Vascular calcification of chronic kidney disease: A brief review

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Abstract

Vascular calcification (VC) is highly prevalent among patients with chronic kidney disease (CKD). There is growing evidence that there is more underlying this condition than the histological presentation of atherosclerotic plaque and arteriosclerosis and that the risk of cardiovascular disease in the context of CKD might be explained by the presence of VC. While VC has been observed in the absence of overt abnormal mineral metabolism, this association is coupled to abnormal homeostasis of minerals in patients with CKD, due to hyperphosphatemia and hypercalcemia. Furthermore, recent studies have shown that the differentiation of vascular smooth muscle cells into an osteogenic phenotype is highly regulated by pro-calcifying and anti-calcifying factors. There are several imaging modalities currently used in clinical practice to evaluate the extent and severity of VC; each has different advantages and limitations. Although there is no universally accepted method for the treatment of VC, there is growing evidence of the beneficial effects of medical therapy for the condition. This study discusses the mechanism underlying VC, imaging modalities used for evaluation of the condition, and possible treatments.

Keywords: Cardiovascular disease, Chronic kidney disease, Image, Treatment, Vascular calcification

Introduction

Vascular calcification (VC) is highly prevalent among the elderly, particularly those with diabetes mellitus (DM) and chronic kidney disease (CKD) [1,2]. The Multi-Ethnic Study of Atherosclerosis is an ongoing study investigating the prevalence, correlations, and progression of subclinical cardiovascular disease (CVD) among 6814 community-dwelling participants [3]. The prevalence of coronary artery calcification (CAC) was assessed by chest computed tomography (CT) and found to be CKD stage ½, 3, 4, and 5 have been reported to be 37%, 58%, 75%, and 77%, respectively [4], and the prevalence of CAC among patients with end-stage renal disease (ESRD) undergoing dialysis is higher than that of similar-aged individuals, highlighting the role of renal function in the progression of VC [5]. Therefore, VC is common among patients with CKD, occurring at a lower age in such patients and leading to poor vascular compliance and concomitant high cardiovascular (CV) morbidity and mortality [6,7]. Histopathologically, VC can present as punctate or patchy crystals of atherosclerotic neointima media or occur in the medial layer of the vascular wall (known as Monckeberg medial sclerosis) [Table 1]. Loss of arterial elasticity may result in increased pulse pressure being transmitted to the distal arterial, resulting in arteriosclerosis, vascular insufficiency, and organ damage [8]. In this study, we present a brief review of the mechanisms, diagnosis, and treatments of VC to provide a valuable overview to researchers and clinicians in the field.

Mechanism of vascular calcification

In vitro studies have revealed that serum from uremic patients could induce VC [1,2,5,9], suggesting that patients with CKD may have factors that contribute to the development of VC. Traditional CV risk factors, such as aging, DM, hypertension (HTN), hyperlipidemia, and obesity, have been suggested to accelerate atherosclerosis, with consequent increased pulse wave velocity (PWV) in the elastic arteries demonstrated to be caused by VC [10-14]. Studies involving CT have shown VC to be associated with arterial stiffness (AS) and PWV [15]. The process of calcification affects both the intimal and medial layers of vessels, but medial calcification has more adverse effects on vascular distensibility, which may contribute to the development of AS [8,9]. Besides the disruption of mineral metabolism causing elastin fragmentation and calcification...
The presentation of VC can range from small crystals to bone-like tissue; thus, the condition is an active and highly regulated process involving multiple reciprocal signaling pathways [25], which form an interactive network within the vascular wall, influencing the process of calcification [Figure 1]. In vitro studies have identified vascular smooth muscle cells (VSMCs), pericytes, endothelial cells, adventitial cells, and progenitor cells as sources of cells, which contribute to VC [26]. In vivo studies have shown that these cells undergo osteogenic differentiation into phenotypically osteoblast-like cells, which may secrete collagenous extracellular matrix and deposit minerals, resulting in VC [26].

### Upregulation of Inducers of Vascular Calcification

An *in vitro* study has shown that hyperphosphatemia induces calcification of VSMCs in a dose-dependent manner, dependent on the sodium-dependent phosphate co-transporter Pit-1 and upregulation of runt-related transcription factor 2 (RUNX2), core-binding factor alpha 1 (Cbfa1), and osterix.
transcription factors [27]. In addition to hyperphosphatemia, hypercalcemia (either alone or in combination with high phosphate levels) has been shown to accelerate the development of VC of VSMCs, as a calcium/phosphate product is formed via Pit-1 [28]. In patients with CKD, serum phosphate and/or calcium load and calcium/phosphate product have been shown to be associated with increased incidence of VC [2,5,29,30]. Thus, these studies demonstrate the role of abnormal calcium and phosphate balance in the initiation of both phenotypic changes and mineralization of VSMCs in the process of VC.

Bone morphogenetic proteins (BMPs), a subgroup of the transforming growth factor β superfamily, have been reported to regulate the development of VC [31-33]. There is increased expression of BMP-2a in calcified human atherosclerotic plaque and studies revealed that a positive correlation exists between increased expression of BMP-2 and hyperglycemia, high phosphate levels, and AS [31-33], all of which increase osteogenesis in calcifying vascular cells. Li et al. demonstrated that the mechanism underlying BMP-2-regulated calcification of VSMCs involves the Pit-1 co-transporter in conditions of high phosphate levels [32]. There is evidence demonstrating the essential role of BMP in the development of VC in conditions of matrix gla protein (MGP) deficiency [34], and the increased expression of activin-like kinase receptor 1 and vascular endothelial growth factor [33] or promotion of transformation VSMC to an osteogenic phenotype via activation of RUNX2 [32].

Fibroblast growth factor (FGF)-23 is a bone-derived hormone, which regulates phosphate and 1,25-hydroxyvitamin D₃ homeostasis FGF receptors and the klotho co-receptor in kidney and parathyroid gland tissues, which has been shown to be negatively correlated with renal function [4]. Although in vivo studies have revealed conflicting results regarding the role of FGF-23 in the calcification of VSMCs [35], human studies have indicated elevated serum FGF-23 as an independent predictor for VC in patients with CKD [4,36] and HD [37]. Also, a longitudinal study revealed serum FGF-23 level to be associated with progression of PWV and abdominal aortic calcification (AAC) [38]. The rates of CV and all-cause mortality have been shown to be lower among patients with HD whose serum FGF-23 levels can be lowered by more than 30% through administration of cinacalcet [39]. Therefore, the role of FGF-23 in VC has been suggested, but the phenomenon of reverse causality, in which increased FGF-23 is a result rather than a cause of VC, requires further studies to clarify the mechanism.

Uremic toxins such as indoxyl sulfate accumulate as renal function declines, causing further renal damage [40]. Endothelial dysfunction along with traditional risk factors such as age, HTN, and DM are progressive risk factors for CVD in patients with CKD [27]. Serum levels of uremic toxin are significantly related to graded aortic calcification and PWV and are predictors of overall and CV mortality in patients with CKD [41]. Additionally, uremic toxins could promote endothelial dysfunction and AS by inducing oxidative stress, impairing endothelial cell repair, and inducing the proliferation of VSMCs, causing worsened overall outcomes in patients with CKD [42].

**DOWNREGULATION OF INHIBITORS OF VASCULAR CALCIFICATION**

The 10-kDa protein MGP is expressed by chondrocytes and VSMC and is an endogenous inhibitor of VC; extensive arterial calcification along with mortality due to rupture of blood vessels has been observed in MGP knockout mice [43]. Moreover, mice with MGP mutations exhibit early expression of RUNX2 and Cbfal and trans-differentiation of VSMCs into osteochondrogenic precursor- and chondrocyte-like cells in calcified vessels [44]. Warfarin inactivates gamma-carboxylation of MGP, resulting in progression of VC [45], which is supported by studies showing that MGP only induces VC in uremic rats in the absence of pyrophosphate [46]. Furthermore, MGP has been shown to inhibit the development of BMP-mediated VC in transgenic mice [31-33]. Taken together, these results indicate that MGP, either alone or together with other factors, plays a role in the development of VC.

Fetuin A is produced by hepatocytes and causes severe extraosseous calcification in vivo [47] and inhibits VC by reducing matrix vesicle calcification with resulting inhibiting of crystal formation and mineral deposition in vitro [30]. A cohort study involving individuals without CVD revealed that serum level of fetuin A is inversely correlated with the severity of CAC [48]. Moreover, serum fetuin A levels have been found to be negatively associated with C-reactive protein level and the rates of VC and mortality in patients with HD [49,50]. Therefore, through the inflammatory responses [49], fetuin A could be a predictor of the development of VC and long-term prognosis of patients with HD.

Pyrophosphate is known to be an inhibitor of the precipitation of calcium phosphate in urine and has been shown to play a direct role in the inhibition of VC independent of hyperphosphatemia and hypercalcemia in vivo [51]. Moreover, injection of pyrophosphate into rats causes the incidence and amount of aortic calcification to decrease [52]. Furthermore, knockout mice lacking the enzyme that synthesizes extracellular pyrophosphate experience accelerated VC [53], confirming the inhibition of VC by pyrophosphate.

**DIAGNOSIS OF VASCULAR CALCIFICATION**

Plain radiography

The development of methods for quantifying the severity of VC may enable the prevention of CV events and mortality [8,19]. Currently used methods range from plain radiography to CT, and we will briefly discuss these modalities (Table 2). Lateral lumbar spine X-rays can enable semiquantitative estimation of AAC [54], and electron beam tomography has revealed AAC to increase with decreased renal function [55] and to be significantly positively associated with CAC [56] and independently correlated with mortality and nonfatal CV events in patients with CKD and HD [57,58]. Thus, risk assessment for CV events and mortality in patients with CKD through evaluation of lateral spine X-ray images is recommended by Kidney Disease Improving Global Outcomes clinical practice guidelines [59]. Measurement of AAC on chest X-ray images shows good agreement with CT results of
Aortic volume [60], and a meta-analysis revealed that assessment of baseline AAC by plain chest radiography predicts future all-cause and CV mortality in patients with HD [61].

**Ultrasonography**

Although ultrasonography has been criticized as being a subjective and operator-dependent method for the detection of VC, an independent correlation with CAC has been confirmed by CT studies [62]. There is evidence that the incidence of carotid calcified plaques detected by ultrasonography is higher in patients with ESRD than in age- and sex-matched controls [62,63]. Blacher et al. measured and summarized the sites of calcification using ultrasonography along with plain X-ray and identified that in the carotid artery, abdominal aorta, iliofemoral axis, and legs, a higher calcification score was associated with higher carotid pulse pressure, increased intima-media thickness, and poor compliance and distensibility of the carotid artery [8]. Moreover, every unit increase in calcification score was found to be associated with a 1.9- and 2.6-fold increase in all-cause and CV mortality in patients with HD [8].

**Computed tomography of the coronary artery**

CT has revealed aortic calcification to be associated with CV events and mortality [58,64] and that CAC appears about 10 years prior to aortic calcification and is correlated with future CV events and mortality [65,66]. The quantification of CAC by CT has been shown to have excellent inter-observer agreement and good sensitivity, specificity, and predictive values for coronary artery disease [66,67]. Furthermore, decreased renal function exhibits a significant graded relationship with CAC [68], and CT has shown the prevalence of CAC to be high among patients with ESRD [5]. Moreover, the severity of CAC has been reported to be directly related with the occurrence of myocardial infarction and angina [69] and being a predictor for long-term survival [70]. Noncontrast CT is thus considered the gold standard for detection and quantification of CAC, with high sensitivity and accuracy during follow-up [71-73].

**TREATMENTS OF VASCULAR CALCIFICATION**

The high CVD and all-cause mortality rates associated with VC [2,8,19] mean that slowing or reversing VC is important. Controlling traditional risk factors such as hyperlipidemia, DM, and HTN and managing hyperphosphatemia may benefit patients with CKD, and noncalcium-based phosphate binders have been shown to reduce the progression of CAC [73] and improve mortality rates [71]. Successful treatment of VC is correlated with the management of disordered bone and mineral metabolism through inhibition of hyperphosphatemia or hypocalcemia without producing hypercalcemia with phosphate binders, and the administration of Vitamin D and calcimimetics that could potentially affect VC [71] (Figure 2).

Table 3 summarizes the current treatments for VC. As hyperphosphatemia is a direct risk factor for VC, lowering serum levels to lessen the harmful effects is a priority during treatment of VC. The Treat-To-Goal study revealed the incidence of CAC and aortic calcification to be decreased among patients undergoing dialysis who were administered sevelamer than calcium carbonate or acetate [73]. This finding extended to patients with CKD, with annual increases of coronary calcium score of 48%, 39%, and 9% reported in response to low-phosphate diet, calcium carbonate, and sevelamer, respectively [74]. Sevelamer treatment is reportedly associated with an increase in fetuin A, suggesting that the nonphosphate-binding mechanism of sevelamer may be involved in the prevention of uremic extraosseous calcification [73,75]. Thus, lowering hyperphosphatemia through the administration of noncalcium-based phosphate binders may be a valid approach to block the progression of VC.

Lanthanum is another noncalcium phosphate binder, which may contribute to the control of phosphate levels and decrease the severity of VC and reduce oxidation, inflammation, calcium content, and FGF-23 levels in VSMCs compared with calcium-based phosphate binders [76,77]. Lanthanum counteracts the high phosphate induced by VC while preventing the trans-differentiation of VSMCs into osteoblast-like cells.

| Table 2: Comparison of different modalities to measure vascular calcification |
|---------------------------------|----------------|-----------------|-----------------|
| **Location**                    | **AAC [54,55]** | **AAC [60]**    | **CAC [67]**    |
| Exam                            | Abdominal aorta| Aortic arch     | Coronary artery |
| Score                           | X-ray          | X-ray           | Thoracic CT     |
|                                | Lateral lumbar spine | Chest       | Coronary arteries |
|                                | 0-24 (each position score 0-3) | 0-16       | 1=130-199 HU |
| **Description**                 | Sum of ant. and posterior wall |
| of AAC in front of L1-L4         | of at least 0.5 mm² with a threshold density ≥130 |
| **Outcome prediction**          | CV events, mortality |
| **Limitation**                  | CV events, mortality |
| **Ultrasongraphy**              | CV events, mortality |
|                                | CV events, mortality |
|                                | Number of calcified arteries |
|                                | (carotid, abdominal aorta, iliofemoral axis, legs) |

AAC: Abdominal aortic calcification, AAC: Aortic arch calcification, Ant.: Anterior, CAC: Coronary artery calcification, CT: Computed tomography, CV: Cardiovascular, D/Dx: Differential diagnosis, HU: Hounsfield unit.
cells by modulating BMP-2 and preventing apoptosis and consequently, vascular mineralization [78]. An 18-month cohort study revealed a similar reduction of serum phosphate among patients with HD, with lanthanum associated with reduced progression of VC compared with calcium carbonate [64].

Traditionally, treatment of secondary hyperparathyroidism involves administration of Vitamin D analogs, which caused increased levels of pro-calcific factors and decreased levels of anti-calcific factors, leading to hypercalcemia and hyperphosphatemia [79-81]. However, lower dosages of calcitriol and paricalcitol can reduce serum levels of intact parathyroid hormone and inhibit aortic calcification by reducing the expression of Cbfa1 and RUNX2 [79]. Treatment with calcitriol also results in higher serum levels of calcium and phosphate and increased aortic mineral content than treatment with paricalcitol [81]. Additionally, paricalcitol has been shown to reduce the severity of VC by decreasing the expression of BMP-2, tumor necrosis factor α, monocyte chemotactic protein-1, and interleukin 1 [80].

Calcimimetics increase the sensitivity to extracellular calcium and binding to calcium-sensing receptor in parathyroid gland and in VSMCs [82] and can be used alone or in combination with Vitamin D analogs to suppress parathyroid hormone, with preferable outcomes to calcitriol [81,83] or paricalcitol [81]. Regression of VC and restoration of arterial distensibility have been observed in rats following treatment with calcimimetics in combination with a low-phosphate diets [84]. A longitudinal randomized placebo-controlled trial has shown cinacalcet in combination with conventional therapies to benefit patients with HD in terms of nonatherosclerotic diseases, for example, attenuation of VC and reduced myocardial calcium loading [85]. Additionally, combination therapy involving calcimimetics and low-dose Vitamin D analog has been shown to mitigate the progression of VC in patients with HD [86].

Inactivating the gamma-carboxylation of MGP is important in the progression of VC [45]. Given this, together with the high prevalence of subclinical Vitamin K deficiency observed in patients with CKD, supplementation of Vitamin K is recommended in patients with HD, which has been shown to reduce the level of uncarboxylated MGP in such patients [87]. Currently, the effects of Vitamin K on CAC scores are being validated by Holden et al. through a multicenter, prospective double-blind randomized study involving patients with ESRD [88].

**Conclusion**

VC is correlated with rates of CV morbidity and mortality, and the mechanism of the condition has been intensively investigated. An imbalance of pro-calcifying and anti-calcifying conditions leads to differentiation of VSMCs into osteoblast-like cells, which then express osteoblast transcription factors and other bone-related proteins. This is associated with downregulation of contractile proteins, and...

### Table 3: Effects of treatments on the progression of vascular calcification

| Population                  | Follow up (months) | Effects                                                                 |
|-----------------------------|--------------------|-------------------------------------------------------------------------|
| Sevelamer versus Ca-based   | HD [71-73]         | Baseline CAC score predict all-cause mortality                           |
|                             |                    | Treatment with sevelamer associated with better survival and less        |
|                             |                    | progression of calcification of coronary artery and aorta               |
|                             | CKD Stage 3/4 [74] | Total CAC score: Low-IP diet alone >low-IP diet + calcium carbonate     |
|                             |                    | >low IP diet + sevelamer                                                 |
| Lanthanum Ca. versus Ca.    | HD [64]            | Less aortic calcification (adjusted difference −98.1 [−149.4−−46.8] HU) |
| Carbonate                   | 18                 | with lanthanum Ca. than Ca. carbonate                                     |
| Cinacalcet versus Vitamin D | HD (Agatston CAC  | Median Agatston and corresponding percent changes in volume CAC score   |
|                             | score ≥30) [86]    | Cinacalcet + low dose Vitamin D: 24% and 22%                           |
|                             | 13                 | Flexible Vitamin D: 31% and 30%                                         |
|                             |                    | Progression of thoracic aorta and aortic and mitral valves calcification |
| Vitamin K                   | HD (Agatston CAC  | Cinacalcet + Vitamin D <flexible Vitamin D                              |
|                             | score ≥30) [87]    | To evaluate the effects of reducing the progression of CAC scores by     |
|                             | 12                 | Vitamin K supplement during HD sessions                                 |

CAC: Coronary artery calcification, HU: Hounsfield units, HD: Hemodialysis, Ca: Calcium, IP: Inorganic phosphate
the transformed cells generate matrix vesicles, which initiate the process of mineralization within the vessel wall. There is growing evidence of the involvement of genetic, metabolic, and hormonal signaling in the regulation of VC development, but the active and predominant mechanisms are unknown, as is the interconnection of signaling pathways in various disease states.

Plain radiography is a simple and low-cost method of detecting and quantifying VC, while ultrasonography can reveal arterial architecture and calcification. CT offers the highest sensitivity, accuracy, and objectivity for analysis of VC severity. The most suitable method will depend on the specific requirements of the case, for example, accurate monitoring of regression or progression of VC after intervention.

Since VC rarely regresses once it has developed, prevention and slowing the progression of existing VC are major goals of treatment. Calcium-free phosphate binders and low-dose Vitamin D analogs combined with calcimimetics may reduce the severity of VC, while active Vitamin D analogs or calcium-containing phosphate binders may promote VC. Treatments that address hyperphosphatemia without causing an increase in serum calcium concentration or restoration of calcification inhibitors may reduce the rate of VC; however, since the precise regulation of VC is unclear, optimal treatment for VC remains to be found.

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**Conflicts of interest**

There are no conflicts of interest.

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