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Management of Vascular Calcification in CKD Patients

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Vascular calcification is common in patients with chronic kidney disease (CKD) and it may affect almost every artery. It is associated with a significant increase in morbidity and mortality. Therefore, the detection, prevention and treatment of vascular calcification in CKD patients are critical for the overall approach for the management of these patients. Hyperphosphatemia, especially when the blood levels of serum phosphorus are above 5.5 mg/dl, plays a major role in the development of vascular calcification. Hyperphosphatemia induces vascular calcification by both passive and active processes. By increasing calcium-phosphate product, hyperphosphatemia results in direct deposition of calcium salts in the arteries and in cardiac valves. The active process involves the uptake of phosphate by the smooth muscle cells of the arteries by a Na-P co-transporter. This increase in cell phosphate then induces phenotypic changes of these cells, rendering them into osteoblasts which in turn, begin laying calcium salts in the arterial walls. Therefore, it is critical that the blood levels of serum phosphorus be maintained below 5.5 mg/dl in CKD patients. Inflammation and the production of C-reactive protein (CRP) and interleukin 6 are also risk factors for vascular injury and vascular calcification. In a study of 254 dialysis patients with elevated blood levels of CRP (>1.0 mg/l) and 258 patients with CRP levels equal to or less than 1.0 mg/l, it was found that higher levels of CRP are significantly associated with the presence of both atheromatous and medial calcification of the aorta and hand arteries. Also, it was reported that a significant association between CRP levels and cardiac valves calcification in patients undergoing continuous ambulatory peritoneal dialysis. The reasons for the elevation in CRP in dialysis patients are not clear, but certainly, is more evident in those with obvious inflammatory processes. Therefore, any inflammation that is detected should be treated appropriately.
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Vascular calcification is common in patients with chronic kidney disease (CKD).[1,2] The incidence of vascular calcification among patients treated with hemodialysis ranges from 3% to 83% and the incidence of this abnormality increases with the duration of dialysis treatment. In a series of 135 patients published in 1977, the incidence of vascular calcification increased from 27% in those treated for less than 1 year to 83% in patients treated for more than 8 years.[1] Calcification of the coronary arteries also is common in dialysis patients; indeed, the prevalence determined by electron beam computed tomography (EBCT) ranged from 83% to 92%.[3-5] Coronary artery calcification was noted even in young patients 20 to 30 years old.[3]

Vascular calcification may involve almost every artery and has been seen in arteries of the forearm, wrist, hands, eyes, feet, abdominal cavity, breast, pelvis, and brain. There are 2 types of vascular calcification. The first is intimal calcification, which is seen in 80% to 90% of atherosclerotic plaques, and the second is medial calcification, which occurs diffusely throughout the tunica media (Mönckeberg's arteriosclerosis). In addition to the vascular calcification, there also is increased prevalence of cardiac valve calcification in dialysis patients. In 1 study of 92 hemodialysis patients studied with echocardiograms, mitral valve calcification was noted in 45% of the patients and calcification of the aortic valve in 52%, compared with 10% and 4%, respectively, in 92 sex- and age-matched nondialysis control patients.[6] Similarly, Braun et al,[7] using EBCT, found that 59% of dialysis patients had

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Table 1 Factors Responsible for Vascular Calcification

Hyperphosphatemia and increased calcium-phosphate product
Hypercalcemia and/or increased calcium burden
Inflammation resulting in acute phase proteins, such as CRP or interleukin 6
Atherosclerosis and diabetes
Age
Duration of hemodialysis
Severe hyperparathyroidism

mitral valve calcification and 55% had aortic valve calcification.

The medial arterial calcification may be very extensive, rendering the artery so rigid that the pulse is not palpable and the Korotkoff sound may be difficult to hear during measurement of blood pressure. Such calcification also may present difficulty during surgery for the creation of arteriovenous shunts or fistules for maintenance hemodialysis or during kidney transplantation. Cardiac valve calcification may lead to valvular stenosis or valvular incompetence with significant hemodynamic consequences.

The most ominous outcome associated with vascular or cardiac valve calcification is increased risk for cardiovascular mortality.[8] Indeed, the probability of survival decreases with the number of arteries showing vascular calcification.[9] Similarly, overall survival is reduced in the presence of either mitral or aortic valve calcification and is decreased further when both valves are calcified.[10]

It appears, therefore, that the detection, prevention, and treatment of vascular calcification in CKD patients are critical in the overall approach for the management of these patients. There are several technologies that permit the detection of vascular or cardiac valve calcifications. Regular radiographs allow the detection of significant calcification of peripheral or abdominal arteries. Echocardiography is useful in finding cardiac valve calcification. EBCT permits the quantitative estimation of the calcification of coronary arteries and cardiac valves by measuring calcium scores.

To design a therapeutic approach for the prevention and management of vascular calcification, one must understand the causes of vascular calcification. Table 1 lists the factors that potentially are responsible for vascular calcification.

The most important factor in the development of vascular calcification and subsequent increased risk for cardiovascular mortality is hyperphosphatemia. Indeed, the relative risk for coronary artery disease is 41% higher in dialysis patients with hyperphosphatemia.[11] Increased morbidity and mortality occur when the serum phosphorous level is greater than 5 to 6 mg/dL and progresses with greater hyperphosphatemia.[12]

Hyperphosphatemia induces vascular calcification by both passive and active processes. By increasing the calcium-phosphate product, hyperphosphatemia results in direct deposition of calcium salts in the arteries or cardiac valves. The active process involves the uptake by the smooth muscle cells of the arteries of phosphate by the Na-P cotransporter. This increase in cell phosphate level then induces phenotypic changes of these cells, rendering them into osteoblast-like cells that in turn begin laying calcium in the arterial wall. This process is shown in Figure 1.

Fortunately, we have 3 therapeutic modalities that allow us to prevent and/or manage hyperphosphatemia. These include dietary phosphate restriction, the use of phosphate binders, and increased frequency of hemodialysis. Guideline 4 of the K-DOQI Guidelines for Bone Metabolism and Bone Diseases recommended limiting dietary phosphate intake to 800 to 1,000 mg/d.[13] During dietary phosphate restriction, it is important to maintain adequate protein intake.

There are many phosphate binders and each has its benefits and limitations. The ideal phosphate binder should bind phosphate in the digestive tract directly and form nonabsorbable complexes, or through resin exchange. It should have specific and high affinity for binding phosphorus and a lack of toxicity. The calcium-based phosphate binders are effective but they increase the calcium burden to the patient and may induce hypercalcemia. Both of these effects also may promote vascular calcification (Table 1). Therefore, KDOQI guideline 5 recommended that the total calcium intake per day by dialysis patients should not exceed 2,000 mg (500 mg dietary intake and 1,500 mg calcium-based phosphate binders) and that noncalcium-based phosphate binders are preferred in patients with vascular calcification.[13] Indeed, the administration of a high dose of calcium-based phosphate binders was associated with increased risk for vascular calcification.[3] Further, in a prospective study comparing calcium-based phosphate binders and sevelamer (Renagel [Genzyme, Boston, Mass.]), Chertow et al[14] found that calcium scores in the coronary arteries and aorta progressed in the patients receiving calcium-based phosphate binders, whereas the calcium scores did not increase in the patients receiving sevelamer.

In patients with marked hyperphosphatemia that is difficult to control with dietary phosphate restriction and/or the use of phosphate binders, increasing the frequency of dialysis such as daily dialysis[15] or nocturnal dialysis[16] is very effective in the management of hyperphosphatemia.

Because atherosclerosis predisposes to vascular calcification, it is important that factors that participate in the genesis of atherosclerosis be avoided and managed. Thus, hyperlipidemia should be controlled, diabetes should be managed appropriately, smoking should be avoided, and exercise should be practiced whenever it is feasible.

Inflammation and the production of C-reactive protein (CRP) and interleukin 6 are risk factors for vascular injury[17] and vascular calcification.[18] The potential mechanism for this effect is shown in Figure 1. Ishimura et al[18] studied 254 dialysis patients with increased blood levels of CRP (>1.0 mg/L) and compared them with 258 patients with CRP levels equal to or less than 1.0 mg/L. They found that higher levels of CRP are associated significantly with the presence of both atheromatous and medial calcification of the aorta and hand arteries. In addition, Wang et al[19] reported a significant association between CRP levels and cardiac valve calcification in patients undergoing continuous ambulatory peritoneal dialysis. The reasons for the increase in CRP levels in dialysis

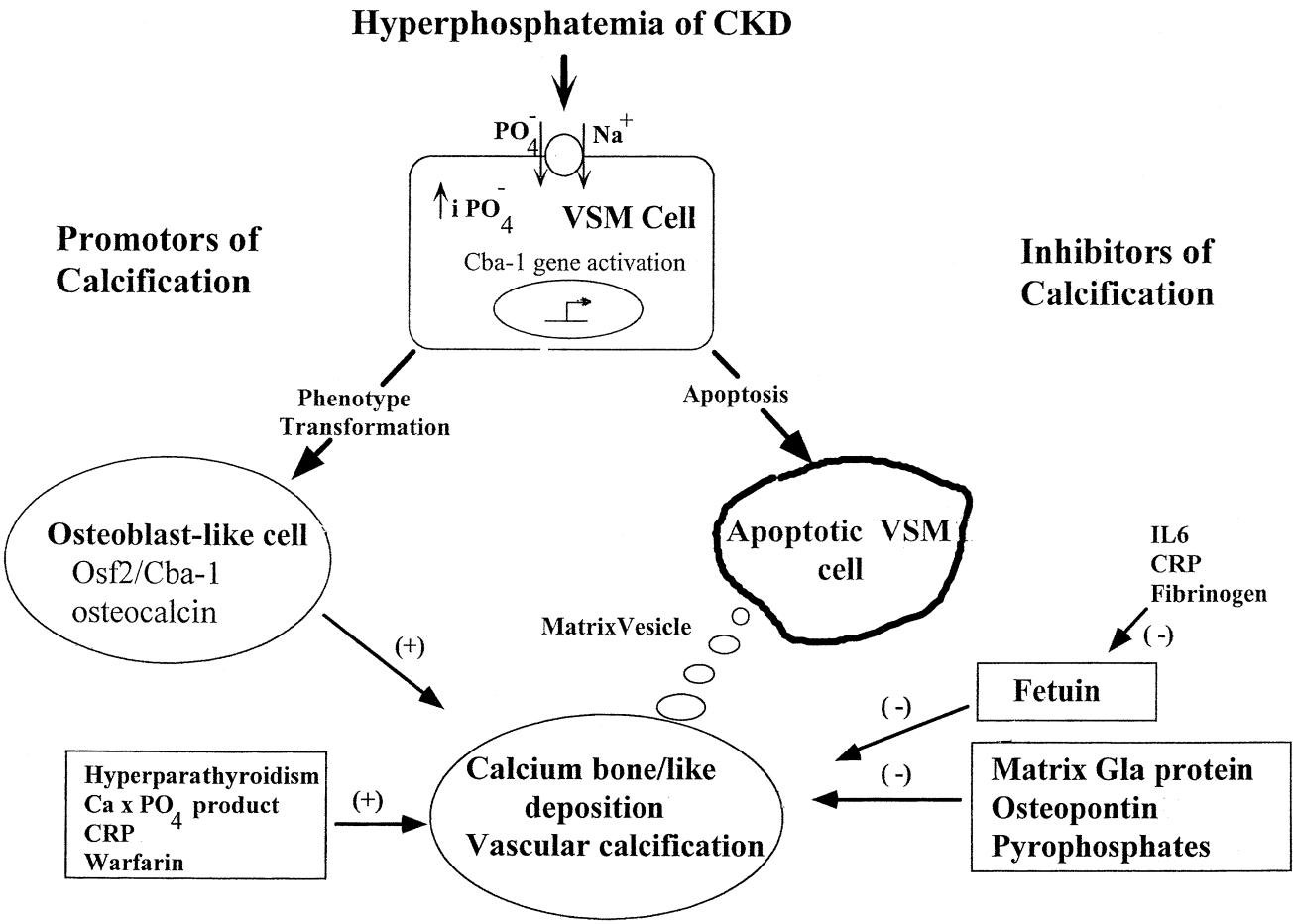

Figure 1 The mechanisms through which hyperphosphatemia and/or CRP and interleukin 6 induce vascular calcification. During hyperphosphatemia, phosphate enters the vascular smooth muscle (VSM) cell. The increased intracellular phosphate (iPO_4) causes apoptosis of some cells and these apoptotic bodies become niduses (matrix vesicles) for crystalline calcification. In addition, other VSM cells undergo phenotypic changes through Cba-1 (core binding factor 1) gene activation, rendering them into osteoblast-like cells, which express many bone morphogenic proteins such as Cba-1, Osf2 (osteoblast f2 gene), and osteocalcin. These proteins promote calcification. There also are calcification inhibitors such as Feutin, matrix Gla protein, osteopontin, and pyrophosphate. CRP and interleukin 6 inhibit Feutin action, a process that would favor calcification.

patients are not clear, but certainly are more evident in those with obvious inflammatory processes. Therefore, any inflammation that is detected should be treated appropriately.

Severe hyperparathyroidism predisposes to vascular calcification, either by worsening hyperphosphatemia or by direct influx of calcium into the vessel walls caused by the ionophoric effect of the hormone. Therefore, severe hyperparathyroidism in CKD patients should be managed by vitamin D therapy using either calcitriol, doxercalciferol (Hectorol [Bone Care International, Middleton, Wisconsin]), or one of the less-calcemic vitamin analogues such as paricalcitol (Zemplar [Abbott, Chicago, IL]). The reader is referred to guideline 8 of the K-DOQI guidelines.[13]

Another rare but serious and life-threatening variant of vascular calcification in CKD patients is calcific uremic arteriolopathy (calcifylaxis). It usually is observed in patients treated with hemodialysis or peritoneal dialysis,[20] rarely in patients before dialysis therapy,[20,21] and, occasionally, after renal transplantation.[22] Female sex and obesity predisposes for the development of this entity and the relative risk for this syndrome increases with weight increase. Local trauma may be a contributory factor to the site where the lesion may appear. Indeed, in some patients, the necrotic lesions began in areas where insulin, heparin, or iron dextran were injected.[23] The overall incidence of calcific uremic arteriolopathy among dialysis patients is 1% per year,[24] with a prevalence of 4%.[25]

This entity is characterized by the development of ischemic skin ulcerations involving the fingers, toes, thighs, legs, and ankles. The patients almost always have vascular calcification of the media of the arteries and they usually exhibit radiographic evidence of subperiostal bone resorption. The serum calcium level usually is normal and occasionally is increased. A period of hyperphosphatemia has been present for some time before the appearance of this syndrome. The ulcerative lesions may be preceded or accompanied by severe pain. Before the appearance of the ulcers or the tissue necrosis, tender, slightly erythematous, subcutaneous nodules

may develop, or there may be blotchy bluish discoloration. Raynaud's phenomenon may precede the lesions of the fingers or toes. The ulcers may develop slowly over several months, or skin and muscle necrosis may appear and progress rapidly over a few weeks. Infection may supervene, leading to sepsis and death. Histologic examination of skin and soft tissues show calcification of the media of the arteries and arterioles, thrombosis of both arteries and veins, and varying degrees of ischemic necrosis.

The exact pathogenesis of calcifylaxis is not known. Although disturbances in divalent ion metabolism, secondary hyperparathyroidism, and vascular calcification appear to play an important role in the genesis of this entity, other factors also may contribute to its emergence and progression. Acquired protein C deficiency has been reported in patients with CKD[26] and such a derangement may lead to a hypercoagulability state and consequently to vascular occlusion and tissue necrosis.

At present, there is no definite therapy for this entity. Parathyroidectomy has been followed by healing in many, but not all, patients.[22,25,27,28] Parathyroidectomy is useful especially in those patients with very high blood levels of parathyroid hormone.

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