Vascular Calcification and ESRD: A Hard Target

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End-stage renal disease (ESRD) is associated with both accelerated cardiovascular disease and alterations in vitamin D and mineral metabolism. Calcification of both coronary and extra-cardiac vessels is common in ESRD. Several studies suggest that vascular calcification is associated with coronary atherosclerosis, vascular wall stiffness, left ventricular hypertrophy, and subsequent increased mortality, but it is not yet clear if vascular calcification is a direct cause of these changes or merely a marker of disease. Reviewed here is the current state of research on the biology and the significance of vascular calcification in ESRD, the role of vitamin D therapy in its development, and options for management.

Clinical Significance of Vascular Calcification in ESRD

Although the coronary arteries are often the focus on cardiovascular disease in the general population, the peripheral arteries may be of equal, if not greater, importance in ESRD. Left ventricular hypertrophy (LVH) and associated diastolic dysfunction are associated with significantly increased mortality in patients with kidney disease and likely develop in part from progressive stiffening of the vasculature that is seen in ESRD. Normal, compliant vessels are able to dampen the increased intravascular pressure generated during systole. As this compliance is lost, higher BP and greater afterload are generated during systole, leading to the development of LVH. During diastole, in contrast, lack of vascular recoil leads to lower pressures and consequentially reduced pressure for coronary perfusion, which may already be compromised by existing coronary artery disease (3).

Does extra-cardiac vascular calcification from a disordered vitamin D-PTH axis lead to increased LVH and early mortality in ESRD? Pulse wave velocity is commonly used in research studies as a measure of arterial stiffness and predicts both cardiovascular and overall mortality in ESRD (8). Decreased bone density, as measured by quantitative computed tomography, has been linked to both increased pulse wave velocity and aortic calcification (9), supporting the model that displaced calcium from bone is inappropriately deposited in the vessel wall, leading to increased vascular stiffness and progressive cardiac disease. Indeed, mortality risk appears to increase steadily as a greater number of large arteries outside the heart (carotid, abdominal aorta, iliofemoral axis, and lower extremities) show involvement with calcification (3,10). In retrospective studies, this risk was found to be independent of other potential risk factors for mortality such as age, race, gender,
duration of hemodialysis, presence of diabetes, albumin, and inflammatory markers (11,12). This risk may spread beyond the dialysis population: one study of renal transplant recipients found that over one-third of patients had evidence of aortic calcification, and this finding was predictive of future cardiovascular events (13).

Although several studies have linked vascular calcification to worsened outcomes in dialysis, there is contradictory evidence that suggests it may be a bystander, rather than a cause, of changes in cardiac structure and function. In one animal study, LVH, diastolic dysfunction, and aortic stiffness were not associated with calcification but rather with subendothelial dysfunction and degree of chronic renal failure (14). There is likely a direct or indirect connection between kidney function and vascular integrity, but whether this is manifest directly by vascular calcification remains unknown. It is not yet known which aspects of the changes in vascular structure and function are reversible and therapeutically important. Calcification may be a treatable consequence of vascular and endothelial dysfunction, but treatment of the underlying vascular disease may be necessary to realize improvement in patient outcomes. The efficacy of therapies that can prevent or curb vascular calcification may help define the presence or absence of a causative role in increased mortality in dialysis.

Potential Therapies

If vascular calcification is linked with a heightened risk of poor cardiovascular outcomes, a logical question is how best to minimize its development and slow its progression, particularly since few therapies have been effective at reducing cardiovascular risk in ESRD. Over the past several years, there has been increasing excitement over a multitude of retrospective studies in both ESRD and pre-ESRD CKD that have demonstrated an association between the use of vitamin D receptor agonists (VDRAs) and a reduction in cardiovascular mortality. Given the central role of VDRAs in mineral metabolism and particularly their potential for increasing serum calcium and phosphorus levels, the association of VDRAs with improved outcomes at first blush appears to be somewhat of a paradox.

Evidence that directly links vitamin D therapy to vascular calcification largely stems from animal and in vitro studies. Many of these studies exposed animals to doses of calcitriol much greater than that used for suppression of PTH in clinical practice. More recent research has presented contrasting data: one animal study showed that at the lower doses optimal for control of secondary hyperparathyroidism, VDRAs reduced aortic expression of osteoblastic genes and decreased aortic calcification (15). At higher doses, calcitriol increases the calcium-phosphate product and promotes calcification (16); thus, dosing information is critical for evaluation of these data. A human study in patients with moderate to high risk of coronary disease but without CKD found that levels of 1,25-dihydroxyvitamin D inversely correlated with the degree of vascular calcification (17), while studies in advanced CKD have been mixed. One dialysis study demonstrated that children with the lowest or highest 1,25-dihydroxyvitamin D levels had the highest vascular calcification scores (18). It is also possible that the choice of VDRA may be consequential in determining effects on vascular calcification; however, clinical trials to support or refute this notion are lacking (19,20). Lastly, recent data suggest that levels of 25-hydroxyvitamin D, which reflect vitamin D obtained from the diet or sun exposure, may be inversely correlated with vascular calcification, as individuals with low levels were more likely to develop incident coronary artery calcification (21).

These conflicting results likely reflect the multifaceted nature of vitamin D biology. While increased serum calcium and phosphorus levels might confer an increased risk of vascular calcification, vitamin D also appears to modulate several factors that may impede its development. Type 1 collagen, which can serve as a scaffold for calcium deposition in vessels, is suppressed by vitamin D. Core binding factor alpha 1, a transcription factor that also may promote calcification by converting vascular smooth muscle cells to an osteoblast-like phenotype, is similarly suppressed. Suppression of other factors, such as bone morphogenic protein-2, beta catenin, and IL 6 may also be important mechanisms (22). In contrast, the production of matrix Gla protein, which is produced by vascular smooth muscle cells and can inhibit vascular calcification, is stimulated by calcitriol (23). Mutants of the klotho gene, whose product may serve as part of a receptor complex for the phosphaturic hormone fibroblast growth factor-23 (FGF23), have been linked to a phenotype of accelerated aging in animal studies, including increased vascular calcification (24). Administration of 1,25-dihydroxyvitamin D has been demonstrated to induce klotho expression, thus potentially suppressing this phenotype (25). As vitamin D has wide-ranging effects on bone metabolism, calcium and phosphate homeostasis, and vascular biology, it is likely that its ultimate effect will depend on dosage, the clinical context, and concomitant use of other medications. Studies addressing the safety of vitamin D therapy will continue to shed light on whether nutritional or active vitamin D accelerate, regress, or are indifferent to vascular calcification in humans.

Hyperphosphatemia is likely to be an important contributor to vascular calcification and may be a mechanism by which vitamin D is associated with this phenomenon in some studies. Phosphate levels correlate with vascular calcification and may be a mechanism by which vitamin D is associated with this phenomenon in some studies.

Phosphate levels correlate with vascular calcification in humans (4) and, in FGF23-null mice, a low-phosphate diet prevents both hyperphosphatemia and vascular calcification despite elevated 1,25-dihydroxyvitamin D levels (26). Retrospective data from a large cohort of incident dialysis patients suggest that the use of phosphate binders is associated with reduced mortality in dialysis (27). Sevelamer has garnered particular interest as it has the potential to reduce phosphorus levels without the additional calcium load associated with calcium-based binders. An animal model of CKD suggested that the addition of sevelamer to a high-fat diet could reduce vascular calcification (15). The “treat-to-goal” study randomized prevalent dialysis patients to either calcium-based binders or sevelamer found similar reductions in phosphorus, but a higher risk of hypercalcemia and worsening of both aortic and coronary calcification in subjects treated with the calcium-based binder (28,29). These findings were echoed in the RIND study of incident hemodialysis patients, which found both a lower
progression of coronary calcification and reduced mortality in those treated with sevelamer, rather than calcium-based binders (7,12).

In contrast to these studies, a systematic review comparing calcium-based binders to sevelamer failed to identify a mortality reduction associated with this therapy (30). The more recent CARE-2 study demonstrated similar progression of coronary calcification in 203 dialysis patients randomized to either sevelamer or calcium acetate, although the study was limited to 1 yr (31). Of note, the RIND and “treat-to-goal” studies both observed a reduction in LDL associated with sevelamer treatment, whereas CARE-2 included aggressive LDL-lowering in both arms; it is possible, although not definitive, that statin therapy is of greater importance than binder choice in control of vascular calcification. A larger, open label trial comparing sevelamer with calcium-based binders in 2103 dialysis patients found no difference in overall or cardiovascular mortality, although subgroup analysis suggested that patients over 65 may have decreased mortality with sevelamer (32).

Early studies in animals suggest that the noncalcium-based phosphate binder lanthanum, as well as calcimimetics, may decrease vascular calcification, but this has yet to be verified in humans or linked to reduced mortality (33,34). Human trials involving the use of a wide range of therapies including VDRAs (35), calcimimetics (36), bisphosphonates (37), and sodium thiosulfate (38) are planned or already underway.

Summary and Future Directions
Cardiovascular disease is the leading cause of mortality in patients with ESRD and is commonly associated with the finding of both coronary and extra-coronary vascular calcification. These findings have been linked to CKD-associated mineral bone disorder and often progress on dialysis, although individuals without calcification at baseline appear to be at low risk of developing it once dialysis therapy has begun. Vascular calcification is associated with increased vascular stiffness, promoting the development of LVH and diastolic dysfunction, both commonly seen in dialysis patients. Treatment with vitamin D analogs has been linked to a reduction in mortality in retrospective studies; while high doses of vitamin D are likely to promote calcification by increasing calcium and phosphorus absorption, the lower doses typically used for suppression of PTH may be protective. Conflicting evidence remains surrounding the advantage of sevelamer versus calcium-based binders on vascular calcification, and a definitive survival advantage has yet to be seen with its use, particularly in the setting of intensive lipid control.

Future prospective studies of therapies aimed at reducing or preventing vascular calcification will be important in defining whether it plays a direct role in the promotion of cardiovascular mortality or whether it is merely a marker of risk. Vascular calcification has not yet met the threshold of a true surrogate, although neither have several other potential intermediates available to nephrologists, including vitamin D levels. It thus remains a potentially important finding that must be used in the context of the entirety of available clinical data. Future studies of VDRAs and related agents should continue to assess vascular calcification to clarify potential effects of these drugs. Several interventions with the potential to prevent or reverse vascular calcification hold great promise. In the absence of a clearly established causative relationship between vascular calcification and clinical outcomes, however, the value of vascular calcification as a clinical trial end point remains to be determined.

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References


