Vascular Calcification and Osteoprotegrin in Chronic Kidney Disease

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How Does Calcium Decide Where to Go?

This anthropomorphic question has increased importance for people with chronic kidney disease (CKD). Metabolic bone disease, which may include inadequate mineralization of bone, is very common in CKD. Calcium supplementation is often advised in an attempt to bind phosphate.

In contrast, calcium deposition in large- and medium-sized arteries is associated with atherosclerosis. Importantly, cardiovascular disease is the most common cause of death in dialysis patients [1]. This may be due in part to excess vascular calcification (VC), particularly coronary artery calcification (CAC). Worsening renal function and proteinuria are associated with the development of cardiovascular disease and increased rates of mortality [1], and progression of CAC is predictive of cardiac events after adjusting for traditional risk factors [2].

The prevalence of VC and elevated levels of CAC are extremely high for patients on dialysis; the prevalence can approach 80% when measured by CT scanning [3]. Intimal calcification of arteries has been more closely associated with cardiovascular disease than medial calcification, although both have been associated with increased mortality. The process of VC resembles ossification. Osteogenic proteins such as osteocalcin and osteonectin collect in the calcified arterial vessel and can promote differentiation of smooth muscle cells into osteoblasts. This is

often accompanied by the loss of inhibitors such as osteoprotegrin (OPG) [4].

The presence of CAC in patients with CKD requiring dialysis is independently and significantly related to the risks of not only cardiovascular disease and myocardial infarction but also to hypertension and heart failure. The progression of VC progresses with duration of hemodialysis.

Is the Risk of VC More Related to Dialysis or Is It Associated with CKD Itself?

This important question has been addressed recently by Chen et al. [5] in *JAMA Cardiology*. This prospective study included adults with CKD who were dialysis-naïve. The majority (80.4%) had an eGFR >30 mL/min/1.73 m², so they were not only dialysis naïve but also not requiring dialysis in the immediate future. The participants, who were without cardiovascular disease, were followed for a mean of 5.9 years, and all participants were measured for CAC by CT. The investigators found that the hazard ratios associated with 1 SD log of CAC were about 1.40 for cardiovascular disease, myocardial infarction, and heart failure. This relationship was found even after adjusting for traditional cardiac risk factors, including age, gender, race, physical activity, systolic blood pressure, current cigarette smoking, diabetes status, body mass index, esti-

mated glomerular filtration rate, and important biomarkers like total and HDL cholesterol levels, C-reactive protein, hemoglobin A1C, phosphorus, troponin T, and N-terminal pro-B-type natriuretic peptide. The increased risk for cardiovascular disease in patients with early CKD in this study did not appear to be quite at the magnitude of those seen in patients on dialysis. The study suggests that CAC starts early in CKD, is independent of other risk factors, and progresses as the CKD advances to dialysis.

This study, and many others, shows the value of measuring CAC in high-risk patients. But measuring CAC requires a CT scan, which may not always be convenient, practical, or affordable.

Are There Biomarkers That Might Assist the Analysis?

An article in this issue of the *American Journal of Nephrology* by Avila-Diaz et al. [6] provides more data. OPG is a glycoprotein in the tumor necrosis factor-receptor superfamily, and is known to inhibit osteoclastogenesis by acting as a decoy receptor for the receptor activator of nuclear factor- κ B ligand. In vascular smooth muscle cells, receptor activator of nuclear factor- κ B ligand appears to promote calcification, whereas the action of OPG may be protective [7]. Many retrospective studies have shown that elevated serum OPG levels are associated with the presence and severity of coronary artery disease and CAC. Retrospective studies, however, cannot show anything more than an association.

Therefore, the study by Avila-Diaz et al. [6] provides important additional information, as this appears to be the first prospective study to examine OPG and VC in patients with CKD. This study followed patients, on incident peritoneal dialysis for less than 3 months, for 1 year

and measured calcification of the abdominal aorta and pelvic vessels by CT. The study showed an expected association between VC and traditional risk factors such as older age, diabetes, high systolic blood pressure, body mass index and cholesterol. There was also a strong association with OPG, and in multivariate logistic analysis this association was the most significant (OR 1.27, $p < 0.001$). The strength of the association between OPG and VC trumped markers of inflammation (C-reactive protein) and osteoblastic activity (osteocalcin). In vitro studies have shown that osteocalcin is a continuous inhibitor of calcification in the vessel wall [8], although in vivo studies of patients with and without coronary artery disease have shown conflicting results. The link between OPG and VC in the multivariate logistic analysis in the study by Avila-Diaz et al. [6] was very strong, whereas osteocalcin was not associated. Our own research as well as that of others has shown a similar finding.

Is OPG Involved in the Pathogenesis of Arterial Calcification, Protective against It, or Merely an Innocent Bystander?

This question is not completely answered yet, but the preponderance of data suggests that it is protective, and the rise in OPG seen with VC may be compensatory. It is hoped that future research will allow clinicians to utilize tests like CAC scores and OPG levels to better predict those patients with CKD who are at a greater risk for cardiac mortality.

Disclosure Statement

The authors have no conflict of interests to declare.

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