

Coronary Calcification in Chronic Kidney Disease: Morphology, Mechanisms and Mortality

Alisha N. Wade and Muredach P. Reilly

Cardiovascular Institute and Institute of Diabetes, Obesity and Metabolism, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

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Chronic kidney disease (CKD) is associated with increased cardiovascular disease (CVD) morbidity and mortality (1,2). The precise contribution of coronary atherosclerotic disease (CAD) to mortality is unclear. Although acute myocardial infarction (MI) ranks behind sudden cardiac death as a cause of fatal events, sudden cardiac death has heterogeneous causes and CAD is likely a substantial contributor (3). The burden of CAD in patients with CKD makes it imperative to identify both subclinical disease and modifiable risk factors that might be potential targets for intervention.

In patients without CKD, coronary artery calcification (CAC) has emerged as a marker of subclinical atherosclerosis. In addition to an association with traditional CAD risk factors (4,5), CAC scores are correlated with the burden of coronary atherosclerosis at coronary angiography (6,7) and histopathologically at autopsy (8). CAC has been shown to be a strong predictor of future cardiovascular events across a spectrum of CVD risk (9–11).

CAC is frequently seen in patients with all stages of CKD (12–14). As with patients with normal renal function, CAC is associated with traditional CAD risk factors (15), correlates with coronary angiography (16), and provides prognostic value (17). Morphologically, CAC histopathologic lesions in patients with CKD seem to differ from those with normal renal function. In the non-CKD setting, CAC deposition is limited almost entirely to the vessel intima in association with atherosclerosis (18). In CKD, calcification is thought to be both intimal and medial (19). Both intimal and medial CAC are likely to predict CVD events, although not necessarily through the same mechanisms, with medial calcification likely contributing through hypertension and vascular stiffness (20,21). However, current imaging techniques are unable to distinguish between intimal and medial calcification, reducing the specificity of CAC as a screening tool for atherosclerosis *per se* in CKD. In patients with CKD, the relationship of traditional risk factors to CAC becomes less robust as renal impairment progresses (15,22). In contrast to statin trials in patients without CKD, such trials in

patients who had ESRD and were on hemodialysis showed no reduction in CVD outcomes (20,21). This suggests that many cardiovascular events in CKD are not driven by atherosclerosis *per se*. Whether CAC captures both atherosclerotic and nonatherosclerotic CVD risk in CKD is an important unanswered question.

Current evidence suggests that CAC is an active process in which novel regulatory factors related to inflammation and bone metabolism play a role. Vascular smooth muscle cells may de-differentiate into osteochondritic cells that are capable of mineralization. For example, osteoprotegerin, a member of the TNF superfamily, prevents osteoclast differentiation and bone resorption and has been associated with atherosclerosis in humans (23). Additional regulatory factors such as osteopontin and matrix Gla protein modulate vascular calcification. Overall, 25-hydroxyvitamin D, fetuin-A and the calcium–phosphate axis seem to be of particular importance in vascular calcification in patients with CKD but may also contribute to CAC and CVD events more generally (24).

In this issue of *CJASN*, Nakamura *et al.* (25) provide novel data on the specific anatomic location of CAC across the spectrum of CKD while Tuttle *et al.* define predictors of incident CAC of specific relevance in CKD (26). Nakamura *et al.* examined the relationship of renal function to the burden and location of histopathologic CAC in 117 patients with known CAD at autopsy. Patients were divided into five CKD categories, ranging from normal renal function to ESRD. Intimal but not medial calcification was identified in patients with stages 1 through 3 CKD, and intimal CAC increased with decreasing renal function. Medial calcification was present only in those with estimated GFR <30 ml/min per 1.73 m² but was present in coronary segments that often also contained intimal calcification. This supports previous work in which both intimal and medial coronary calcification were identified in patients with ESRD (27). Unlike previous work, Nakamura *et al.* establish the relationship of intimal and medial CAC with the full spectrum of CKD and demonstrate, importantly, that progressive intimal calcification and atherosclerosis dominate until more severe CKD ensues. These data suggest that medial calcification may be a lesser contributor to CVD mortality until CKD is more severe, whereas progressive atherosclerosis is likely to predominate in CVD across mild to moderate CKD. Ongoing lipid-lowering trials across the spectrum of CKD will provide critical

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Correspondence: Dr. Muredach P. Reilly, Cardiovascular Institute, University of Pennsylvania Medical Center, 609 BRB 2/3, 421 Curie Boulevard, Philadelphia, PA 19104-6160. Phone: 215-573-1214; Fax: 215-573-2094; E-mail: muredach@mail.med.upenn.edu

experimental evidence that supports or refutes this concept (e.g., Study of Heart and Renal Protection, NCT00125593).

Previous work demonstrated that serum phosphorous levels predict clinical CVD events in the general population and are associated with CAC in patients with CKD (28–30). Whether serum phosphorous is a causal factor is unclear. Tuttle *et al.* (26) examined the relationship of phosphorus to baseline and incident CAC in 883 community-dwelling, healthy individuals with normal renal function and without CVD at enrollment. Twenty-eight percent of participants had CAC at baseline; during 6 yr of follow-up, incident CAC developed in 33%, and prevalence at the 6-yr time point was 50%. Increasing phosphorus concentrations were associated with increased risk for CAC, with a 1-mg/dl increase associated with a prevalence odds ratio of 1.54 ($P = 0.002$) and incidence odds ratio of 1.61 ($P = 0.001$). These findings provide support for a role of serum phosphorous as either a causal or a confounding regulatory factor in driving progressive calcification and, by extension, CVD events in this setting of relatively normal kidney function. A causal role is supported by animal models in which hyperphosphatemia, without renal impairment, was associated with increased soft tissue calcification (31). Unfortunately, several potentially causal confounders, including 25-hydroxyvitamin D, parathyroid hormone, osteoprotegerin and additional novel factors, were not considered.

These two studies raise new questions that should prompt further focused research. First, Nakamura *et al.* (25) do not provide direct information about CKD patients without CAD, who represent the majority of the CKD population and have a known increase in CVD risk. Such patients could arguably benefit from noninvasive imaging of subclinical atherosclerosis. Specific knowledge of the relationship between intimal and medial coronary calcification across the spectrum of renal function in this population will be important to understand the relative role of atherosclerosis *versus* medial disease in CVD. Serum phosphorus may be a significant predictor of CAC and clinical CVD in CKD and non-CKD settings; however, additional studies are required to define whether confounding factors that regulate phosphorous and bone-vascular calcification are more important or perhaps causal. In patients with CKD, noncalcemic phosphate binders reduce arterial calcification, but whether such interventions can lower clinical CVD events remains uncertain (32). Larger cardiovascular outcome trials, perhaps targeted to patients with vascular calcification, are warranted to prove causality and define the appropriate clinical targeting in patients who are at risk for CVD across the spectrum of CKD.

In conclusion, intimal (atherosclerotic) and medial CAC both can be present in patients with CKD but occur differentially across the spectrum of renal function, and their relative contribution to clinical CVD may differ depending on where in that spectrum a patient falls. Phosphorus may be a significant predictor of CAC and CVD even when renal function is normal, but whether the relationship is causal and whether interventions that target phosphorous can affect CVD outcomes requires further study. Finally, CAC detection may be a particularly useful tool in patients with CKD. Whether CAC captures

both atherosclerotic and nonatherosclerotic CVD risk in CKD is an attractive hypothesis that warrants further study.

Disclosures

None.

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See related articles, "Coronary Calcification in Patients with Chronic Kidney Disease and Coronary Artery Disease," on pages 1892–1900, and "Longitudinal Relationships among Coronary Artery Calcification, Serum Phosphorus, and Kidney Function," on pages 1968–1973.