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COMMENTARY

Malnutrition–inflammation complex syndrome: link between end-stage renal disease, atherosclerosis and valvular calcification

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Traditional atherosclerotic risk factors are not accurate prognostic predictors in patients with chronic kidney disease. Consequently, new markers to predict cardiovascular involvement in uremic patients are needed. The non-invasive identification of individuals at risk for cardiovascular events is a significant clinical dilemma, and there are many ongoing studies searching for new risk-stratification indices.[1]

Calcification of different tissues is an end-stage event in the inflammation process. Vascular calcification is detected either in the tunica intima or in the tunica media. Calcification in the intima is characteristic of most stages of atherosclerosis. Medial calcification is particularly common in patients with end-stage renal disease (ESRD) and may occur independently of atherosclerosis. Medial wall calcification increases vascular stiffness and reduces arterial compliance. Both vascular calcification and inflammation are common in patients with chronic kidney disease. Vascular calcification and arterial stiffness are independent predictors of mortality in dialysis patients.[2] Moreover, there is a strong association between valvular calcification (VC) and aortic stiffness in patients with ESRD[3] (Figure 1).

Dystrophic calcification, which was first described by Möckenberg in 1904, is characteristically localized in the tunica media and is the most common pathological finding in operatively excised heart valves. Cardiovascular risk factors for dystrophic calcification that are shared with atherosclerosis include hyperlipidemia, hypertension and diabetes. The pathological features of dystrophic, calcified valves include lipid endothelial damage, lipid deposition, inflammatory infiltration and calcification, making aortic valve lesions appear similar to atheromas. One study suggests that aortic valve calcification (AVC), mitral annulus calcification and aortic root sclerosis are highly associated with aortic atheromatosus disease and cardiovascular disease.[4]

In patients with ESRD, the pathophysiology of vascular and cardiac calcification is not entirely determined but is certainly multifactorial. Metabolic disorders characterized by abnormal calcium and phosphorus are very important in calcification formation. Factors that induce calcification are numerous and have not been fully determined, but that uremic toxins may contribute to this process has been taken into account.[5] A higher incidence of traditional cardiovascular risk factors such as age, hypertension, dyslipidemia and diabetes in combination with specific risk factors for chronic kidney disease suggests a link between these two disorders.

Several lines of evidence suggest that degenerative aortic valve disease is not simply a consequence of aging. The risk factors for aortic stenosis are the same as those for coronary artery disease. Histopathologically, the early lesions of aortic valve sclerosis resemble arterial atherosclerotic plaques. The inflammatory reactions include increased local concentrations of macrophages and activated T lymphocytes. Besides the infiltration of inflammatory cells, mature lamellar bone formation and osteopontin bone expression in calcified human aortic valves founded by Mohler *et al.*[6] indicate a similar etiology for aortic stenosis and atherosclerosis, which are described in textbooks as two distinct diseases. Patients with valvular aortic stenosis have a higher prevalence of coronary atherosclerosis, myocardial infarction and myocardial revascularization compared with patients without aortic valve degeneration. There is a strong correlation between aortic valvular stenosis and symptomatic, peripheral arterial disease in older persons.

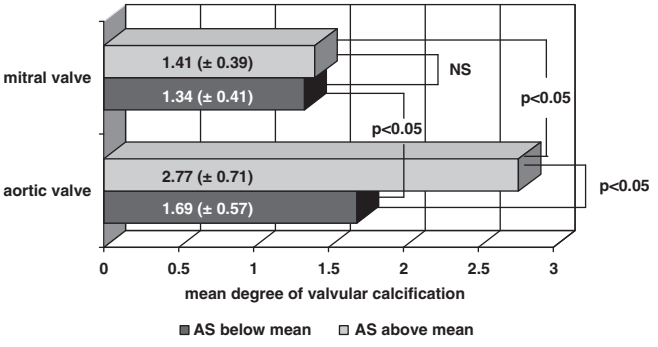

Figure 1 Aortic stiffness (AS) and the mean degree of aortic and mitral leaflets calcification in patients with chronic renal failure. NS, not significant.

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Inflammation is likely to have a pivotal role in linking chronic kidney disease and atherosclerosis. It is well known that inflammation has a key role in coronary artery disease and other manifestations of atherosclerosis.[7] Several plasma markers of inflammation have also been evaluated as potential tools for predicting the risk of coronary events. These include markers of systemic inflammation produced in the liver, such as high-sensitivity C-reactive protein (hs-CRP) and serum amyloid A, cytokines such as interleukin-6 and adhesion molecules such as soluble intercellular adhesion molecule type 1. A study performed by Wang *et al.*[8] showed that elevated CRP and interleukin-6 levels and low fetuin-A level predict a worse prognosis for ESRD patients with VC. This observation clearly demonstrates that inflammation has an additional negative impact on the outcome of ESRD patients particularly complicated with VC. As inflammation is believed to have a role in the pathogenesis of cardiovascular events, the measurement of inflammation markers has been proposed as a method to improve the prediction of the risk of these events.

The paper presented by Ikee *et al.*[9] addresses an interesting and important issue in the pathophysiology of heart VC in a hemodialysis patient with ESRD. Their group used a novel cardiovascular risk factor, β2-microglobulin, to investigate the associated factors of aortic and mitral VC. β2-Microglobulin is related to inflammatory diseases and may be altered in cardiovascular disorders such as coronary artery stiffness, coronary artery disease and peripheral arterial disease, as well as in renal abnormalities such as dialysis-related amyloidosis and estimation of the glomerular filtration rate. The results showed significant correlation between β2-microglobulin and mitral valve calcification (MVC), but not AVC; this finding suggests different courses of pathogenesis, perhaps involving differences in localized calcium depositions. Other data also suggest that the etiologies of AVC and MVC are completely different. MVC is rather calcium balance related, whereas AVC is believed to be due to inflammation, which is part of the atherosclerotic process. The data presented by Tenenbaum *et al.*[10] support these observations. Their data show a higher prevalence of mitral annulus calcification in women than in men, whereas the prevalence of coronary calcification was significantly higher in men. Investigators have suggested that the inverted gender predominance in the prevalence of annular calcification and coronary calcifications could be explained by the additional etiological (likely osteoporotic) mechanisms of mitral annulus calcification development among post-menopausal women.

Despite the different correlations between β2-microglobulin and mitral and aortic calcification demonstrated by Ikee *et al.*,[9] there is still clear evidence of a pro-inflammatory pathophysiology of valvular calcium deposits in hemodialysis subjects, such as the strong association between hs-CRP and aortic and mitral calcification. According to the presented results, carotid intima–media thickness was significantly associated with AVC but not MVC, suggesting that AVC may be more closely associated with systemic atherosclerosis compared with MVC. Surprisingly, patients with AVC had lower total cholesterol concentration compared with patients without AVC, but AVC is considered to be a manifestation of atherosclerosis. Lower total cholesterol concentration is a sign of metabolic disturbances observed in chronic kidney disease and may be associated with abnormal thyroid gland function, which is common in ESRD. Such metabolic circumstances may also be a manifestation of malnutrition, which is common in ESRD. Besides low total cholesterol concentration, malnutrition in ESRD includes low weight, a low body mass index, decreased serum prealbumin, transferrin (TIBC) levels, and high homocysteine concentration. Low serum albumin and high serum CRP are two main features observed in dialysis patients.[9] Epidemiological studies have consistently shown a strong association between clinical outcome and measures of both malnutrition and inflammation in dialysis subjects. These two conditions tend to occur concurrently and to coexist in patients with ESRD. Many factors that engender one of these conditions may also lead to the other. Therefore, the term malnutrition–inflammation complex syndrome or malnutrition, inflammation, and atherosclerosis syndrome has been proposed

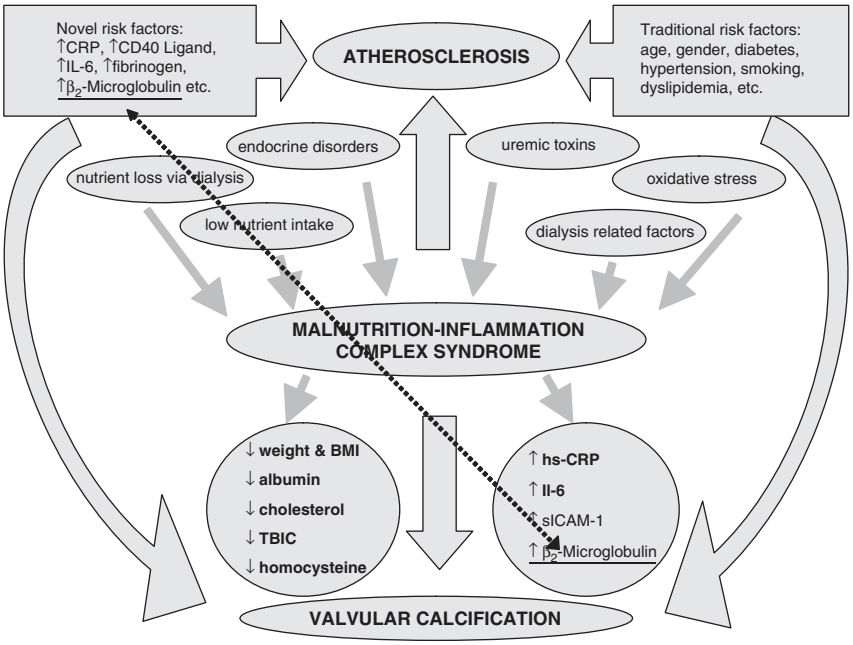

Figure 2 Association between malnutrition–inflammation complex syndrome and atherosclerosis and valvular calcification in dialysis patients with ESRD.

to indicate the combination of these two conditions in such patients.[11] Concurrent laboratory findings of low albumin, low total cholesterol, high hs-CRP and high β2-microglobulin likely reflect the malnutrition–inflammation complex syndrome (Figure 2). The correlation between such abnormalities and VC in hemodialysis patients has been previously studied by Ikee *et al.*[12] The correlation between VCs and intima–media thickness and associations between VCs and the laboratory markers may explain a missing link between chronic kidney disease and atherosclerosis.

Further research is needed to elucidate whether traditional and novel risk factors of cardiovascular burden and metabolic abnormalities that are present in chronic kidney disease can account for links between these diseases. The malnutrition–inflammation syndrome offers an attractive and reliable pathological model of the relationship among chronic kidney disease, atherosclerosis and VC.

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