Vascular calcification (VC) is prevalent among patients with CKD and has been associated with high cardiovascular mortality in patients on dialysis (1,2). The risk factors that probably predispose patients with CKD to vascular mortality in patients on dialysis (1,2). The risk factors that are more specific to patients with CKD such as hyperphosphatemia, uremic toxins, calcium-containing phosphate binders, vitamin D therapy, and dialysis vintage (3).

VC can occur in both the intima and media of the vessel wall. Intimal calcification is an indicator of atherosclerosis and is associated with ischemic heart disease (4). Medial calcification is characterized by diffuse mineral deposition (5) and is associated with arterial stiffness, systolic hypertension, and left ventricular hypertrophy (2,6). Mönckeberg medial sclerosis is the most common variant of medial calcification and was first described in 1903 (7). Patients with CKD are at high risk of both intimal and medial calcification. However, medial calcification is a characteristic feature of CKD. This was supported by the presence of VC in young patients with CKD without the traditional risk factors of atherosclerosis and the high percentage of medial calcification without classic atherosclerosis in the epicardial arteries of patients with ESRD at the time of kidney transplantation (8,9).

The relationship between intimal and medial calcification is controversial and of interest in the nephrology community (10–12). Intimal and medial calcification are definitely related, have similar risk factors, and develop in parallel. Some have suggested that they are a continuum of vascular pathology (12). Clinically, it is difficult to differentiate them. However, it is important to distinguish them because of their associations with different clinical outcomes. VC is an active and complex process reminiscent of osteogenesis. There are some specific aspects in the pathophysiology that are more relevant to intimal or medial calcification. For example, a localized inflammatory response is observed in intimal calcification but not in medial calcification (13). Dysregulated mineral metabolism, such as hyperphosphatemia in CKD, accelerates calcium phosphate deposition in medial calcification, but may not in intimal calcification (14). Genetically, there are also several defined vascular diseases associated with primarily medial calcification. One of these rare disorders is arterial calcification due to the deficiency of CD73, in which the NT5E gene that produces the enzyme CD73 is mutated (15).

In this issue of CJASN, Górriz et al. assessed VC using the Kaupilla and Adragao scores (16). VC occurs in both large elastic arteries and medium-size muscular arteries. Elastic arteries such as the aorta receive blood directly from the heart and are more prone to intimal calcification (17). Muscular arteries have more smooth muscle, distribute blood to various organs, and are more susceptible to medial calcification (18). The Kaupilla scores evaluate lumbar aortic calcification and include the assessment of the individual aortic segments and a summary score (19). They were developed by Kaupilla et al. in 1997, using participants from the Framingham Heart Study. Kaupilla et al. found that abdominal aortic calcification detected by lateral lumbar radiography was an independent predictor of subsequent vascular morbidity and mortality (1). The Adragao score, developed in 2004, assesses VC in muscular arteries including iliac, femoral, radial, and digital arteries. Adragao et al. demonstrated that dialysis patients with an Adragao score ≥3 had a 3.9-fold higher risk of cardiovascular mortality (18). In other words, the Kaupilla scores assess aortic calcification and thus likely reflect intimal calcification, whereas the Adragao score evaluates VC in muscular arteries and thus reflects medial calcification.

Górriz et al. studied VC using plain radiographs in 742 nondialysis patients with CKD from a cohort in Spain with a 3-year follow-up (Study of Mineral and Bone Disorders in CKD in Spain [OSERCE-2]). Consistent with previous literature, the authors found that VC is common in patients with CKD (mean eGFR $27\pm12$ ml/min per 1.73 m²), with a prevalence of 79%. It is important to study VC in the nondialysis CKD population because patients with CKD are far more likely to die from cardiovascular disease than progress to ESRD (20,21). Most previous studies examined VC in the dialysis population. Thus, this study importantly shows that VC starts earlier in the course of CKD, which suggests that it may be potentially modifiable long before the initiation of dialysis.

Górriz et al. found that correlates of VC in predialysis CKD included age, diabetes mellitus, serum phosphorus levels, diastolic BP, pulse pressure, and waist circumference, as well as the use of anticoagulant therapy for models of medial calcification and statins for...
intimal calcification (16). The findings of associations with anticoagulant therapy and statins are unclear and require further investigation. Although this study is cross-sectional and cannot establish causality, elevated phosphorus levels have been associated with VC in multiple human and animal studies (9). In the cohort, only 21% of the participants were taking a phosphate binder. The authors were not able to tease out whether taking a phosphate binder was associated with less VC; however, recent studies suggest that phosphate binders may not slow VC in CKD (22). The study by Górriz et al. is important because it shows that VC is common in predialysis CKD; therefore, clinical trials to try to slow the progression of VC in this population may be feasible.

Górriz et al. also examined the ability of VC to predict death, time to hospitalization, and kidney disease progression. After multivariate adjustment, the Adragao score ≥3 was independently associated with all-cause and cardiovascular mortality with hazard ratios of 2.07 (95% confidence interval, 1.07 to 4.01, \( P=0.03 \)) and 3.46 (95% confidence interval, 1.27 to 9.45, \( P=0.02 \)), respectively. It was also associated with a shorter hospitalization-free period. Furthermore, when they analyzed the Adragao score highlighting calcifications in peripheral arteries (radial and cubital), there was a stronger association. No association was observed between the high Kauppila scores (≥6) and the outcomes. No association was found between VC and kidney disease progression. The results suggest that medial calcification may have a greater prognostic power and may be a useful index to identify patients with CKD who are at higher risk of death and hospitalizations.

The question now is how good current imaging techniques are in differentiating intimal and medial calcification. To detect and quantify VC, electron-beam computed tomography is thought to be the gold standard; however, it does not distinguish intimal from medial calcification. The 2009 National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines (23) do not suggest routine screening of VC using any imaging technique because of the unclear clinical utility. If a practitioner chooses to perform testing for VC, KDOQI guidelines suggest the use of the plain radiography-lateral abdominal radiography, which can be quantified by the Kauppila scores like in the Górriz et al. study. In addition, breast arterial calcification is thought to be specific and a useful marker of medial calcification in patients with CKD (24). Overall, the sensitivity and specificity of plain radiography in differentiating intimal and medial calcification are unknown. However, the study by Górriz et al. reveals that VC scored from plain radiography is associated with a higher risk of mortality and hospitalization, and therefore should be tested for wider use in CKD.

Other imaging techniques that can be used to differentiate intimal and medial calcification include vascular ultrasonography and optical coherence tomography. Vascular ultrasonography can be done externally or internally. For example, carotid ultrasonography can be performed externally to measure the thickness of the intima and media in carotid arteries. Carotid intimal-medial thickness has been used in research as a surrogate marker for atherosclerosis. Intravascular ultrasonography can be utilized in patients undergoing endovascular interventions, and acoustic shadowing would suggest the presence of intimal calcification (25). Optical coherence tomography is an emerging technology that uses light to capture three-dimensional images and can provide higher resolution and better visualization of vessel walls. In addition, because medial calcification can lead to arterial stiffness, measuring arterial stiffness using the ankle-brachial index and pulse wave velocity has been used to indicate the presence of medial calcification. There is thus far no standardized laboratory test or validated biomarker for VC. Future studies of nondialysis patients with CKD can use some of these techniques.

The findings from Górriz et al. show that VC starts early in the course of CKD; therefore, studies trying to prevent or slow progression of VC should start early in CKD. The study supports the importance of differentiating intimal and medial calcification because participants with medial calcification had a higher risk of all-cause and cardiovascular mortality, but patients with intimal calcification did not (based on plain radiography). The findings also support the search for possible modifiable factors in the pathogenesis of VC including the role of serum phosphate, phosphate binders, vitamin D, and other CKD–mineral and bone disorder markers that were not fully evaluated in the study. In summary, nephrologists know that our patients are sick and have a high risk of morbidity and mortality. It appears that VC likely plays a large role either as the cause or as a marker of this risk; therefore, the nephrology community needs to focus on studies of VC as a way of improving outcomes for our patients.

Disclosures
None.

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See related article, “Vascular Calcification in Patients with Nondialysis CKD over 3 Years,” on pages 654–666.