Cardiac Valvular Calcification in Hemodialysis Patients

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The frequency of vascular calcification is significantly increased in patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD). This complication was reported even in predialysis era and before widespread use of calcium and vitamin D supplements and calcium-containing phosphate binders.[1,2] Coronary artery calcification has been shown in up to 92% of young ESRD patient with sequential computed tomography and electrocardiography gating.[3] Even conventional radiographic studies have revealed vascular calcification in about 60% of ESRD patients with 57% progression over time.[4]

Vascular calcification is histologically divided into 4 main types of atherosclerotic intimal calcification, medial artery calcification (Monckeberg sclerosis), cardiac valve calcification, and arteriole calcification in the form of calciphylaxis.[5] Various risk factors have been associated with the pathogenesis of vascular calcification, including valvular calcification. Generally, the underlying risk factors can be divided into genetic susceptibility, mineral metabolism-related factors, and mineral metabolism-unrelated factors.[6] Polymorphism in glucose transporter-1 XbaI gene has been linked to the increased risk of vascular calcification in ESRD patients, and a number of murine models susceptible to vascular calcification have been developed, which are null in various genes inhibiting vascular calcification such as apolipoprotein E, low-density lipoprotein-receptor, matrix Gla protein, Klotho, and fetuin-A. Regarding the factors related to mineral metabolism, increased phosphate level and high dose active vitamin D supplement are the mainly suggested promoters of vascular calcification. Also, most authorities believe that parathyroid hormone (PTH) may have a protective effect against vascular calcification, and the severity of vascular calcification may increase in conditions of adynamic bone disease and low PTH.[6] Among factors unrelated to mineral metabolism, derangements in activators of vascular calcification, such as bone morphogenetic protein 2 and receptor activator of nuclear factor-kappa B ligand or inhibitors of vascular calcification such as matrix Gla protein, bone morphogenetic protein 7, osteopontin, osteoprotegerin, fetuin-A, Smad6, and pyrophosphate, may be linked to vascular calcification. Decreased levels of fetuin-A is observed in maintenance hemodialysis patients and has been correlated with higher rates of vascular calcification, cardiovascualr mortality, and malnutrition-inflammation states as assessed by subjective global assessment and high C-reactive protein levels.[7-9] Results of these studies suggest that fetuin-A is both a calcification inhibitor protein and a negative acute-phase reactant and acts as a link between inflammation and atherosclerosis in patients with CKD. Also, circulating matrix Gla protein is decreased in dialysis patients and has been proposed as a predictor of mortality in these patients. Low levels of vitamin K, which is needed for activation of this calcification inhibitor, have been shown in the majority of dialysis patients. Whether vitamin K supplementation improves outcome in these patients is pending to further studies.[10]

Cardiac valve calcification has been reported in up to 47% of hemodialysis patients with increased risk of mortality compared to those without valvular calcification.[11-13] The mechanisms responsible for the increased cardiovascular mortality and morbidity in valvular calcifications are not well understood. Mitral annulus calcification has been associated with higher frequency of rhythm and cardiac conduction defects.[14] However, aortic valve calcification may represent a surrogate marker either for underlying atherosclerotic disease or

some generalized inflammatory process.[15,16] In the general population, other than rheumatic fever and congenital cases, the main risk factor for aortic valve calcification is age, together with diabetes mellitus and other conventional atherogenic risk factors.[17] Also, higher serum phosphorus level even in normal range is correlated with aortic valve sclerosis and aortic and mitral annular calcification in the elderly population.[18] However, in patients with CKD or ESRD the risk factors have been different between the studies. Some studies showed a correlation between the incidence of vascular calcification and age, dialysis vintage, and history of diabetes mellitus as well as calcium-phosphorus product and PTH levels.[13,14,19] On the other hand, there are other studies that have correlated valvular calcification with the common atherogenic risk factors as well as dialysis duration, but did not find any correlation between valvular calcification and parathyroid hormone or calcium-phosphorus status in ESRD patients.[20]

In this issue of the *Iranian Journal of Kidney Diseases*, Sayarlioglu and colleagues have reported the results of their study on the prevalence and risk factors of cardiac valvular calcification in a cohort of hemodialysis patients.[21] They could show prevalence rates of 33% for vascular calcification, 23.3% for mitral valve calcification, and 21.7% for aortic valve calcification in 129 maintenance hemodialysis patients. In this study, dialysis vintage was longer in patients with either kind of valvular calcification and they were older than those without valvular calcification. Diabetes mellitus was more common in patients with mitral valve and bivalvular calcification and mean albumin level was lower in these patients. The authors could not show any correlation between valvular calcification and total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride calcium, phosphorus, calcium-phosphorus product, or PTH concentrations. Interestingly, they found lower mean albumin levels in patients with vascular calcification, and although they did not check more specific inflammatory markers such as high-sensitivity C-reactive protein or interleukins, this finding may indicate a correlation between vascular calcification and inflammation.

The correlation between vascular calcification and inflammation has been shown in a number of recent studies. Briand and colleagues showed a clear correlation between bioprosthetic valve degeneration and metabolic syndrome defined as high body mass index, fasting blood glucose, triglyceride, and blood pressure plus low high-density lipoprotein cholesterol .[22] On the other hand, it is believed that expanded abdominal adipose tissue produces numerous cytokines, including the proinflammatory interleukin-6, and tumor necrosis factor-alpha, which contribute to the association between the metabolic syndrome and inflammation.[23] Circulating levels of C-reactive protein is elevated in patients with metabolic syndrome and has been suggested to be largely the result of the frequent presence of abdominal obesity.

In conclusion, the prevalence of vascular calcification and cardiac valvular calcification, as one of its main types, are increased in hemodialysis patients and are one of the important risk factors responsible for increased morbidity and mortality in these patients. The underlying causes are not clearly known, although common atherogenic risk factors, derangements in mineral metabolism, and malnutrition-inflammation syndrome are known to increase the risk of vascular calcification. The results of future studies may help us to decrease the rate of this complication in CKD and ESRD patients and help to prolong the lives of these patients with a higher quality.

CONFLICT OF INTEREST

None declared.

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Bisphosphonates for Treatment of Severe Idiopathic Infantile Hypercalcemia

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Hypercalcemia is associated with severe volume contraction, life threatening complications, and even death in the case of unsuccessful therapy. Definition of hypercalcemia is age-dependent and the cutoff values of calcium are different for infants (> 11.3 mg/dL) and children (> 10.8 mg/dL). The underlying diseases in infants are different form children, adolescents, and adults. Hyperparathyroidism and metastasis are the main causes of hypercalcemia in adolescence, but inherited disorders and vitamin D intoxications are the most prevalent in infancy.[1,2] In general, hypercalcemia in infants can be due to parathyroid related disorders, inactivating mutations in