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Arterial Calcification in Chronic Kidney Disease

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Hyperphosphatemia is associated with soft-tissue calcification and bone disease. Nephrologists prescribe phosphate binders to decrease dietary phosphate absorption, reduce serum phosphorus concentrations, and minimize the risk for soft-tissue calcification and bone disease. Recent data suggest that the dose of calcium used as a phosphate binder may contribute to the risk for cardiovascular calcification. Chronic positive calcium balance from diet, dialysis, and calcium-based phosphate binders or intermittent hypercalcemia may favor precipitation of calcium and phosphate into tissues. Calcium suppresses parathyroid hormone (PTH) secretion and bone turnover, limiting the ability of bone to incorporate calcium and phosphorus. Sevelamer, a nonabsorbed polymer, allows physicians to bind dietary phosphate and decrease serum phosphorus without unwanted absorption of metals or calcium or oversuppression of PTH. In a comparative trial, calcium-based phosphate binders were associated with progressive coronary artery and aortic calcification that was attenuated by sevelamer. The optimal phosphate binder is one that controls hyperphosphatemia prevents soft-tissue calcification and preserves bone health.
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Cardiovascular disease remains the leading cause of death in the chronic kidney disease (CKD) population. Half of all deaths in dialysis patients are caused by cardiovascular disease.[1,2] CKD patients are at greater risk for myocardial ischemia and infarction, and other cardiovascular complications, likely owing to both classic risk factors and risk factors unique to renal failure. Hyperphosphatemia has emerged as one of the more important renal cardiovascular risk factors because it clearly increases the risk for all-cause and cardiovascular mortality.[3-5] Treatment traditionally has used serum phosphorus control as a surrogate for clinical benefit. New advances in imaging have made it possible to look at intermediate outcomes such as cardiovascular calcification, which may predict clinical outcome.

Disorders of Phosphorus, Calcium, and Parathyroid Hormone in CKD

Disturbances of calcium and phosphorus metabolism are among the most common adverse metabolic consequences of end-stage renal disease (ESRD). The majority of patients undergoing hemodialysis have serum phosphorus concentrations greater than 5.5 mg/dL.[4] Conventional hemodialysis is an inefficient mechanism for the removal of phosphorus, requiring the use of phosphate binders in most dialysis patients.

Hypercalcemia is found in as many as 38% of dialysis patients.[6-9] In persons with normal renal function, transient increases in calcium absorption do not result in hypercalcemia owing to renal excretion of calcium. The calcium not excreted immediately by the kidneys is incorporated into remodeling bone. In dialysis patients there are at least 5 sources of calcium burden. First, ESRD patients ordinarily receive vitamin D therapy (1,25-dihydroxyvitamin D or one of its analogues) to control secondary hyperparathyroidism. This treatment has the side effect of increasing intestinal calcium absorption.[10] Second, patients absorb calcium from the dialysate. The most common formulation has a calcium concentration of 2.5 mEq/L, which can cause a net positive calcium balance during a 4-hour dialysis session.[11,12] Third, many ESRD patients receive calcium-containing phosphate binders. A patient who consumes 5 g/d of calcium acetate has a daily calcium intake of 1,250 mg from the binder alone. Fourth, there is calcium efflux from bone, the extent of which depends on the relative balances of parathyroid hormone (PTH), phosphorus, and calcitriol. Finally, there is calcium obtained from the diet. In aggregate, the calcium intake of dialysis patients is far in excess of the recommended

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1,200-mg daily allowance for calcium. In a person with normal renal function, such a load could be handled through renal and intestinal excretion and bone buffering. However, in patients with ESRD, the only way the body has of disposing excess calcium is through intestinal excretion, which accounts for only about 130 mg/d.[12]

Hyperparathyroidism is highly prevalent in patients with ESRD based on epidemiologic data.[4] However, in other patients, intact (iPTH) levels are inappropriately low owing to aluminum intoxication, excessive intake of oral calcium, or overtreatment with calcitriol. Low PTH levels result in abnormally low bone turnover. This low turnover, or adynamic bone, makes the body less able to buffer serum calcium concentrations and increases the risk for hypercalcemia.[7,8]

It is now known that abnormalities in phosphorus and calcium metabolism increase the risk for cardiovascular events and cardiac death in dialysis patients. The association of hyperphosphatemia and mortality risk was first noted by Lowrie and Lew[3] in 1990 and confirmed in 1998 by Block et al,[4] and was determined to be caused by excess cardiovascular death.[5] These results were confirmed most recently by Teng et al[13] in an analysis of over 60,000 dialysis patients and showed that all-cause mortality was related directly to serum phosphorus, calcium, and PTH. Interestingly, paracalcitol, an analogue of calcitriol producing less hyperphosphatemia and hypercalcemia, was associated with a lower mortality than calcitriol.

Soft-Tissue Calcification

Soft-tissue calcification has been reported in the majority of CKD patients. In an article published in 1977, Kuzela et al[14] described autopsy findings in 56 patients who had received dialysis for at least 6 months and 18 patients with chronic renal failure who had survived a similar time without hemodialysis. Among these patients, 79% of the former and 44% of the latter had generalized calcification. Similar degrees of calcification have been detected using radiographic methods. Braun et al[15] first reported the use of electron beam computed tomography (EBCT) to detect calcification in ESRD patients. They obtained EBCT scans in 49 patients aged 28 to 74 years who were receiving hemodialysis. They compared the results with those in 102 patients of similar age without ESRD who underwent angiography because of angina-like chest pain. The dialysis patients underwent a second scan 11 to 13 months later. The mean calcification score in the dialysis patients was 4,290 ± 1,509, whereas the mean score in the patients without ESRD but with suspected heart disease was 406 ± 791. Scores of greater than 400 are considered severe.[16] Mitral valve calcification was seen in 59% of the ESRD patients and aortic valve calcification was seen in 55%. Interestingly, there was an inverse correlation between the calcification score and the density of the trabecular bone. There was a significant increase in the calcification score found at the second scan approximately 1 year after the first.

Calcification has been associated strongly with disturbances of phosphorus and calcium. In a series of 137 patients, Kimura et al[17] sought to identify correlates of aortic calcification determined by abdominal CT scanning. Only 2 such factors were found: persistently high systolic blood pressure and an increased calcium-phosphorus product. Those patients who had a calcium-phosphorus product of at least 60 mg^2/dL^2 on 4 or more of 24 measurements over a 1-year period had an average aortic calcification score (area of calcification divided by the aortic cross-sectional area) of 26.1% ± 13.6%, whereas the corresponding figure was 17.8% ± 17.2% in patients who had high calcium-phosphorus product on fewer than 4 occasions ($P < .05$).

Goodman et al[18] reported an EBCT study of young ESRD patients. Scans of 39 dialysis patients who ranged in age from 7 to 30 years were compared with those of 60 normal subjects aged 20 to 30 years. Of the 16 dialysis patients 20 years of age and older, 14 had calcification, the average score being 1,157 ± 1,996 and the median score being 297. Only 3 of the normal subjects in this age range showed calcification. Among the dialysis patients, those with calcification had higher serum phosphorus concentrations and calcium-phosphorus products, were older, had been receiving dialysis longer (14.5 ± 5 versus 4 ± 4 y), and consumed twice as much calcium as a phosphate binder than those without calcification. Calcification progressed rapidly. After a mean of 22 ± 7 months, 2 of the 12 patients who were calcium free on the first scan had coronary calcification on the second scan. In the 10 patients who had calcification at baseline, 9 had higher scores on follow-up evaluation at 20 ± 3 months, with the amount of calcium nearly doubling (125 ± 104 to 249 ± 216). The serum phosphorus concentration and calcium-phosphorus product correlated with the change in the calcification score.

Raggi et al[19] performed EBCT in 205 patients receiving hemodialysis and found coronary calcium in 83% of patients. Calcification of at least one valve was detected in 58%, and 73% of the patients had calcification scores above the 75th percentile for their age and sex. Older age, longer duration of dialysis, male sex, diabetes, higher serum phosphorus levels, and higher serum calcium levels were associated with more severe calcification. Calcification was associated strongly with a history of cardiovascular disease (eg, myocardial infarction).

Tamashiro et al[20] reported the results of EBCT scanning in a group of 24 Japanese dialysis patients. Patients underwent baseline and repeat scans between 12 and 19 months later (average, 17 mo). The mean score increased from 449 ± 605 to 669 ± 894, with the mean change in calcification score of 220 ± 78. Rapid progression was associated significantly with high triglyceride levels, low high-density lipoprotein cholesterol, and severity of baseline calcification score.

It is clear from these data that EBCT can be used effectively to detect and monitor coronary calcification in patients with ESRD. Spiral CT with retrospective cardiac gating also is accurate and is more widely available, particularly in Europe. However, a number of other radiographic techniques including Doppler ultrasound and plain radiographs are effective in detecting calcification.

Clinical Consequences of Arterial Calcification

Arterial calcification is damaging primarily by stiffening large arteries, leading to arterial dilation and hypertrophy, increasing systolic pressure and pulse pressure, and reducing diastolic pressure. These changes increase left ventricular afterload and reduce coronary perfusion.

Guerin et al[21] reported an extensive study of the functional consequences of vascular calcification. They studied 120 nondiabetic ESRD patients who were free of significant valvular disease and common carotid stenosis and had not suffered myocardial infarction or heart failure. All underwent B-mode echocardiography of the common carotid and femoral arteries and the aorta. The investigators determined the presence or absence of calcification in the common carotid artery, abdominal aorta, ileofemoral axis, and legs, and added the information to create a calcification score from 0 to 4. A score of 0 indicated no calcification in any location whereas a score of 4 indicated calcification in all locations. The investigators also calculated vessel distensibility and elastic incremental modulus (Einc), both of which are measures of stiffness. Higher calcification scores were associated with reduced stroke volume, left ventricular fractional shortening, and the ratio of the maximum early diastolic flow velocity to the maximum late atrial flow velocity. Higher scores were associated with greater diameters of the common carotid artery, aortic root, and aortic bifurcation and higher intima-medial thickness. The aortic pulse wave velocity and the carotid Einc likewise increased with higher score. The distensibility of the common carotid artery decreased with greater calcium deposition. After adjustment for confounding factors, carotid distensibility, aortic pulse wave velocity, and carotid Einc were significantly associated with the degree of calcification as well as patient age and mean blood pressure. This research team also noted an independent association of age, duration of dialysis, high serum fibrinogen concentration, and the prescribed dose of calcium-based phosphate binder with calcification.

Blacher et al[22] reported an association between the increased aortic pulse-wave velocity (PWV), a classic marker of increased arterial stiffness, and all-cause mortality and cardiovascular mortality. In a group of 241 hemodialysis patients, 73 deaths occurred including 48 cardiovascular and 25 noncardiovascular fatal events. At entry, together with standard clinical and biochemical analyses, patients underwent echocardiography and aortic PWV measured by Doppler ultrasonography. On the basis of Cox analyses, 2 factors emerged as predictors of all-cause and cardiovascular mortality: age and aortic PWV. After adjustment for all the confounding factors, the odds ratio for PWV greater than 12.0 m/s versus less than 9.4 m/s was 5.4 (95% confidence interval, 2.4-11.9) for all-cause mortality and 5.9 (95% confidence interval, 2.3-15.5) for cardiovascular mortality. For each PWV increase of 1 m/s in the study population, the all-cause mortality adjusted odds ratio was 1.39 (95% confidence interval, 1.19-1.62).

This same group also has linked calcification directly to cardiovascular death. They followed-up 110 patients for an average of 53 $\pm$ 21 months, during which 25 cardiovascular and 14 noncardiovascular deaths occurred.[23] Carotid Einc, a measure of arterial stiffness, was associated with arterial calcification and most clearly was related to risk for death. Risk for death also increased with the number of vascular sites involved with calcifications. These 2 predictors of death were additive. Each increase in calcification score of one unit was associated with a 1.9 and 2.6 hazard ratio for all cause and cardiovascular mortality, respectively.

There has been debate about the location of calcification in ESRD patients because calcification can occur in either the intima in association with atherosclerotic plaque or in the media in association with the elastic lamina. London et al[24] addressed this question by categorizing 202 dialysis patients as having either intimal or medial calcification using soft-tissue radiographs of the pelvis and thighs. Intimal was defined as discrete irregular and patchy arterial calcification and medial was defined as uniform linear railroad track–type calcifications. Intimal calcification usually was observed in older patients with more traditional risk factors for atherosclerosis. The calcium carbonate dose was higher in patients with medial calcification compared with those without calcification. Medial calcification was observed in young and middle-aged patients and was more associated with duration of dialysis and increased levels of serum phosphorus, serum calcium, and the dose of calcium carbonate. Both forms of calcification were associated with low diastolic pressure, increased pulse pressure, arterial dilation, arterial stiffening, and dramatically increased relative risk for all-cause and cardiovascular mortality. The relative risk for death in those with medial calcification versus no calcification was 15.7, and intimal calcification versus no calcification was 4.85. The relative risk for calcification versus no calcification for cardiovascular mortality was 45.7 for medial and 7.50 for intimal disease.

Effect of Phosphate Binders on Arterial Calcification

Only a single published comparative trial has assessed the effects of phosphate binders on calcification. However, previous observational studies of patients showed calcification progression. In the Braun et al[15] study, 49 German adult hemodialysis patients were scanned at baseline and 11 to 13 months later. Calcification scores increased in every patient on the repeat scan. For the entire group of patients the second measurement was significantly ($P < .05$) greater than the first measurement. In the Goodman et al[18] study, 10 young adult dialysis patients with baseline coronary artery calcification had repeat scans an average of 20 months later. Scores doubled over this time period. In both studies, almost all patients were using calcium-based phosphate binders. Clearly calcium-based phosphate binder therapy is not sufficient to prevent arterial calcification.

The single interventional trial, the Treat to Goal study, assessed the effects of sevelamer, a nonabsorbed, calcium-

and metal-free phosphate binder, compared with calcium on the progression of coronary artery and aortic calcification.[25] Patients underwent EBCT scans at the start of the trial and after 6 and 12 months of therapy.

A total of 200 patients on hemodialysis who were taking one or more phosphate binders and became hyperphosphatemic (>5.5 mg/dL) during a 2-week washout period were randomized in a 1:1 design to receive either sevelamer or calcium acetate (United States)/calcium carbonate (Europe), stratified by the presence or absence of diabetes. Sevelamer was supplied as Renagel 800-mg tablets (Genzyme, Cambridge, MA). Calcium acetate was supplied to patients in the United States as PhosLo 667-mg tablets (Nabi, Boca Raton, FL). Calcium carbonate was supplied to patients in Europe (EU) as CalciumCarbonat Sertuerner 500-mg tablets (Sertuerner Arzneimittel GmbH, Guertersloh, Germany).

Serum phosphorus levels reached a mean of 5.1 mg/dL in both treatment groups at 12 months. Serum calcium level was significantly higher in the calcium group compared with the sevelamer group ($P = .002$). A significantly greater percentage of patients in the calcium group experienced hypercalcemic events, defined as serum calcium levels of 10.5 mg/dL or greater (sevelamer, 17%; calcium, 43%; $P = .0005$). The percentage of patients who were hypercalcemic (≥10.5 mg/dL) at any point over time varied between 11% and 22% for calcium-treated patients compared with 3% to 8% for sevelamer-treated patients. Significant ($P < .0001$) reductions in the serum calcium-phosphorus product were observed for both treatment groups at the end of treatment. These differences were not statistically significant between the treatment groups. Patients on sevelamer achieved a mean serum calcium-phosphorus product level of 48 (mg/dL)(2), whereas patients on calcium achieved a mean serum calcium-phosphorus product level of 49 (mg/dL).[2] Oversuppression of PTH occurred in a greater proportion of calcium-treated patients (57% versus 30% of sevelamer-treated patients, $P = .001$) despite protocol-specified reductions in vitamin D.

At baseline, cardiovascular calcification was frequent and severe. More than 4 in 5 patients (83%) had evidence of coronary calcification. Aortic calcification was detected in 80% of patients. Forty-six percent of patients had calcification of the mitral valve, and 35% of patients had calcification of the aortic valve. Overall, the sevelamer group had less progression of coronary artery calcification at both 6 and 12 months. For the group treated with calcium there was significant progression of coronary artery score at 6 months (mean 110, median 56, $P = .0001$) and 12 months (mean 151, median 37, $P = .0002$), and the aorta at 6 months (mean 230, median 11, $P = .02$) and 12 months (mean 185, median 75, $P = .0007$). In contrast, patients treated with sevelamer had mean decreases (P-NS) in calcification scores and median changes of zero in both the coronary artery and aorta. The differences between treatments were statistically significant at both 6 months and 12 months at both anatomic locations. In percentage change analyses among patients with baseline calcification scores of at least 30, the sevelamer-treated group had significantly less progression than the calcium group at both the coronary artery (6% versus 25%, $P = .01$) and aorta (5% versus 28%, $P = .04$).

Half the patients in the Treat to Goal study were from US centers and the remaining half were from European centers (Germany and Austria). There were independent randomizations for both regions, creating 2 independent estimates of the treatment effects. In both regions, sevelamer attenuated the progression of calcification relative to the calcium groups (calcium acetate in the United States and calcium carbonate in Europe). Results for the US randomized portion have been published separately.[26] Although the study was not designed to answer the question of whether calcium acetate offers any advantage over calcium carbonate, the data suggest that there are no appreciable differences in preventing hypercalcemia, calcium loading, oversuppression of iPTH, and coronary artery and aortic calcification.

Conclusions

Hyperphosphatemia is a common and serious complication of CKD that leads to metastatic calcification. Increased serum phosphorus levels, calcium levels, and disturbances of PTH increase the risk for cardiovascular death at least in part via cardiovascular calcification that stiffens the normally compliant large arteries. Calcium used as a phosphate binder is associated with increased risk for arterial calcification. Sevelamer, a nonabsorbed phosphate-binding polymer, attenuated coronary artery and aortic calcification relative to calcium in hemodialysis patients despite similar control of serum phosphorus and the calcium phosphorus product. Calcium load or the metabolic consequences of absorbed calcium such as hypercalcemia and low PTH levels may contribute to deposition of calcium and phosphorus into nonosseous tissues.

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