

# Can We Tackle with Vascular Calcification and Arterial Stiffness in Patients with Chronic Kidney Disease?

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**Abstract:** Cardiovascular disease remains the leading cause of increased morbidity and mortality in patients with chronic kidney disease and is attributed to early and accelerated atherosclerosis and arteriosclerosis observed in this patient population. Vascular calcifications, particularly of the media, are commonly found in chronic uremia and are a major contributor to arteriosclerosis and increased arterial stiffness. Epidemiologic data support the correlation of vascular calcification and arterial stiffness to adverse cardiovascular outcomes and mortality. Experimental evidence has shed light on the pathogenetic mechanisms of vascular calcification and arterial stiffness and their relation to impaired bone metabolism and imbalance between promoters and inhibitors of extra-osseous bone formation. However further research is needed to clarify their exact contribution and whether their targeting could significantly affect vascular calcification and arterial stiffening and could improve survival in chronic kidney disease patients.

**Keywords:** Arterial stiffness, bone metabolism, cardiovascular disease, chronic kidney disease, vascular calcification.

## INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of increased morbidity and mortality in patients with chronic kidney disease (CKD) and particularly those on renal replacement therapy [1, 2]. The pathogenesis of vasculopathy in CKD involves traditional risk factors of atherosclerosis (older age, hypertension, dyslipidemia, diabetes mellitus), which are highly prevalent in renal patients, but also several non-traditional or uremia-related risk factors (inflammation, oxidative stress, mineral and bone disorders), which are intensively investigated. In addition, vascular calcifications, particularly of the media, are an almost ubiquitous feature of arterial tree in chronic uremia and a major contributor to accelerated arteriosclerosis and increased arterial stiffness observed in CKD patients [3-5]. The extent of vascular calcification and the degree of arterial stiffness, closely inter-related, are non-traditional CVD risk factors and independent predictors of CVD mortality, both in general population and CKD patients [6-10]. Several studies have shown that mineral-bone disorders and imbalance between promoters and inhibitors of extra-osseous bone formation are associated with vascular calcification and affect significantly the process of arterial stiffening in renal population, potentially leading to adverse clinical outcomes [5, 11]. Moreover, it appears that there is an interaction between bone metabolism and vascular health, placing current understanding of vascular pathophysiology on a bone-vascular axis [12]. This review is focused on the pathogenetic mechanisms underlying

the link between vascular calcification, arterial stiffness and bone turnover, the effect of existing “anti-calcifying” and “de-stiffening” therapeutic approaches and emerging potential novel treatment strategies aimed to improve cardiovascular outcomes in CKD patients.

## PATHOGENETIC MECHANISMS OF VASCULAR CALCIFICATIONS AND ARTERIAL STIFFNESS

Arterial remodeling has been associated with both atherosclerotic and arteriosclerotic vascular changes, which share some common etiologic factors. Atherosclerosis is a focal inflammatory disease, affecting primarily medium-sized arteries and is associated with increase of the arterial intima-media thickness, plaque formation and intimal calcification leading eventually to luminal obstruction with consequent ischemic events, such as myocardial infarction and stroke. Arteriosclerosis is a diffuse disease, affecting mainly large elastic and medium-sized arteries and is characterized by media thickening and calcification resulting in progressive loss of arterial compliance and stiffening [13, 14]. In CKD patients, atherosclerosis and arteriosclerosis often coexist, appear early and follow an accelerated course contributing to the excessive cardiovascular mortality observed in this patient population [2, 15].

Recent evidence suggests that vascular calcification is a highly regulated active process, and that the phenotypic trans-differentiation of vascular smooth muscle cells (VSMCs) into osteoblast-like cells is a key pathogenetic event resulting in production of bone-like structures into the arterial wall [3, 5]. A variety of factors that influence this process have been recognized, including dysregulated mineral homeostasis and bone turnover, as well as imbalance

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between promoters and inhibitors of extra-osseous bone formation which are still under investigation [3, 5]. In chronic uremia, elevated serum phosphorus has emerged as the predominant calcification promoting factor, by exhibiting intracellular activity against vascular smooth muscle cells, which are considered the principal mediators of damage. A variety of other molecules, such as bone morphogenic protein family, Mx-2 and Wnt axis proteins and Cbfa1 transcription factor, acting additionally either directly or indirectly, have been shown to promote the phenotypic changes of VSMCs into osteoblast-like cells. Moreover, several local and systemic inhibitors of vascular calcification have been identified including pyrophosphate, fetuin-A, osteopontin and matrix gla protein [4, 5]. Interestingly, a recent study in hemodialysis patients demonstrated that fetuin-A, the major circulating calcification inhibitor, has an independent significant negative correlation with arterial stiffness, assessed by carotid-femoral pulse wave velocity (cf-PWV). In contrast, osteoprotegerin (an antiosteoclast factor produced by osteoblasts, vascular endothelial and smooth muscle cells) was found to be positively associated with PWV [16].

Recent epidemiologic data indicate a crosslink between vascular calcification and bone loss, both in general population and CKD patients [17]. Thus, in hemodialysis patients vascular calcifications have been found to be associated with osteoporosis and bone fractures [18]. Moreover recently, the Baltimore Longitudinal Study of Aging demonstrated that arterial stiffness has an inverse, age-independent, relation to cortical bone area in women, after adjustment for relevant covariates including mean arterial pressure, obesity, renal function, menopause and serum calcium [19]. Emerging experimental evidence suggests that some inhibitors of the canonical signalling Wnt pathway, which is actively involved in bone formation and vascular calcification, such as secreted frizzled Proteins (SFRPs) 2 and 4 and Dickkopf related protein-1 (DKK-1), play a role linking vascular calcification and bone. SFRPs were found to be over-expressed in areas of severe vascular calcification [12, 20, 21], probably indicating a feedback vascular defence mechanism triggered in order to attenuate mineralization in the calcified arterial wall. However, as the SFRPs are secreted circulating proteins, they may act not only locally, but also systemically, and may impair bone mineralization, resulting in reduced bone mass. The role of sclerostin (another inhibitor of the Wnt axis produced by osteocytes) in vascular calcification is also unclear and currently under investigation. In a recent cohort study of CKD patients, elevated sclerostin levels were found to be associated with aortic calcification. However, multivariate analysis revealed an inverse relationship between sclerostin and aortic calcification [22]. Another study in postmenopausal women, showed a positive correlation between sclerostin and abdominal aortic calcification as well as pulse wave velocity [23].

Despite accumulating evidence supporting the connection between vascular calcification, arterial stiffness, low bone turnover and mortality, further research on the vascular-bone axis is required to identify the underlying pathophysiologic mechanisms and to clarify whether vascular calcification and osteoporosis should be considered modifiable determinants of cardiovascular disease.

## **“ANTI-CALCIFYING” AND “DE-STIFFENING” TREATMENT STRATEGIES IN CKD PATIENTS**

It is well established that in CKD patients mineral and bone disorders contribute to medial calcification and arterial stiffening, thus representing a treatment goal. Particularly, control of hyperphosphatemia and secondary hyperparathyroidism, appear to be associated with amelioration of vascular calcifications and improved survival [24]. In this context, sevelamer, a non-calcium based phosphate binder, was associated with smaller pulse wave velocity increase [25] and when compared with calcium containing binders, with slower rates of coronary arteries calcification in hemodialysis patients, in some, although not all, relevant trials [26, 27]. ADVANCE Study (A Randomized Study to Evaluate the Effects of Cinacalcet plus Low-Dose Vitamin D on Vascular Calcification in Subjects with Chronic Kidney Disease Receiving Haemodialysis) assigned 360 prevalent hemodialysis patients, with moderate to severe secondary hyperparathyroidism, to cinacalcet plus low-dose vitamin D or flexible doses of vitamin D sterols for 52 weeks. The progression of coronary artery and cardiac valve calcification scores were lower in the cinacalcet plus vitamin D group, especially in aortic valve [28]. Moreover, a post-hoc analysis reported attenuated progression of cardiovascular calcification in the cinacalcet plus vitamin D group [29]. However, it should be noted that different vitamin D receptor activators appear to exert variable effects on vascular calcification, in a dose-dependent manner. Thus in an experimental model of CKD, therapeutic doses of calcitriol and paricalcitol for secondary hyperparathyroidism were protective against aortic calcification, whereas higher doses were associated with inverse results [30].

Arterial stiffness is a well-established non-traditional cardiovascular risk factor [31]. Therefore, the probable beneficial effect of several antihypertensive and other agents, known to affect arterial function, on markers of arterial stiffness has been investigated [32]. Antihypertensive drugs, particularly renin-angiotensin-aldosterone system inhibitors, were shown to exert favourable effects on arterial stiffness and central blood pressure indices [33]. A study in end-stage CKD patients demonstrated that the absence of pulse wave velocity decrease in response to blood pressure decrease was an independent predictor of all-cause and cardiovascular mortality. Moreover, the use of angiotensin-converting enzyme inhibitors had a favourable effect on survival that was independent of blood pressure changes [34]. These findings are in agreement with the results of the Conduit Artery Functional Evaluation (CAFE) study in 2073 hypertensive patients. Amlodipine +/- perindopril-based therapy was shown to be superior to atenolol +/- thiazide, -based therapy, in decreasing central aortic pulse pressure, despite equally reducing brachial blood pressure. Notably, the difference between the two regimens was sustained over the 4 year follow-up [35]. Spironolactone, an aldosterone antagonist, as an add-on therapy to either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers versus placebo, was found to improve arterial stiffness in CKD patients with good blood pressure control [36].

The potential impact of lipid-lowering agents on arterial stiffness in CKD patients has been poorly investigated. A

study in early-stage CKD patients reported that atorvastatin administration for 3 years was associated with stabilization of aortic pulse wave velocity whereas the latter increased significantly in patients on placebo; however, no differences were noted between the two groups in the rate of change of aortic augmentation index or central pulse pressure [37].

## FUTURE PERSPECTIVES

Advances in molecular biology could provide alternative therapeutic options aimed to prevent or ameliorate vascular calcifications and to improve arterial structural and functional abnormalities, both in general population and CKD patients. Denosumab, a monoclonal antibody to RANKL, which mimicks the action of osteoprotegerin, appears a promising "anti-calcifying" agent [38]. Also, a humanized monoclonal antibody (AMG 785) that inhibits the action of sclerostin was found to increase bone formation in healthy subjects compared to placebo [39]. Although both regulators of bone metabolism have been administered for the treatment of osteoporosis, any assuming effect on vascular calcification in CKD patients remains to be established. Potential therapeutic role for other mediators of calcification, such as pyrophosphate, fetuin A and bone morphogenic proteins also deserve further investigation.

## CONCLUSIONS

Accelerated vascular calcifications and arterial stiffness considerably contribute to the increased cardiovascular morbidity and mortality observed in CKD patients. Mineral-bone disorders and dysregulation of promoters and inhibitors of extraosseous bone formation have recently received growing attention, as significant determinants of these processes. Moreover, recent clinical and experimental data indicate a crosslink between vascular calcification and bone loss, both in general population and CKD patients. Better understanding of the complex underlying mechanisms linking bone metabolism and vascular health would hopefully offer new and more effective "anti-calcifying" and "de-stiffening" treatment options aimed to reduce cardiovascular mortality in renal population.

## CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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