as at least one instance of serum calcium levels of 11 mg/dL or greater during the 8-week study periods, occurred in 22% of patients while on calcium acetate versus 5% while on sevelamer.

Thus, the two agents had comparable efficacy in reducing hyperphosphatemia and calcium-phosphate products in patients with chronic renal failure, although hypercalcemia was more common with calcium acetate.

Comparative costs

Both treatments required a high daily intake of medication.[12] The mean dosage of calcium acetate started at 3.4 g/d and rose to 5.0 g/d; the mean dosage of sevelamer started at 3.4 g/d and rose to 4.9 g/d. This translates to a cost of about \$22 to \$32 per month for calcium acetate and \$142 to \$205 per month for sevelamer.* Typically, when one product has such a high cost premium and little if any discernible therapeutic advantage, it tends to have little attraction. Sevelamer emerged, however, at a time when a series of independent studies raised questions about a correlation between calcium intake and vascular calcifications in patients on dialysis. A subsequent aggressive marketing program linked these observations to "cardiac calcification."[5]

Coronary atherosclerosis occurs at an earlier age in patients with end-stage renal disease

CORONARY CALCIFICATIONS IN PATIENTS ON DIALYSIS

It has long been held that patients on dialysis have accelerated atherosclerosis.[13] Athero-

*Based on costs from www.drugstore.com (PhosLo 667 mg: \$14.35 per 100 tablets; Renagel 800 mg: \$111.81 per 100 tablets).

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sclerotic plaques tend to calcify. Electron-beam computed tomography (EBCT) is a recent imaging technology that provides a noninvasive, highly sensitive measurement of coronary artery calcification.[14–16] Calcification scores derived from EBCT correlate with atherosclerotic burden, at least in patients without chronic renal failure.

Clinical findings

Goodman et al[17] examined coronary calcification by EBCT in 39 young adults on peritoneal dialysis or hemodialysis and compared the findings to those in 60 age-matched normal subjects. The patients on dialysis were divided into those under age 20 (n = 23) and those between ages 20 and 30 (n = 16). Fourteen of the 16 older patients demonstrated coronary calcifications, and they had a strikingly high average Agatston score of 1,157 (range 2 to 7,047; median 297). None of the 23 patients under age 20 and only 3 of the 60 normal subjects had coronary calcifications. The mean patient age was 26 ± 3 years in the calcification group compared with 15 ± 5 years in the group without calcifications.

Factors other than atherosclerotic burden are involved in calcification

Although both groups were young, their cumulative medical experiences were profoundly different. For the group with coronary calcifications, the median age at the start of dialysis was 13 years, which means that they had lived half their lives on dialysis or with a transplanted kidney. The prevalence of calcifications was much higher (13/27) in patients who had had kidney transplants than in those who had not (1/12). The mean duration of dialysis was longer for the group with coronary calcifications (14 ± 5 years) than for those without calcifications (4 ± 4 years). There was no difference in distribution between patients undergoing peritoneal dialysis as opposed to hemodialysis.

Given the youth of these patients and their strikingly high calcification scores, the authors hypothesized that abnormal divalent ion metabolism and its treatments may contribute to development of coronary calcifications in patients with end-stage renal disease. In this regard, the average serum phosphate concentration was marginally higher in those with coronary calcifications than in those without (6.9 vs 6.3 mg/dL; P = .06), and the calcium-phosphate product was significantly higher in those with coronary calcifications than in those without (65.0 vs 56.4 mg^2/dL^2; P < .04). Serum calcium concentrations and PTH levels were not different. Hyperphosphatemia, which has been correlated with increased mortality risk among patients on dialysis in other studies,[2,4] was not associated with higher coronary calcium scores.[17]

On the basis of these observations, Goodman et al[17] attributed the prevalence of coronary calcifications (ie, coronary atherosclerosis) to the duration of dialysis and attributed the high calcification scores to higher calcium intake, including intake of calcium-containing phosphate binders. This is distinct from concluding (1) that disordered mineral metabolism caused the atherosclerosis that became calcified, (2) that there is concordance between calcium scores in patients with end-stage renal disease and otherwise normal subjects with similar degrees of coronary disease, or (3) that calcification scores in patients on dialysis correlate linearly with cardiovascular events.

Along these lines, Braun et al[18] correlated calcification scores and coronary angiographic findings in 49 patients on chronic dialysis and compared them with findings in 102 patients with coronary artery disease who were not on dialysis. Calcification scores were 2.5 to 5 times higher in patients on dialysis and correlated with age and hypertension but not with serum phosphate, calcium, or PTH concentrations. A similar study by Utsunomiya[19] in 30 patients with and 22 patients without renal failure also found that calcification of coronary atherosclerosis is higher in the presence of renal failure. These two studies were further supported by morphologic and x-ray diffraction analysis of coronary arteries from 27 patients with end-stage renal disease that showed increased medial thickness and increased plaque calcification relative to coronary arteries from matched patients without renal failure.[20]

Calcium scores: the interpretation challenge

The interpretation of coronary artery calcifications as a surrogate for coronary atherosclerosis and cardiovascular events is central to concerns about calcium and phosphate bal-

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ance in patients with chronic renal failure. Other articles in this supplement[14,15] and a consensus statement from the American College of Cardiology and American Heart Association[16] review the technical aspects of assessing coronary artery calcifications and the challenges of interpreting their clinical significance and utility. At least in patients without chronic renal failure, coronary artery calcifications correlate with atherosclerotic burden, although not necessarily with acute coronary events. In asymptomatic patients, EBCT-derived calcification scores have a strong negative predictive value (> 99%) for major coronary events over 3 to 4 years but a much weaker positive predictive value (11% to 18%).[16] Although there is a quantitative relationship between atherosclerosis and calcium scores, this relationship is nonlinear. Interscan reliability is fair to poor, as variability ranges from 14% to 51%. Overall, it is not clear that calcification scores as determined by EBCT provide incremental information to that available from risk analysis by Framingham Heart Study or National Cholesterol Education Program methods.

Only limited additional information is available on the significance of coronary artery calcifications in patients with chronic renal failure and its associated disorders. In a study of 24 dialysis patients with an average age of 53 ± 14 years and average dialysis duration of 64 ± 69 months, 1-year progression of coronary calcification as detected by EBCT was associated with a higher baseline calcium score, preexisting dyslipidemia, a high triglyceride level, and a low high-density lipoprotein cholesterol level.[21] Progression was not associated with serum phosphate concentration.

PHOSPHATE AND VASCULAR CALCIFICATION

Vascular calcification is an active process similar to bone mineralization.[22–24] In cultures of human aortic smooth muscle cells, increasing the concentration of inorganic phosphate in the culture media increased cell mineralization, predominantly bioapatite. This mineralization effect of high ambient phosphate concentrations also occurs in human fetal, adult, and atherosclerotic plaque-derived smooth muscle cells.[22] When cultured in high-phosphate media, human smooth muscle cells upregulate the transcription of osteocalcin, a promoter of vascular calcium deposition. These cells undergo a dramatic phenotypic change to osteogenic cells under in vitro conditions that promote culture or vascular calcification.[23] In addition to osteocalcin, several other bone-related proteins listed in TABLE 1 are involved in either a protective or a promoting effect on vascular calcification in human and cell culture models.[23]

TABLE 1

Bone-associated proteins associated with vascular calcification

INDUCERS	INHIBITORS
Osteocalcin	Osteopontin
Osteonectin	Matrix Gla protein
Bone morphogenic protein type 2a (BMP-2a)	Osteoprotegerin
Alkaline phosphatase	Type 1 collagen
Bone sialoprotein	PTHr-peptide

This background provides a strong foundation for concern about hyperphosphatemia as a key factor that can promote vascular calcification. The clinical significance of this calcification as either a cause or a consequence of atherosclerotic or other vascular pathology may not be entirely clear in patients with chronic renal failure, but it is presumably unfavorable.

Systematic replacement of calcium-containing phosphate binders is not warranted

CALCIUM INTAKE AND DURATION OF DIALYSIS

Because phosphate binders are inherently associated with dialysis therapy, the duration of dialysis and the prescribed intake of phosphate binders are likely to be linearly related. Since aluminum-containing agents were abandoned (because of aluminum-related bone and neurologic diseases[6]), the prevalent phosphate binders have contained calcium. Accordingly, the length of time on dialysis

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therapy, the cumulative prescribed dose of phosphate binders, and the cumulative calcium intake are potentially confounded variables, in that an event related to one is highly likely to be correlated with another. A related point concerns the uncertain relationships among prescribed versus ingested doses of calcium-containing phosphate binders, as well as the net absorption of calcium. Chronic renal failure typically results in decreased intestinal absorption of calcium and negative calcium balance because of reduced intake[25] and reduced calcitriol production.[26] Calcium balance studies show that patients with chronic renal failure have a slightly negative calcium balance but can achieve a positive balance with a normal or high-calcium diet.[7]

Because the kidneys serve as the major alternative route of calcium clearance other than deposition in bone and soft tissue, patients with chronic renal failure who are on dialysis have limited means of accommodating any excess calcium intake from diet or hemodialysis. Hsu[7] outlined the approximate intake of calcium in patients on dialysis three times per week, using a 2.5 or 3.5 mEq/L dialysate calcium concentration. For a 2.5 mEq/L concentration, the net calcium balance per day is estimated to be 216 mg, assuming daily intake of 800 mg. This exceeds the estimated threshold balance of 114 mg/d for 18- to 30-year-olds. The fate of any calcium accumulation is uncertain, but it presumably rests in bone and soft tissue.

Coronary artery disease screening should be as intense for dialysis evaluation as for pretransplant evaluation

RECOMMENDATIONS AND CONCLUSIONS

Hyperphosphatemia is emerging as a strong and unique risk factor for cardiovascular morbidity and mortality in patients on dialysis for chronic renal failure. Control of hyperphosphatemia now assumes added and dominant importance beyond concerns about metabolic bone disease and secondary hyperparathyroidism, conditions that may be overtreated by our current regimens of high-dose vitamin D.

Treatment goals

Overall treatment should focus on achieving and maintaining a normal serum phosphate concentration of less than 5.5 mg/dL (and thereby usually a normal calcium-phosphate product). This can usually be achieved through dietary restrictions, adequate or intensified dialysis, rational use of phosphate binders, and conservative use of oral or intravenous vitamin D or its analogues.

Use of phosphate binders

Calcium-containing phosphate binders remain standard therapy because they are effective, affordable, and safe, and they have an added advantage of providing supplemental calcium. Adjustments in their use are needed if hyperphosphatemia is uncontrolled or hypercalcemia emerges. These adjustments should include attention to correct use, review of vitamin D exposure and dialysate calcium concentration, and assessment of parathyroid function and bone mineralization. Selected patients may benefit from the addition or substitution of calcium-free phosphate binders, but the systematic replacement of calcium-containing phosphate binders is not warranted.

Cardiovascular risk reduction

Reducing cardiovascular risk in patients with chronic renal failure should focus on addressing the traditional risk factors of hypertension, dyslipidemias, diabetes, cigarette smoking, obesity, and homocysteinemia. Screening and evaluation of coronary artery disease should be no less intense for dialysis evaluation than it is for pretransplant evaluation, and it should rely on traditional cardiovascular risk-factor analysis and appropriate stress tests.

Value of calcium scoring

For patients with or without chronic renal failure, the incremental value of coronary artery calcium scoring by EBCT is limited. Because of the very high negative predictive value of EBCT evaluation, its greatest usefulness may be in screening for the *absence* of significant atherosclerotic burden or luminal obstructive coronary disease in patients with one or more risk factors. Alternately, if EBCT evaluation is positive, it may be useful in identifying patients who should be upgraded to a higher risk category.

The limited data on coronary artery calcium scoring in the setting of chronic renal failure and dialysis indicate that factors other than atherosclerotic burden are involved in

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calcification and that scores tend to be higher in patients with rather than without renal failure. Caution is therefore warranted before ascribing the degree of calcification to the extent of atherosclerosis or to the risk of an acute coronary event. In particular, changes in calcification scores cannot now be attributed to changes in either atherosclerotic burden or risk of a coronary event. The data tend to confirm that coronary atherosclerosis occurs at an earlier age in patients with end-stage renal disease, but the limited observations to date do not allow fully adjusted risk comparisons with normal subjects. Within these limitations, coronary artery calcium scores in chronic renal failure show some correlation with age, dyslipidemias, hypertension, duration of dialysis, and exposure to phosphate binders that until most recently were almost exclusively calcium-containing agents.

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