Cardiovascular Calcifications Among Patients With Uremia: Answers to Hard Questions

A 56-year-old woman with long-standing history of diabetes mellitus and end-stage renal disease is evaluated for severely painful indurations covering both thighs. She is obese and has been on warfarin therapy for atrial fibrillation. A skin biopsy obtained from the indurated area demonstrates calcifications involving subcutaneous arterioles and adjacent adipocytes. A diagnosis of uremic calciphylaxis is made. Prior radiological examinations demonstrate diffuse arterial and valvular calcifications involving coronary, mesenteric, carotid, femoral and aortic beds, and mitral and tricuspid valves.

The clinical scenario described evokes a number of questions. The first and foremost is what is/are the origin(s) of diffuse cardiovascular calcifications in this patient? What role does kidney disease play in the development of such calcifications? What are the clinical implications of the calcifications? What therapeutic strategies are currently available to treat and prevent the progression of calcification? Can cardiovascular calcifications be prevented? If yes, how? Finally, how does the presence of subcutaneous microvascular calcifications distinguish this patient from other patients with comparable comorbidities and diffuse cardiovascular calcifications but no cutaneous manifestations?

Cardiovascular calcification is not a new phenomenon. Investigators of the Horus study obtained whole body computed tomography scans of 137 mummies from 4 ancient populations (ancient Egypt, ancient Peru, the Ancestral Puebloans of southwest America, and the Unangan of Aleutian Islands) spanning over 4000 years. Calcified plaques in the wall of an artery or calcifications along the expected course of an artery were discovered in 47 (34%) of 137 mummies and across all 4 geographical populations.[1] This study disclosed that vascular calcifications (mostly, atherosclerotic intimal calcifications) were prevalent among preindustrial humans including preagricultural hunter-gatherers. Notably, simultaneously other individuals, likely based on their characteristics related to genes, environment, and/or other factors, were protected from the development of these primarily intimal atherosclerotic calcifications.

In this issue of Advances in Chronic Kidney Disease, specialists from across the world share their perspectives on uremic cardiovascular calcifications. Vascular calcification is a component of CKD-mineral and bone disorder as espoused by Kidney Disease: Improving Global Outcomes.[2,3] Leading off, Ray and Jovanovich (pp 409-416) review the key aspects of deranged mineral bone metabolism in the context of CKD and link these abnormalities to vascular calcification. They astutely highlight the scarcity of clinical trials designed to evaluate the impact of interventions targeting mineral bone abnormalities on end points of vascular calcification and clinical events. Despite greater mechanistic understanding of the role of mineral abnormalities in the development of cardiovascular calcifications and the widespread clinical use of therapies targeting these biochemical abnormalities, it is humbling that as yet we have no intervention that has been successfully and consistently shown to improve cardiovascular events or mortality. A large trial with more than 3800 hemodialysis randomly assigned patients with moderate-to-severe hyperparathyroidism to either the calcimimetic cinacalcet or placebo with follow-up to 64 months revealed no reduction in risk of cardiovascular events or death, highlighting the complexity of not only vascular calcification pathogenesis but also challenges of conducting clinical trials in this patient population.[4,5]

The trans-differentiation of vascular smooth cells into an osteoblast-like phenotype in the setting of uremia is a fascinating manifestation of plasticity.[6] It is now well-established that in injured tissues, repair and regeneration is linked with cells deviating from their normal lineage pathways and trans-differentiating into a new cell phenotype. Disthabanchong and Srisuwarn (pp 417-426) provide a summary of mechanisms responsible for trans-differentiation and other steps involved in vascular calcification in the setting of uremia. These authors additionally outline differences between intimal and medial vascular calcification. Their summary informs future therapies that will target cell plasticity to prevent, treat, and/or reverse cardiovascular calcifications.

Next, Lim and Kalim (pp 427-436) explore protein modifications that occur in the context of uremia and provide readers with a comprehensive understanding of the event horizon of cardiovascular biomarkers, risk stratification, and novel therapies guided by mechanistic underpinnings. Cozzolino and colleagues (pp 437-444) describe emerging evidence related to vitamin K deficiency among patients with kidney disease and describe how this deficiency instigates development and propagation of vascular calcification. This group highlights a number of clinical trials targeting this topic that inform current and future clinical management of our patients.

Smith and colleagues (pp 445-463) subsequently provide a state-of-the-art summary of the current literature pertaining to preclinical and clinical diagnostic tests for uremic cardiovascular calcifications. They discuss the limitations of the currently available technologies for detection of vascular calcification and describe the limitations pertaining to routine screening of vascular calcification.

Brandenburg and colleagues (pp 464-471) focus their review on cardiac valvular calcifications, outlining the mechanism by which calcific aortic stenosis leads to left ventricular hypertrophy among patients with advanced

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kidney disease. They highlight the requirement for close surveillance of this complication and collaboration with cardiology/cardiac surgery teams for effective therapies.

Evenepoel and colleagues (pp 472-483) bring attention to how our skeletal health in the context of kidney disease is impaired and link those skeletal abnormalities to cardiovascular diseases. Clearly, the demineralization of skeleton and mineralization of vascular and soft tissues represent what Evenepoel and colleagues refer to as the "calcification paradox" requires greater scrutiny to develop therapies that target both abnormalities simultaneously. Otherwise, we may once again commit the same well-intentioned folly of lobbying to improve biochemical parameters and skeletal health with potential unintended consequences as occurred during advocacy for high-dose calcium and vitamin D supplementation. Indeed, the most recent Kidney Disease: Improving Global Outcomes clinical practice guideline update raised a concern regarding calcium overload and made a suggestion to limit/avoid calcium-based phosphate-lowering therapies among CKD patients—an issue met with nontrivial challenges to its implementation related largely to higher costs and gastrointestinal adverse effects of non-calcium-based phosphate-lowering therapies.[2,3]

Next, Seethapathy and Noureddine (pp 484-490) bring all the known concepts of vascular calcification and apply them to our current understanding of calciphylaxis, a rare but devastating complication associated with high morbidity and mortality. They highlight how recent scientific observations regarding the pathogenesis of calciphylaxis translate into potential preventive and treatment strategies that may apply not only to the rare complication of calciphylaxis but more broadly to all vascular calcifications.

Nephrology practitioners are well familiar with the cardiovascular disease burden among patients with kidney disease and momentum is building to prevent and treat vascular calcifications in this patient population. As science and clinical practice evolve, it is important to remember one of the quotes by Hippocrates: As to diseases, make a habit of two things—to help, or at least, to do no harm.

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