Opponent’s comments

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After reading the nicely crafted PRO manuscript of Jordi Bover and colleagues by the CKD-MBD working group of the ERA EDTA, we respectfully maintain our dissent on several major issues of the question at issue. CKD-MBD investigators start by mentioning the CKD-mineral and bone disorder (CKD-MBD) syndrome, a syndrome which the same working group recognized to be of very weak methodological texture in a very recent paper by the same working group [1]. There is no question that ‘intense cross talk exists between the bone and the vasculature’. However, cross talks of similar or greater intensity exist between the heart and the kidney, the kidney and the brain and the liver not to mention the cross talk between the adipose tissue with other organs, from the brain to the bone. CKD is a systemic disease [2] and inappropriately qualifying (i.e. without sound methodology) some of these cross talks as syndromes may hinder scientific research, an issue we discussed elsewhere [3]. Jordy Bover and colleagues review studies showing that cardiovascular calcification is an alteration that can be modified. In our CON manuscript, we summarized the pathobiology of calcium accumulation in the arterial system and showed that inflammation, an early event in human atherosclerosis [4] and a systemic disorder in CKD, has a key role in vascular calcification, which is instead a late event in this process. Vascular calcification is the smog not the fire, thus the problem at issue is not whether vascular calcification is reversible but whether arterial disease leading to vascular calcification is reversible. In the context of today’s knowledge, we (the CON side) believe that hyperparathyphoxemia, hyperparathyroidism and low 1,25 vitamin D are implicated in arterial disease in CKD mainly via mechanisms mediated by inflammation and alterations in the nitric oxide system. We recently showed that osteoblast resistance to PTH in stage 5D CKD patients with peripheral artery disease is a phenomenon strongly was associated with inflammation [5], and that vitamin D receptor activation improves nitric oxide-dependant vasodilation in CKD patients [6]. Recent evidence points to high phosphate load per se as a strong pro-inflammatory stimulus in rats with experimental renal failure [7]. Of note, alterations in bone mineral disorders are implicated in atherosclerotic events well beyond CKD. Indeed, in patients with coronary heart disease and in individuals in the general population [8], high serum phosphate and high serum alkaline phosphatase within the normal range of these biomarkers predict a high risk of
death and cardiovascular events. High alkaline phosphatase, an enzyme providing a gross estimate of bone turnover in subjects without liver disease, reflects a pro-atherogenic pathway deeply intertwined with classical risk factors, including hypertension, low HDL and insulin resistance [9].

Finally, we disagree on the statement that knowledge gathered so far is sufficient to support systematic screening for vascular calcification in CKD patients. Recommending screening for vascular calcification demands that this biomarker meets a stringent series of methodology criteria [10], from the added prognostic value of the biomarker in terms of discrimination ability, calibration and reclassification power, to the availability of treatments that may improve clinical outcomes in the target population. This is clearly not the case in CKD patients. Coronary calcification has a 66% prevalence rate in stage 3 CKD [11] and is nearly universal in stage 5 CKD patients. Relying on this test for selecting patients who should undergo coronary angiography is tantamount saying that almost all CKD patients should undergo coronary angiography. Needless to say that some patients with a high calcium score are false positive, i.e. they may have vessel wall calcification and patent arteries. No solid study exists proving that vascular calcification follows in-arterial injury, including hyperphosphataemia and CKD-MBD disorders in this population. Targeting late arterial lesions like calcifications just diverts attention from the fire to the smog.

Con: Vascular calcification is a surrogate marker, but not the cause of ongoing vascular disease, and it is not a treatment target in chronic kidney disease

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ABSTRACT

In this narrative review, we discuss the dynamics and pathobiology of calcium accumulation in the arterial system and then appraise the validity of vascular calcification as a surrogate end point in cardiovascular (CV) diseases and in chronic kidney disease (CKD) in particular. Calcification follows inflammation in human atherosclerosis and therefore most

REFERENCES


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