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The Enigma of Vascular Calcifications

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It has been well established that cardiovascular mortality is a major cause of morbidity and mortality in patients with chronic kidney disease (CKD).[1] Because the presence of traditional risk factors such as hypertension, aging, smoking, diabetes, and abnormal lipid metabolism does not fully explain the propensity of cardiovascular disease, the presence of other contributing pathophysiology has been postulated. Many studies have shown that a high percentage of patients with CKD have vascular calcifications, stressing its impact on the high morbidity and mortality in this population.[1,2] Vascular calcification is defined as the inappropriate and pathological deposition of mineral in the form of calcium phosphate salts into the vascular tissues.[2] There are 2 distinct types of vascular calcifications based on their location and association with atherosclerotic plaque formation. One affects intimal layer and occurs within atherosclerotic plaques; the other affects the medial layer. The consequences of the 2 types of the calcification differ.[3] The intimal lesions compromise the lumen of the arteries and block the blood supply during advanced stages. These atherosclerotic lesions are associated with disturbances in lipid metabolism, inflammation, and cellular necrosis.[3] The second type of calcification is medial wall calcification and is commonly seen in patients with CKD. Here mineral deposition occurs throughout tunica media, which is rich in elastic collagen and results in increased vascular stiffness; reduction in vessel compliance; rise in systolic blood pressure, leading to left ventricular hypertrophy; and reduced coronary artery blood flow during diastole.[3] In addition to developing in larger arteries, medial calcification also develops in microvessels of the subcutaneous adipose and dermis that may result in ischemic lesions or, rarely, in calcific uremic arteriopathy.[4] Diagnosis of medial calcifications is much more difficult than that of intimal calcification. Routine imaging with either plain films or computed tomographic scanning can easily demonstrate and measure intimal calcification. However, the detection of medial calcification requires imaging of a vascular bed devoid of atherosclerosis and can be easily detected by routine mammograms because calcification is exclusively medial; thus, the radiologic diagnosis of medial calcification requires mammography.[5]

Traditionally, vascular calcification was thought to be a passive process occurring as the result of elevated serum phosphate with deposition of calcium-phosphate product resulting from oversaturated plasma.[6] Although dysregulation of calcium and phosphorus metabolism does play a critical role, more recent studies have shown that calcification is an active and complex process resembling skeletal bone formation, with key regulators of bone formation and bone structural proteins expressed in both calcified medial arterial layers and atherosclerotic plaques.[7]

It has been well described that as CKD progresses, there are early changes in mineral metabolism to maintain normal serum calcium and phosphate concentrations, which include increases in FGF23 and parathyroid hormone and decreases in 1,25-dihydroxycholecalciferol (calcitriol) and 25-hydroxycholecalciferol (vitamin D).[8] In addition, there are changes in various bone proteins and transcription factors within both bone cells and vascular smooth muscle cells, resulting in vascular calcification closely resembling physiologic bone formation. Vascular smooth muscle cells (VSMCs) are of mesenchymal origin and under stress can differentiate into different mesenchymal cells, such as osteoblasts, chondrocytes, or adipocytes. At the sites of calcification, VSMCs undergo phenotypical change and become similar to bone-formative cells. There is also downregulation of smooth muscle–specific genes, such as smooth muscle SMα-actin and SM22α.[2] Simultaneously, VSMCs upregulate expression of

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mineralization regulating proteins that are normally confined to bone and cartilage.[9] These proteins include transcription factors such as Runx2, Osterix, MSX2, and SOX9, that induce differentiation of VSMCs to an osteochondrocytic phenotype.[9] VSMCs are able to produce matrix vesicles, which under normal circumstances contain mineralization inhibitors, such as matrix γ-carboxy glutamic acid protein (MGP) and fetuin-A.[9] Coupled with high extracellular calcium and phosphate with low concentration of mineralization inhibitors, these matrix vesicles serve as nucleation sites for hydroxyapatite.[S1]

Thus, with progressive CKD, numerous factors allow for initiation and progression of vascular calcification. *In vitro* and animal models have demonstrated that initiation of calcification requires increased uptake of calcium and phosphate by VSMCs. Phosphate entry is via sodium-dependent phosphate cotransporters, PiT-1 and PiT-2.[S2] Calcium uptake by VSMCs is regulated by CaSR and voltage-gated calcium channels. *In vitro* exposure of VSMCs to high extracellular calcium can downregulate CaSR.[S2] Loss of CaSR, which also occurs with progressive CKD, can lead to increase in VSMC calcification.[S2] There is also upregulation of RUNX2 and its target protein, osteopontin, independent of serum phosphate concentration. Bone morphogenic protein-2, which is crucial in signaling related to transcriptional activity of RUNX2, and osteoblastic transformation of VSMCs is also increased. Thus, compared with individuals without CKD, mineralization of VSMCs is promoted in CKD.[S3] In addition to ectopic osteogenesis, the lack of inhibitors of calcification play an important role behind vascular calcification. Another important protein is fetuin-A, which is produced primarily in the liver and is a glycoprotein that binds calcium ions and hydroxyapatite and could prevent matrix calcification. However, fetuin-A is decreased with progressive CKD, in part due to inflammation but may also be a result of administration of vitamin D receptor (VDR) activators.[9] VDR activators are widely used for treatment of secondary hyperparathyroidism; however, there are conflicting data regarding the effects on the vasculature. VSMCs express the VDR, and VDR activators can upregulate VDR expression in VSMCs; VDR activation is known to modulate cellular proliferation and differentiation. VDR activators encourage calcification by upregulation of RUNX2, osterix, and osteocalcin and by increasing calcium influx into the VSMCs.[S4]

Unfortunately, to date, there has been no identified therapy that has been shown to reverse or slow vascular calcification. Furthermore, measurement of medial calcifications is limited because most technology cannot distinguish between intimal, or atherosclerotic, and medial calcification. The study by Alappan and colleagues in this issue of *Kidney International Reports* adds significant insight into the problem of medial artery calcifications.[5] Using mammography, they were able to measure medial calcifications in long-term dialysis patients and compare progression of calcifications in patients whom continue dialysis and those who have been transplanted. In a subgroup of the patients, they were able to compare progression of calcifications pre- and post-transplantation. After transplantation, subjects had close to normal renal function; thus, many of the pathophysiologic processes described earlier would be expected to be reversed. Unfortunately, they did not find regression of calcification, even up to 10 years post-transplantation. However, they did observe significant slowing of progression after transplantation. Also, the only factor that seemed to be associated with progression of calcification following transplantation was duration of dialysis. Of note, other factors, thought to be associated with calcification, such as diabetes, baseline calcification, or serum chemistries was not associated with more rapid progression.

This study further supports that changes of bone and mineral metabolism associated with long-term and advanced renal disease are intimately involved in the development of progressive medial calcification in advanced CKD and dialysis patients. It is also interesting to ponder whether the withdrawal of certain therapies, such as the use of VDR activators and calcium-containing phosphate binders, which were presumably discontinued after transplantation, had a significant effect on decreasing the progression of calcifications. Hyperparathyroidism and frequently mild hypercalcemia persist, whereas phosphate levels usually drop and hypophosphatemia may occur following transplantation.[S5] These data provide further insight into medial calcification in CKD/dialysis patients and the potential utility of mammography, at least in women, as a tool to further assess these patients. The development of large prospective studies with measurements of not only biochemical parameters we generally check but also other hormones, proteins, and transcription factors may help us better understand the pathophysiology of medial calcifications and help us devise strategies for prevention or treatment.

DISCLOSURE

The author declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary References.

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