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Editorial

MAC in CKD and dialysis patients: Pathophysiological doubts and clinical implications

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Mitral annulus calcification (MAC) is a chronic, degenerative process in the fibrous base of the mitral valve. This pathological feature is associated with an increased prevalence of atherosclerotic coronary artery disease (CAD), suggesting that MAC and vascular atherosclerosis may be different manifestations of the same disease. MAC is often clinically silent, usually first detected on echocardiography. It appears as an echo-dense, shelf-like structure with an irregular, lumpy appearance involving the mitral valve annulus, with associated acoustic shadowing [1].

It has long been known that valvular calcifications are 4–10 times more frequent in patients with chronic kidney disease (CKD) than in patients with normal renal function [2]. The Framingham Heart Study showed CKD patients had 60% increased odds of having MAC as compared to controls, with a prevalence range between 9% and 22% [3].

There are conflicting data regarding the role of traditional cardiac risk factors and development of MAC in CKD patients. There is general agreement that age, Caucasian ethnicity, malnutrition, diabetes, pro-inflammatory profile, dialysis, and duration of dialysis are associated with MAC. However, there are discordant results regarding the lipid profile and bone metabolism [4,5]. Patients with CKD appear to have a peculiar lipid phenotype, rich in TG and VLDL, with low HDL values but without severe alterations of total and LDL cholesterol [6]. One study of CKD patients actually found lower cholesterol levels in those subjects who had MAC [5]. These observations might be explained by the inflammatory profile of patients with CKD: pro-inflammatory cytokines, besides having a direct role in the pathogenesis and progression of valvular calcifications, tend to lower cholesterol. In support there is a pathological study comparing cardiac valves from end-stage renal disease (ESRD) patients and matched controls: ESRD was associated with moderate to severe inflammation on histologic examination but immunohistochemistry found no differences between groups for markers of bone metabolism (alkaline phosphatase, osteopontin, and bone morphogenic protein 4) [7].

The hypothesis that dysregulation of mineral-bone metabolism is involved in the pathogenesis of MAC in CKD patients derives from the assumption of shared mechanisms with vascular calcification. It is known that CKD patients have a 2–5-fold increased risk of developing vascular calcifications, especially on the coronary tree. Advanced CKD (stages 3 to 5) is frequently associated with coronary artery calcium scores (CACs) ≫ 400 (OR 8.35, 95% CI 1.94–35.95) [8].

In addition to having an increased number of classic atherosclerotic risk factors, patients with ESRD often have "non-traditional" risk factors that may play a pathogenic role. Indeed, these patients show accelerated atherosclerosis and also a pathognomonic pathological finding: calcification of the tunica media [9]. The process is attributed to an active phenomenon that involves differentiation of vascular smooth muscle cells into osteoblast like cells which deposit bone matrix proteins such as osteopontin, BMP 2–4, alkaline phosphatase and collagen I, into vessel walls. Furthermore, it is well established that it is not only phosphorus, but also other uremic toxins, that mediate vascular calcification by positively regulating osteoblast transcription factors. This might explain why, in ESRD patients, good control of the calcium-phosphate product is not sufficient to prevent and limit calcification.

So, beyond biological plausibility, is the pathophysiology of the two diseases (MAC and vascular calcifications) in CKD really the same? The data in this regard is controversial: some studies do not identify the dysregulation of mineral-bone metabolism as a risk factor for MAC, while others identify osteoprotegerin, PTH and phosphorus as independent risk factors [2–5]. Studies conducted in dialysis patients have demonstrated rapid progression of valve calcifications and MAC in some patients. However, the factors responsible for progression have not been identified; neither age, nor duration of dialysis, nor markers of bone metabolism seem to provide an explanation [2].

The literature in this area is still full of questions. The work conducted by Usuku et al. in this issue of the *Journal*, sheds light on this topic. They reviewed records of 95 hemodialysis-dependent patients who underwent transthoracic echocardiography (TTE) in 2017, 72 of whom had undergone TTE 5 years earlier. Regression

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analysis revealed that the number of coronary risk factors (OR: 2.67; 95% CI: 1.24–5.76; $p = 0.01$) and baseline MAC diameter (OR: 1.23; 95% CI: 1.05–1.45; $p = 0.01$) were significantly associated with progression of MAC in ESRD patients. The evidence that the number of atherosclerotic risk factors bear significantly on progression of MAC leads us to reflect on the burden of comorbidities of these patients. In fact, this is a very high-risk population. Approximately 50% of CKD patients die of cardiovascular causes. The risk of CAD increases progressively with decreasing renal function; this appears to be accompanied by an increase in plaque necrotic core and calcifications. CKD may be an even stronger risk factor for future MI than diabetes.

In clinical practice we know that MAC and aortic valve calcification are validated markers of subclinical atherosclerosis, and strong predictors of cardiovascular mortality in the general population [10]. In addition MAC can adversely affect mitral valve function, causing not only mitral regurgitation (MR) but also the production of important MV gradients, mostly when anterior leaflet mobility is reduced. Similarly, progression of aortic valve calcification may be responsible for the development of hemodynamically significant valve stenosis. Further, the direct extension of calcific deposits to the region of the atria, atrioventricular node, and His bundle may lead to a higher incidence of heart block and arrhythmias in MAC patients [1]. Not only in the general population, but also in ESRD patients, MAC is associated with significant angiographic coronary stenoses (luminal stenoses $\gg$ 70%), an increase in strokes, and increased mortality.

Thus, the finding of MAC in ESRD patients identifies an important subpopulation within a group that is already very fragile. This has been formalized in the 2016 ESC Guidelines for cardiovascular disease prevention which consider patients with moderate CKD (GFR 30–59) at high risk and those with severe CKD (GFR $\ll$ 30) at very high-risk for cardiovascular disease. Clinicians need to be aware of these risks in order to intervene promptly if necessary. Further studies will be required to clarify which preventive, diagnostic and therapeutic approaches are best in ESRD patients with MAC.

Declaration of Competing Interest

The authors have no conflict of interest.

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