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Review Article

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

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Table 1: Differences between vascular calcification in intima and media of vascular wall

Layer of vascular wall	Initma	Media
Type of vessels	Large and medium-sized conduit arteries	Any size, including arterioles
Histology	Atherosclerosis	Arteriosclerosis (Monckerberg's sclerosis)
	Diffuse punctate morphology	Linear deposits along elastic lamellae
	Aggregates of Ca crystals	At most severe, a dense circumferential sheet of Ca crystals
Occurrence	Generalized CVD	CKD, DM, aging
Clinical symptoms	Plaque rupture	Vascular stiffness (high SBP, PP)
	Myocardial infarction	Heart failure, LVH, valve calcification
	CV accident	
Risk factor	Hyperlipidemia, macrophages, inflammation, HCVD, DM, oxidative stress	Elastin degradation, hyperphosphatemia, hypercalcemia, Dialysis vintage, decreased inhibitors of calcification
Radiology	Spotty calcification	Linear tram-track calcification
Consequence	Acute occlusion	Vascular stiffness (nonocclusive)

Ca: Calcium, CVD: Cardiovascular disease, CKD: Chronic kidney disease, DM: Diabetes mellitus, HCVD: Hypertensive cardiovascular disease, LVH: Left ventricular hypertrophy, PP: Pulse pressure, SBP: Systolic blood pressure

of the medial layer in CKD, aging has been suggested to contribute to structural and functional changes of vessels, which lead to dysregulation of elastin and collagen remodeling [16-18]. These lead to the loss of arterial elasticity, increased thickening and stiffening of the vascular wall, and abnormal extracellular matrix remodeling [16-18]. Aortic PWV increases with age and with increased aortic bifurcation diameter and decreased aortic taper, indicating that marked age-related AS occurs in patients with ESRD [16]. Reduced arterial lumen diameter has been suggested to lead to premature return of the reflected wave in late systole with resultant increases in pulse pressure and systolic blood pressure and decreased diastolic blood pressure, which indicates a strong relationship between VC and HTN [8,19]. Furthermore, a systemic review found that, other than classical risk factors such as sex, dyslipidemia, smoking, and body mass index, arterial aging and elevation of BP are independently associated with AS [20]. Impaired glucose metabolism and DM have been shown to increase central AS [21], and longer duration of DM has been found to be independently associated with higher incidences of AS and macrovascular events [22]. Additionally, increased body mass index and waist circumference are positively correlated with carotid-femoral PWV, indicating that adiposity may be a predictor of AS [23]. Moreover, VC is a process of gradual osteogenesis initiated by inflammatory factors in vessels; higher levels of serum C-reactive protein are associated with the development of VC in patients with CKD or HD independent of age or DM [18,24]. All these factors are thought to contribute to the process of VC by promoting inducers or downregulating inhibitors [Figure 1].

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].

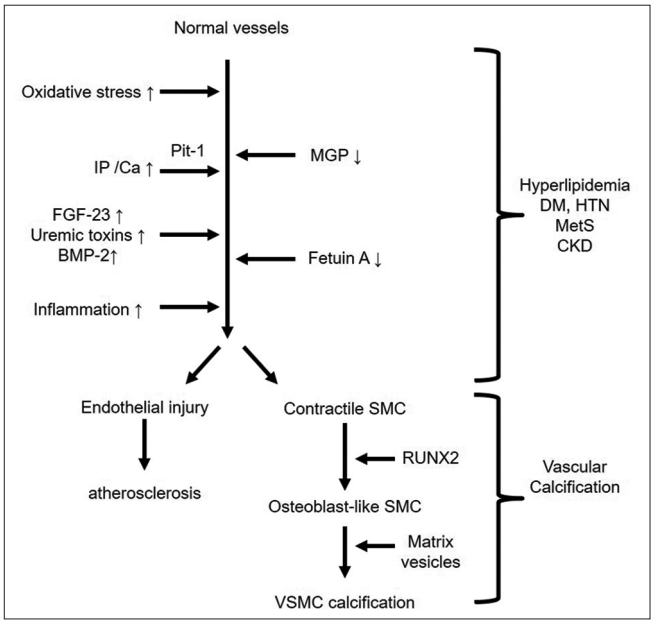

Figure 1: Pathophysiology of vascular calcification. After stimulation by pro-calcific diseases such as hyperlipidemia, DM, HTN, MetS or CKD, decreased anti-calcify and increased pro-calcify factors stimulated differentiation of VSMC into osteoblast-like SMC and then vascular calcification by the generation of mineralization-competent extracellular matrix vesicles (↓↑ indicated increased and decreased expression). BMP-2: Bone morphogenic protein 2, Ca: Calcium, FGF-23: Fibroblast growth factor 23, IP: Inorganic phosphate, MGP: Matrix Gla protein, VSMC: Vascular smooth muscle cell, SMC: Smooth muscle cell, CKD: Chronic kidney disease, HTN: Hypertension, DM: Diabetes mellitus

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 D_3 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 Cbfa1 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

Table 2: Comparison of different modalities to measure vascular calcification

	AAC [54,55]	AAC [60]	CAC [67]	Ultrasonography [8]
Location	Abdominal aorta	Aortic arch	Coronary artery	Carotid, femoral, peripheral arteries
Exam	X-ray	X-ray	Thoracic CT	Ultrasound
Score	Lateral lumbar spine 0-24 (each position score 0-3)	Chest 0-16	Coronary arteries 1=130-199 HU 2=200-299 HU 3=300-399 4=≥400	0-4
Description	Sum of ant. and posterior wall of AAC in front of L1-L4	Scale with 16 circumferences attached to aortic knob Sections of calcification are counted	Calcified lesion is the area of at least 0.5 mm^2 that has a threshold density ≥130	Number of calcified arteries (carotid, abdominal aorta, ilio-femoral axis, legs)
Outcome prediction	CV events, mortality	CV events, mortality	CV events, mortality	CV events, mortality
Limitation	Semiquantitative, subjective	Semiquantitative, subjective	Cost, radiation Difficulty in D/Dx intima and medial calcification	Semiquantitative, subjective, only superficial arteries

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

AAC 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 operative-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-medial 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 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].

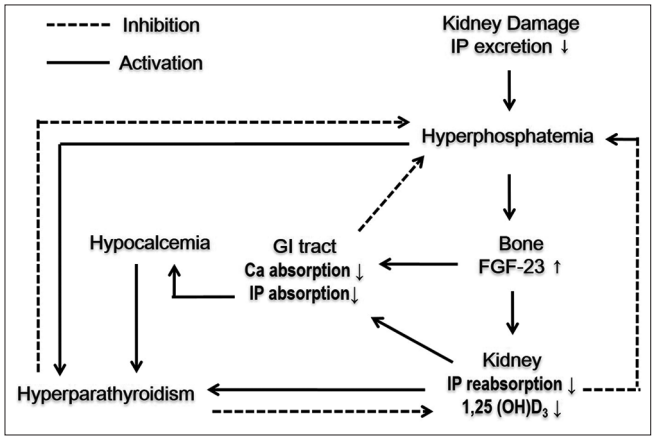

Figure 2: Mechanism and treatments of hyperphosphatemia and secondary hyperparathyroidism. As renal function worsened, renal phosphate excretion decreased and resulted in hyperphosphatemia, elevation of FGF-23 and then secondary hyperparathyroidism. Solid lines indicated abnormal regulation of mineral and hormones in CKD patients. Dashed lines indicate potential treatments against these harmful pathways. Ca: Calcium, FGF-23: Fibroblast growth factor 23, IP: Inorganic phosphate, GI: Gastrointestinal, CKD: Chronic kidney disease

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]	13-44	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]	24	Total CAC score: Low-IP diet alone >low-IP diet + calcium carbonate >low IP diet + sevelamer
Lanthanum Ca. versus Ca. carbonate	HD [64]	18	Less aortic calcification (adjusted difference −98.1 [−149.4-−46.8] HU) with lanthanum Ca. than Ca. carbonate
Cinacalcet versus vitamin D	HD (Agatston CAC score ≥30) [86]	13	Median Agatston and corresponding percent changes in volume CAC score
			Cinacalcet + low dose Vitamin D: 24% and 22%
			Flexible Vitamin D: 31% and 30%
			Progression of thoracic aorta and aortic and mitral valves calcification
			Cinacalcet + Vitamin D <flexible Vitamin D
Vitamin K	HD (Agatston CAC score a≥30) [87]	12	To evaluate the effects of reducing the progression of CAC scores by 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 treatments for VC remain to be found.

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Conflicts of interest

There are no conflicts of interest.

References

1. Amann K. Media calcification and intima calcification are distinct entities in chronic kidney disease. Clin J Am Soc Nephrol 2008;3:1599-605.
2. Nakamura S, Ishibashi-Ueda H, Niizuma S, Yoshihara F, Horio T, Kawano Y. Coronary calcification in patients with chronic kidney disease and coronary artery disease. Clin J Am Soc Nephrol 2009;4:1892-900.
3. Bild DE, Detrano R, Peterson D, Guerci A, Liu K, Shahar E, et al. Ethnic differences in coronary calcification: The Multi-Ethnic Study of Atherosclerosis (MESA). Circulation 2005;111:1313-20.
4. Nakayama M, Kaizu Y, Nagata M, Ura Y, Ikeda H, Shimamoto S, et al. Fibroblast growth factor 23 is associated with carotid artery calcification in chronic kidney disease patients not undergoing dialysis: A cross-sectional study. BMC Nephrol 2013;14:22.
5. Goodman WG, Goldin J, Kuizon BD, Yoon C, Gales B, Sider D, et al. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. N Engl J Med 2000;342:1478-83.
6. Hsu CC, Hwang SJ, Wen CP, Chang HY, Chen T, Shiu RS, et al. High prevalence and low awareness of CKD in Taiwan: A study on the relationship between serum creatinine and awareness from a nationally representative survey. Am J Kidney Dis 2006;48:727-38.
7. Wen CP, Cheng TY, Tsai MK, Chang YC, Chan HT, Tsai SP, et al. All-cause mortality attributable to chronic kidney disease: A prospective cohort study based on 462 293 adults in Taiwan. Lancet 2008;371:2173-82.
8. Blacher J, Guerin AP, Pannier B, Marchais SJ, London GM. Arterial calcifications, arterial stiffness, and cardiovascular risk in end-stage renal disease. Hypertension 2001;38:938-42.
9. Moe SM, Duan D, Doehle BP, O'Neill KD, Chen NX. Uremia induces the osteoblast differentiation factor Cbfa1 in human blood vessels. Kidney Int 2003;63:1003-11.
10. Nam HJ, Jung IH, Kim J, Kim JH, Suh J, Kim HS, et al. Association between brachial-ankle pulse wave velocity and occult coronary artery disease detected by multi-detector computed tomography. Int J Cardiol 2012;157:227-32.
11. Laurent S, Boutouyrie P. Arterial stiffness: A new surrogate end point for cardiovascular disease? J Nephrol 2007;20(Suppl 12):S45-50.
12. Levisianou D, Melidonis A, Adamopoulou E, Skopelitis E, Koutsovasilis A, Protopsaltis I, et al. Impact of the metabolic syndrome and its components combinations on arterial stiffness in Type 2 diabetic men. Int Angiol 2009;28:490-5.
13. Gong J, Xie Q, Han Y, Chen B, Li L, Zhou G, et al. Relationship between components of metabolic syndrome and arterial stiffness in Chinese hypertensives. Clin Exp Hypertens 2020;42:146-52.
14. Palombo C, Kozakova M. Arterial stiffness, atherosclerosis and cardiovascular risk: Pathophysiologic mechanisms and emerging clinical indications. Vascul Pharmacol 2016;77:1-7.
15. Haydar AA, Covic A, Colhoun H, Rubens M, Goldsmith DJ. Coronary artery calcification and aortic pulse wave velocity in chronic kidney disease patients. Kidney Int 2004;65:1790-4.
16. London GM, Safar ME, Pannier B. Aortic Aging in ESRD: Structural, Hemodynamic, and Mortality Implications. J Am Soc Nephrol 2016;27:1837-46.
17. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: A systematic review and meta-analysis. J Am Coll Cardiol 2010;55:1318-27.
18. Jean G, Chazot C, Bresson E, Zaoui E, Cavalier E. High serum sclerostin levels are associated with a better outcome in haemodialysis patients. Nephron 2016;132:181-90.
19. London GM, Guérin AP, Marchais SJ, Métivier F, Pannier B, Adda H. Arterial media calcification in end-stage renal disease: Impact on all-cause and cardiovascular mortality. Nephrol Dial Transplant 2003;18:1731-40.
20. Cecelja M, Chowienczyk P. Dissociation of aortic pulse wave velocity with risk factors for cardiovascular disease other than hypertension: A systematic review. Hypertension 2009;54:1328-36.
21. Schram MT, Henry RM, van Dijk RA, Kostense PJ, Dekker JM, Nijpels G, et al. Increased central artery stiffness in impaired glucose metabolism and type 2 diabetes: The Hoorn Study. Hypertension 2004;43:176-81.
22. Agnoletti D, Mansour AS, Zhang Y, Protogerou AD, Ouerdane S, Blacher J, et al. Clinical interaction between diabetes duration and aortic stiffness in type 2 diabetes mellitus. J Hum Hypertens 2017;31:189-94.
23. Brunner EJ, Shipley MJ, Ahmadi-Abhari S, Tabak AG, McEniery CM, Wilkinson IB, et al. Adiposity, obesity, and arterial aging: Longitudinal study of aortic stiffness in the Whitehall II cohort. Hypertension 2015;66:294-300.
24. Claes KJ, Viaene L, Heye S, Meijers B, d'Haese P, Evenepoel P. Sclerostin: Another vascular calcification inhibitor? J Clin Endocrinol Metab 2013;98:3221-8.
25. Ketteler M, Wanner C, Metzger T, Bongartz P, Westenfeld R, Gladziwa U, et al. Deficiencies of calcium-regulatory proteins in dialysis patients: A novel concept of cardiovascular calcification in uremia. Kidney Int Suppl 2003;63:S84-7.
26. Leopold JA. Vascular calcification: Mechanisms of vascular smooth muscle cell calcification. Trends Cardiovasc Med 2015;25:267-74.
27. Jono S, McKee MD, Murry CE, Shioi A, Nishizawa Y, Mori K, et al. Phosphate regulation of vascular smooth muscle cell calcification. Circ Res 2000;87:E10-7.

28. Yang H, Curinga G, Giachelli CM. Elevated extracellular calcium levels induce smooth muscle cell matrix mineralization *in vitro*. Kidney Int 2004;66:2293-9.
29. Moe SM, O'Neill KD, Duan D, Ahmed S, Chen NX, Leapman SB, et al. Medial artery calcification in ESRD patients is associated with deposition of bone matrix proteins. Kidney Int 2002;61:638-47.
30. Reynolds JL, Joannides AJ, Skepper JN, McNair R, Schurgers LJ, Proudfoot D, et al. Human vascular smooth muscle cells undergo vesicle-mediated calcification in response to changes in extracellular calcium and phosphate concentrations: A potential mechanism for accelerated vascular calcification in ESRD. J Am Soc Nephrol 2004;15:2857-67.
31. Boström KI, Jumabay M, Matveyenko A, Nicholas SB, Yao Y. Activation of vascular bone morphogenetic protein signaling in diabetes mellitus. Circ Res 2011;108:446-57.
32. Li X, Yang HY, Giachelli CM. BMP-2 promotes phosphate uptake, phenotypic modulation, and calcification of human vascular smooth muscle cells. Atherosclerosis 2008;199:271-7.
33. Yao Y, Bennett BJ, Wang X, Rosenfeld ME, Giachelli C, Lusis AJ, et al. Inhibition of bone morphogenetic proteins protects against atherosclerosis and vascular calcification. Circ Res 2010;107:485-94.
34. Malhotra R, Burke MF, Martyn T, Shakartzi HR, Thayer TE, O'Rourke C, et al. Inhibition of bone morphogenetic protein signal transduction prevents the medial vascular calcification associated with matrix Gla protein deficiency. PLoS One 2015;10:e0117098.
35. Yamada S, Giachelli CM. Vascular calcification in CKD-MBD: Roles for phosphate, FGF23, and Klotho. Bone 2017;100:87-93.
36. Scialla JJ, Xie H, Rahman M, Anderson AH, Isakova T, Ojo A, et al. Fibroblast growth factor-23 and cardiovascular events in CKD. J Am Soc Nephrol 2014;25:349-60.
37. Baralić M, Brković V, Stojanov V, Stanković S, Lalić N, Đurić P, et al. Dual Roles of the Mineral Metabolism Disorders Biomarkers in Prevalent Hemodilysis Patients: In Renal Bone Disease and in Vascular Calcification. J Med Biochem 2019;38:134-44.
38. Krishnasamy R, Tan SJ, Hawley CM, Johnson DW, Stanton T, Lee K, et al. Progression of arterial stiffness is associated with changes in bone mineral markers in advanced CKD. BMC Nephrol 2017;18:281.
39. Moe SM, Chertow GM, Parfrey PS, Kubo Y, Block GA, Correa-Rotter R, et al. Cinacalcet, Fibroblast Growth Factor-23, and Cardiovascular Disease in Hemodialysis: The Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events (EVOLVE) Trial. Circulation 2015;132:27-39.
40. Motojima M, Hosokawa A, Yamato H, Muraki T, Yoshioka T. Uremic toxins of organic anions up-regulate PAI-1 expression by induction of NF-kappaB and free radical in proximal tubular cells. Kidney Int 2003;63:1671-80.
41. Barreto FC, Barreto DV, Liabeuf S, Meert N, Glorieux G, Temmar M, et al. Serum indoxyl sulfate is associated with vascular disease and mortality in chronic kidney disease patients. Clin J Am Soc Nephrol 2009;4:1551-8.
42. Vanholder R, Schepers E, Pletinck A, Nagler EV, Glorieux G. The uremic toxicity of indoxyl sulfate and p-cresyl sulfate: A systematic review. J Am Soc Nephrol 2014;25:1897-907.
43. Luo G, Ducy P, McKee MD, Pinero GJ, Loyer E, Behringer RR, et al. Spontaneous calcification of arteries and cartilage in mice lacking matrix GLA protein. Nature 1997;386:78-81.
44. Speer MY, Yang HY, Brabb T, Leaf E, Look A, Lin WL, et al. Smooth muscle cells give rise to osteochondrogenic precursors and chondrocytes in calcifying arteries. Circ Res 2009;104:733-41.
45. Price PA, Faus SA, Williamson MK. Warfarin causes rapid calcification of the elastic lamellae in rat arteries and heart valves. Arterioscler Thromb Vasc Biol 1998;18:1400-7.
46. Lomashvili KA, Wang X, Wallin R, O'Neill WC. Matrix Gla protein metabolism in vascular smooth muscle and role in uremic vascular calcification. J Biol Chem 2011;286:28715-22.
47. Schafer C, Heiss A, Schwarz A, Westenfeld R, Ketteler M, Floege J, et al. The serum protein alpha 2-Heremans-Schmid glycoprotein/fetuin-A is a systemically acting inhibitor of ectopic calcification. J Clin Invest 2003;112:357-66.
48. Ix JH, Katz R, de Boer IH, Kestenbaum BR, Peralta CA, Jenny NS, et al. Fetuin-A is inversely associated with coronary artery calcification in community-living persons: The Multi-Ethnic Study of Atherosclerosis. Clin Chem 2012;58:887-95.
49. Ketteler M, Bongartz P, Westenfeld R, Wildberger JE, Mahnken AH, Böhm R, et al. Association of low fetuin-A (AHSG) concentrations in serum with cardiovascular mortality in patients on dialysis: A cross-sectional study. Lancet 2003;361:827-33.
50. Turkmen K, Gorgulu N, Uysal M, Ozkok A, Sakaci T, Unsal A, et al. Fetuin-A, inflammation, and coronary artery calcification in hemodialysis patients. Indian J Nephrol 2011;21:90-4.
51. Lomashvili KA, Cobbs S, Hennigar RA, Hardcastle KI, O'Neill WC. Phosphate-induced vascular calcification: Role of pyrophosphate and osteopontin. J Am Soc Nephrol 2004;15:1392-401.
52. O'Neill WC, Lomashvili KA, Malluche HH, Faugere MC, Riser BL. Treatment with pyrophosphate inhibits uremic vascular calcification. Kidney Int 2011;79:512-7.
53. Lomashvili KA, Narisawa S, Millán JL, O'Neill WC. Vascular calcification is dependent on plasma levels of pyrophosphate. Kidney Int 2014;85:1351-6.
54. Kauppila LI, Polak JF, Cupples LA, Hannan MT, Kiel DP, Wilson PW. New indices to classify location, severity and progression of calcific lesions in the abdominal aorta: A 25-year follow-up study. Atherosclerosis 1997;132:245-50.
55. Biyik Z, Selcuk NY, Tonbul HZ, Anil M, Uyar M. Assessment of abdominal aortic calcification at different stages of chronic kidney disease. Int Urol Nephrol 2016;48:2061-8.
56. Bellasi A, Ferramosca E, Muntner P, Ratti C, Wildman RP, Block GA, et al. Correlation of simple imaging tests and coronary artery calcium measured by computed tomography in hemodialysis patients. Kidney Int 2006;70:1623-8.
57. Peeters MJ, van den Brand JA, van Zuilen AD, Koster Y, Bots ML, Vervloet MG, et al. Abdominal aortic calcification in patients with CKD. J Nephrol 2017;30:109-18.
58. Verbeke F, Van Biesen W, Honkanen E, Wikström B, Jensen PB, Krzesinski JM, et al. Prognostic value of aortic stiffness and calcification for cardiovascular events and mortality in dialysis patients: Outcome of the calcification outcome in renal disease (CORD) study. Clin J Am Soc Nephrol 2011;6:153-9.
59. Liabeuf S, Desjardins L, Diouf M, Temmar M, Renard C, Choukroun G, et al. The addition of vascular calcification scores to traditional risk factors improves cardiovascular risk assessment in patients with chronic kidney disease. PLoS One 2015;10:e0131707.
60. Ogawa T, Ishida H, Matsuda N, Fujiu A, Matsuda A, Ito K, et al. Simple evaluation of aortic arch calcification by chest radiography in hemodialysis patients. Hemodial Int 2009;13:301-6.
61. Zhang A, Wang S, Li H, Yang J, Wu H. Aortic arch calcification and risk of cardiovascular or all-cause and mortality in dialysis patients: A meta-analysis. Sci Rep 2016;6:35375.
62. Sumida Y, Nakayama M, Nagata M, Nakashita S, Suehiro T, Kaizu Y, et al. Carotid artery calcification and atherosclerosis at the initiation of hemodialysis in patients with end-stage renal disease. Clin Nephrol 2010;73:360-9.
63. Savage T, Clarke AL, Giles M, Tomson CR, Raine AE. Calcified plaque is common in the carotid and femoral arteries of dialysis patients without clinical vascular disease. Nephrol Dial Transplant 1998;13:2004-12.
64. Toussaint ND, Lau KK, Polkinghorne KR, Kerr PG. Attenuation of aortic calcification with lanthanum carbonate versus calcium-based

phosphate binders in haemodialysis: A pilot randomized controlled trial. Nephrology (Carlton) 2011;16:290-8.

65. Allison MA, Criqui MH, Wright CM. Patterns and risk factors for systemic calcified atherosclerosis. Arterioscler Thromb Vasc Biol 2004;24:331-6.
66. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr., Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol 1990;15:827-32.
67. Agatston AS, Janowitz WR, Kaplan G, Gasso J, Hildner F, Viamonte M Jr. Ultrafast computed tomography-detected coronary calcium reflects the angiographic extent of coronary arterial atherosclerosis. Am J Cardiol 1994;74:1272-4.
68. Budoff MJ, Rader DJ, Reilly MP, Mohler ER 3rd, Lash J, Yang W, et al. Relationship of estimated GFR and coronary artery calcification in the CRIC (Chronic Renal Insufficiency Cohort) Study. Am J Kidney Dis 2011;58:519-26.
69. Raggi P, Boulay A, Chasan-Taber S, Amin N, Dillon M, Burke SK, et al. Cardiac calcification in adult hemodialysis patients. A link between end-stage renal disease and cardiovascular disease? J Am Coll Cardiol 2002;39:695-701.
70. Matsuoka M, Iseki K, Tamashiro M, Fujimoto N, Higa N, Touma T, et al. Impact of high coronary artery calcification score (CACS) on survival in patients on chronic hemodialysis. Clin Exp Nephrol 2004;8:54-8.
71. Block GA, Raggi P, Bellasi A, Kooienga L, Spiegel DM. Mortality effect of coronary calcification and phosphate binder choice in incident hemodialysis patients. Kidney Int 2007;71:438-41.
72. Block GA, Spiegel DM, Ehrlich J, Mehta R, Lindbergh J, Dreisbach A, et al. Effects of sevelamer and calcium on coronary artery calcification in patients new to hemodialysis. Kidney Int 2005;68:1815-24.
73. Chertow GM, Burke SK, Raggi P, Treat to Goal Working Group. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. Kidney Int 2002;62:245-52.
74. Russo D, Miranda I, Ruocco C, Battaglia Y, Buonanno E, Manzi S, et al. The progression of coronary artery calcification in predialysis patients on calcium carbonate or sevelamer. Kidney Int 2007;72:1255-61.
75. Caglar K, Yilmaz MI, Saglam M, Cakir E, Acikel C, Eyileten T, et al. Short-term treatment with sevelamer increases serum fetuin-a concentration and improves endothelial dysfunction in chronic kidney disease stage 4 patients. Clin J Am Soc Nephrol 2008;3:61-8.
76. Neven E, Dams G, Postnov A, Chen B, De Clerck N, De Broe ME, et al. Adequate phosphate binding with lanthanum carbonate attenuates arterial calcification in chronic renal failure rats. Nephrol Dial Transplant 2009;24:1790-9.
77. Yamada S, Tatsumoto N, Tokumoto M, Noguchi H, Ooboshi H, Kitazono T, et al. Phosphate binders prevent phosphate-induced cellular senescence of vascular smooth muscle cells and vascular calcification in a modified, adenine-based uremic rat model. Calcif Tissue Int 2015;96:347-58.
78. Ciceri P, Elli F, Brenna I, Volpi E, Romagnoli S, Tosi D, et al. Lanthanum prevents high phosphate-induced vascular calcification by preserving vascular smooth muscle lineage markers. Calcif Tissue Int 2013;92:521-30.
79. Mathew S, Lund RJ, Chaudhary LR, Geurs T, Hruska KA. Vitamin D receptor activators can protect against vascular calcification. J Am Soc Nephrol 2008;19:1509-19.
80. Guerrero F, Montes de Oca A, Aguilera-Tejero E, Zafra R, Rodríguez M, López I. The effect of vitamin D derivatives on vascular calcification associated with inflammation. Nephrol Dial Transplant 2012;27:2206-12.
81. Lopez I, Mendoza FJ, Aguilera-Tejero E, Perez J, Guerrero F, Martin D, et al. The effect of calcitriol, paricalcitol, and a calcimimetic on extraosseous calcifications in uremic rats. Kidney Int 2008;73:300-7.
82. Molostvov G, James S, Fletcher S, Bennett J, Lehnert H, Bland R, et al. Extracellular calcium-sensing receptor is functionally expressed in human artery. Am J Physiol Renal Physiol 2007;293:F946-55.
83. Lopez I, Aguilera-Tejero E, Mendoza FJ, Almaden Y, Perez J, Martin D, et al. Calcimimetic R-568 decreases extraosseous calcifications in uremic rats treated with calcitriol. J Am Soc Nephrol 2006;17:795-804.
84. Henley C, Davis J, Miller G, Shatzen E, Cattley R, Li X, et al. The calcimimetic AMG 641 abrogates parathyroid hyperplasia, bone and vascular calcification abnormalities in uremic rats. Eur J Pharmacol 2009;616:306-13.
85. Wheeler DC, London GM, Parfrey PS, Block GA, Correa-Rotter R, Dehmel B, et al. Effects of cinacalcet on atherosclerotic and nonatherosclerotic cardiovascular events in patients receiving hemodialysis: The EValuation Of Cinacalcet HCl Therapy to Lower CardioVascular Events (EVOLVE) trial. J Am Heart Assoc 2014;3:e001363.
86. Raggi P, Chertow GM, Torres PU, Csiky B, Naso A, Nossuli K, et al. The ADVANCE study: A randomized study to evaluate the effects of cinacalcet plus low-dose vitamin D on vascular calcification in patients on hemodialysis. Nephrol Dial Transplant 2011;26:1327-39.
87. Westenfeld R, Krueger T, Schlieper G, Cranenburg EC, Magdeleyns EJ, Heidenreich S, et al. Effect of vitamin K2 supplementation on functional vitamin K deficiency in hemodialysis patients: A randomized trial. Am J Kidney Dis 2012;59:186-95.
88. Holden RM, Booth SL, Day AG, Clase CM, Zimmerman D, Moist L, et al. Inhibiting the progression of arterial calcification with vitamin K in HemoDialysis patients (iPACK-HD) trial: Rationale and study design for a randomized trial of vitamin K in patients with end stage kidney disease. Can J Kidney Health Dis 2015;2:17.