The Impact of Systemic Calcified Atherosclerosis in Patients With Chronic Kidney Disease

There is increasing interest in the impact of chronic kidney disease (CKD) on the cardiovascular system.[1,2] Because approximately half of all deaths in those with CKD are attributed to cardiovascular causes, many of which may not be myocardial infarction or ischemia related, there is rationale to explore CKD as a "cardiovascular risk state" and understand the pathobiological evidence for changes in the entire vascular tree.[3,4] A core concept is that atherosclerosis is a ubiquitous process found in nearly every adult human who has been examined at autopsy. In this issue, Dr McCullough et al take a critical look at the supposition in the literature that Mönckeberg's sclerosis, or vascular medial calcification, is a proposed vascular disease not related to atherosclerosis. In a compelling review, it is clear that Mönckeberg's sclerosis is really advanced atherosclerosis with little or no subintimal lipid material or inflammatory cells present and has dense vascular medial calcification as its hallmark. There is considerable variation in the location of the calcification that occurs within the necrotic core as well as in and around transformed vascular smooth muscle cells in the media extending to the vascular adventitia depending on the outward remodeling of the vessel (Fig 1). It is important for the field to move forward and recognize that the CKD state transforms atherosclerotic lesions and potentially alters their responsiveness to conventional therapies including statins.[5]

Dr Khella explores the important relationship between CKD and stroke. Acute neurologic injury and long-term impairment caused by atherosclerotic plaque rupture and thrombosis, cardiac emoblism, and hypertensive vascular injury and bleeding is recognized as one of the most disastrous events in a patient with CKD. All 3 major mechanisms of stroke are more common and pose increased risk in patients with CKD and, thus, are treatment targets. Dr Govindarajan et al review the current trials of carotid revascularization as they are related to CKD patients at risk for or after acute stroke. Washam and Adams add to the knowledge base concerning the use of antiplatelet agents in patients with CKD who have uremic platelet dysfunction by summarizing the available outcomes studies of various agents in patients with CKD.

Drs Kendrick and Chonchol tackle the epidemiology and diagnostic approach to renal artery stenosis, a condition that should always be considered in a patient with CKD and clinical clues such as resistant hypertension and markedly impaired renal function after renin-angiotensin system inhibition and in smokers with peripheral arterial disease. Dr Kiernan et al follow with a detailed, multidisciplinary approach to the management of renal artery stenosis including a summary of the most recent data on revascularization. This is important because in appropriately selected patients revascularization may influence the natural history of this disease.[6]

Finally, the issue finishes with a focus on peripheral arterial disease (PAD) in CKD patients. PAD is often severe and is refractory to revascularization attempts in CKD (Fig 2). Drs Ix and Criqui review recent epidemiologic observations concerning PAD from the Rancho Bernardo study and special populations including the Pima Indians. The key points are that PAD identifies a very high-risk patient for coronary events and death and that in CKD dense peripheral calcification complicates the use of noninvasive and invasive diagnostic techniques. Dr Casserly presents a highly graphical approach to the invasive management of critical limb ischemia in renal patients. Despite the high level of cormorbidities and complications in these patients, it appears that, when feasible, urgent

1548-5595/08/1504-0002$34.00/0
doi:10.1053/j.ackd.2008.07.001

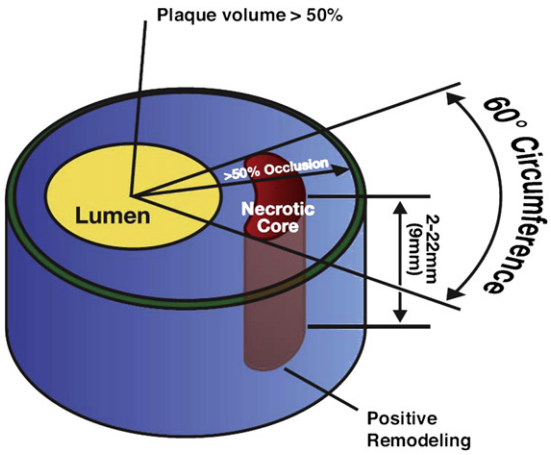

Figure 1. Geometry of a typical atherosclerotic lesion with outward remodeling and involvement of the media. The necrotic core and the vascular smooth muscle cells become sites of calcification in patients with chronic kidney disease.

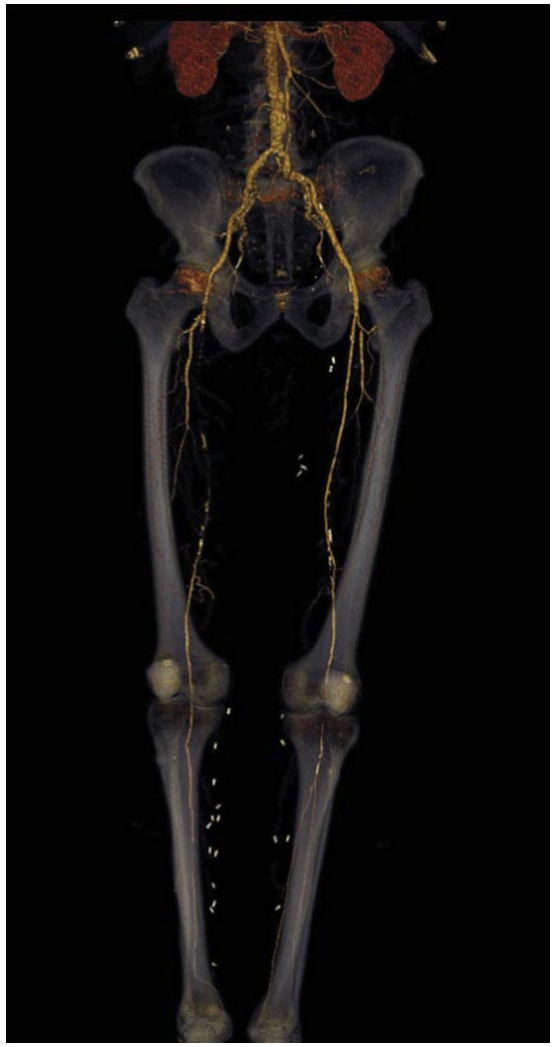

Figure 2. Peripheral computed tomography angiography showing severe peripheral arterial disease with distal vascular occlusions and surgical clips from prior revascularization attempts.

percutaneous revascularization of the ischemic limb is of considerable benefit in reduction of morbidity and long-term disability.[7]

Fundamental questions remain including the optimal blood pressure, particularly in patients on dialysis. In addition, the efficacy of combined angiotensin-converting enzyme inhibition with angiotensin receptor blockade is being questioned based on results in large general population trials. Lastly, optimal diabetes and lipid management have been called into question lately, giving us pause in considering the next steps forward in clinical trials of cardiovascular protection in CKD patients.

To summarize, this issue of *Advances in Chronic Kidney Disease* updates the reader with the state-of-the-art concerning diffuse, systemic atherosclerosis in patients with CKD. This issue highlights the fact that CKD is truly a unique cardiovascular risk state with amplified and accelerated vascular calcification, more vascular damage because of diabetes and hypertension, uremic changes in hemostasis, and likely a variety of injurious processes including inflammation and oxidative stress at work.[8] Ischemic injury to the brain, kidneys, and limbs results in defined syndromes that call into play diagnostic and treatment strategies. It is the aim of this issue to raise awareness and possibly prompt new and innovative approaches at managing this important problem in CKD patients.

Peter A. McCullough, MD, MPH
Guest Editor

References

1. Whaley-Connell AT, Sowers JR, McFarlane SI, et al: Diabetes mellitus in CKD: Kidney Early Evaluation Program (KEEP) and National Health and Nutrition

and Examination Survey (NHANES) 1999-2004. Am J Kidney Dis 51:S21-S29, 2008 (suppl 2)
2. McCullough PA: Cardiovascular disease in chronic kidney disease from a cardiologist's perspective. Curr Opin Nephrol Hypertens 13:591-600, 2004
3. McCullough PA, Li S, Jurkovitz CT, et al: CKD and cardiovascular disease in screened high-risk volunteer and general populations: The Kidney Early Evaluation Program (KEEP) and National Health and Nutrition Examination Survey (NHANES) 1999-2004. Am J Kidney Dis 51:S38-S45, 2008 (suppl 2)
4. McCullough PA: Spectrum of cardiorenal disease. Int J Geriatric Cardiol 2:131-135, 2005
5. McCullough PA, Rocher LR: Statin therapy in renal disease: Harmful or protective. Curr Atheroscler Rep 9:18-24, 2007
6. Hanzel GS, Downes M, McCullough PA: Editorial: Renal function after renal artery stenting. J Geriatr Cardiol 2:196-197, 2005
7. McCullough P: Outcomes of contrast-induced nephropathy: Experience in patients undergoing cardiovascular intervention. Catheter Cardiovasc Interv 67:335-343, 2006
8. McCullough PA: Evaluation and treatment of coronary artery disease in patients with end-stage renal disease. Kidney Int Suppl 95:s51-s58, 2005