REVIEW

Vascular calcifications in chronic kidney disease – clinical management

I. A. Checheriţă[1], Diana Smarandache[1], Cristiana David[1], Al. Ciocâlteu[1], Daniela Adriana Ion[2], I. Lascăr[3]

[1]Department of Nephrology, Urology and Transplant Immunology
[2]Department of Pathophysiology
[3]Department of Microsurgery and Plastic Surgery
"Carol Davila" University of Medicine and Pharmacy, Bucharest

Abstract

Chronic kidney disease (CKD) patients could present various types of calcifications causing different pathological conditions that would contribute to the renal disease progression and high risk of mortality. Extra-skeletal calcifications represent a common consequence of mineral bone disorders in CKD patients. Vascular calcifications represent a complex systemic manifestation caused by phospho-calcium homeostasis disorders, by imbalance among promoters and inhibitors of calcification and the presence of various arterial diseases and other risk factors. Consequently, vascular calcification can be considered an active pathological process that resembles osteogenesis. Therefore, before starting a suitable therapy for the prevention or delay of vascular calcifications, our recommendations are: to perform lateral abdominal radiography or CT-based techniques in CKD stages 3–5 patients for an early vascular calcification detection, to assess thoroughly patients presenting hyperphosphatemia, hyperparathyroidism, vitamin D deficiency and to understand clearly the pathophysiology of arterial calcification and calciphylaxis.

Keywords: CKD, vascular calcifications, physiopathology, risk factors, therapy management.

Introduction

In the last decades, vascular calcifications have been associated with unfavorable clinical prognostic in CKD patients, including high risk of mortality [1–7]. Vascular calcifications pathogenesis represents an imbalance between calcification promoters and inhibitors, caused by an improper mineral-bone metabolism [1, 8–12]. In addition, age, diabetes, dyslipidemia, hypertension, smoking can be considered as important risk factors not only for vascular calcification development, but also for healthy bone [1]. Furthermore, recent experimental studies reported that vascular smooth muscle cells could suffer a phenotype transformation (osteoblast-like cells) with a clear impact on vascular calcifications genesis [1, 13–18]. For this reason, similar to osteogenesis, vascular calcification can also be interpreted as an active cell-regulated pathological process [19–21].

Up to this moment, all researches have proved that calcification occurs in the intima and media of the vessel walls [1]. If the calcification of the intima usually involves the aorta and coronaries, the calcification of the media is localized in the elastic lamina of the large and medium arteries, especially in CKD and diabetes patients [1]. Additionally, it increases with age [1]. Even if, these two types of vascular calcifications determine different complications, they equally are associated with high risk of morbidity and mortality in CKD patients [1, 22–24]. In addition, there is a strong correlation among vascular calcifications and the caliber of the arteries. Rodríguez-García M *et al.* [1] study proved that vascular calcification prevalence was higher in large caliber arteries than in the medium and small once (70.7% compared to 55.6% and 14.1%, respectively). They also noticed that the severity of vascular calcifications in small caliber arteries was more important in men than in women (20.3% *vs.* 5%, *p*<0.05). Even more, hemodialysed (HD) patients presented higher prevalence of aortic calcifications compared to the general population (79% *vs.* 37.5%, *p*<0.001), with an OR of 8.7 (5–15). This difference was observed in both sexes (77.8% *vs.* 29.7% in women, *p*<0.001 and 80.3% *vs.* 45.4% in men, *p*<0.001) emphasized by women OR of 9 (3.8–21) compared to men OR of 7.7 (3.7–16.1). This experiment also noticed that renal replacement therapy (RRT) *per se* represents a severe risk factor for vascular calcifications development, especially in medium caliber arteries. Consequently, each year spent on dialysis increases the chances with 15% of having vascular calcifications, results in agreement with previous clinical trials [4, 5, 25, 26].

In concordance with data from the literature [27–30], Rodríguez-García M *et al.* [1] research reported a clear correlation between osteoporotic vertebral fractures and vascular calcifications in large and medium caliber arteries (mostly in femoral and uterine/spermatic arteries). Interestingly, this association was not proved in small arteries, maybe because of the reduced amount of muscle cells.

Although there is no consensus regarding a clear separation among intimal and medial calcification [31], there are some data from the literature suggesting these two forms of calcifications present distinct clinical features independent of one other [32]. Intimal calcification, characterized by foam cell formation, lipid accumulation, inflammation, oxidative stress and apoptosis, is tightly associated to atherosclerosis and determines focal calcification of atherosclerotic plaques [33]. On the other hand, medial calcification (arteriosclerosis or Mönckeberg's sclerosis) is a more frequent condition with increased cardiovascular risk, characterized by vessel stiffening (increased pulse pressure and elevated pulse wave velocity) [25, 33, 34]. Mostly, it affects the elderly and patients diagnosed with CKD, osteoporosis, hypertension or diabetes [33].

⊟ Vascular calcification pathogenesis

Recently, vascular calcification pathogenesis has been viewed as an active arterial biomineralization process that could also be considered as a tightly regulated form of calcified tissue metabolism [33]. Additionally, the importance of oxidative stress in vascular activation of the osteogenic gene was emphasized [33, 35–37].

A series of risk factors (hypercholesterolemia, hypertension, diabetes, and end-stage renal disease) linked to vascular calcification genesis are correlated with increased oxidative stress, which is characterized by an imbalance between oxidant production and antioxidant activity [33]. A recent study reported the importance of hydrogen peroxide (H_2O_2) in transforming the vascular smooth muscle cells phenotype in an osteogenic one, process emphasized by the presence of Runx2 elevated expression, known as an important transcription factor for osteogenic differentiation [33, 37]. The same study observed that H_2O_2 inhibition prevented vascular smooth muscle cell calcification [33, 37].

Apoptosis represents another oxidative stress pathway in signaling vascular calcification activation process by predisposing to calcium-phosphate crystals deposits formation [17, 33, 38, 39]. Additionally, reactive oxygen species (ROS) accumulation around calcified vascular cells determines osteoblast/osteoclast signaling and not macrophage one [33, 40].

Another study noticed that, *in vitro*, advanced oxidative protein products (AOPPs) contribute to vascular calcification pathogenesis by (a) increasing calcium deposition, expression of corebinding factor-alpha-1 (Cbfa-1) and osteopontin and by (b) decreasing alpha-smooth muscle actin expression in human aortic smooth muscle cells [33, 41].

As it has previously been presented, vascular calcification may be considered an actively regulated process, resembling to skeletal mineralization, because atherosclerotic plaques present bone morphogenic protein 2 (BMP2) and osteopontin [42]. Osteopontin is expressed in the outer margins and central site of coronary artery plaques [43]. In addition, hyperphosphatemia, high calcium-phosphate product levels, deficiency of calcification inhibitors, and direct effects on vascular smooth muscle cells (VSMCs) are equally involved in the calcification process [42]. In arterial calcification, medial and intimal calcium deposits present matrix vesicles influenced by cultured VSMCs that are linked to their content of calcification inhibitory factors [42], including fetuin and MGP (matrix gla protein) [44].

Converging evidence showed that most of the atherogenic factors (oxidized lipids, inflammatory cytokines, upregulated activity of monocyte–macrophages) [45], influenced by vitamin D activation [46], induce osteogenesis in human vascular cell.

It is believed that transcription factor core binding factor α_1 (Cbfa-1; encoded by the *RUNX2* gene) is responsible for the phenotypic transformation of VSMCs to osteoblast cells [42]. Cbfa1 was found in CKD patients with vascular calcification and in subjects diagnosed with atherosclerotic disease without CKD [47]. This finding emphasizes that, perhaps, intimal and medial calcification mechanisms are similar [47]. This idea can be sustained by the VSMCs pivotal role in the vascular calcification process [48].

These hypotheses are not fully supported by *in vivo* studies and cannot explain the elevated prevalence of atherosclerosis in CKD patients [42]. A research regarding coronary atherosclerotic injuries made on 27 patients diagnosed with CKD (21 on chronic dialysis) and 27 age- and sex-matched subjects from the control group reported that atherosclerotic plaques were more calcified in CKD patients [42]. Additionally, medial thickness was significantly greater in renal impairment individuals [42].

The study of Nakano T *et al.* [49] noticed, in their sample of 126 patients, that advanced atherosclerotic lesions are more frequent in patients with a lower estimated GFR linked to higher prevalence of calcified coronary lesions and thickened arterial intima. Furthermore, hypertension and diabetes were associated with high risk of calcification in subjects presenting estimated GFR <60 mL/min/1.73 m^2 [49]. If Nakano T *et al.* [49] study failed to prove any medial lesions, Fitzpatrick LA *et al.* detected concomitant intimal and medial calcifications in the coronary artery walls, lesions extended even [43].

Therefore, vascular calcification represents an active process that consists in documented morphological modifications both in intima and in medial artery that is influenced by renal impairment and consequently by the inflammatory state of patients.

⊟ Vascular calcifications – treatment options

Before presenting a suitable therapy scheme in preventing and decreasing vascular calcification development, we should emphasize that major changes in understanding uremic vascular calcification process have been made, in the last decade (Table 1) [50].

Table 1 – *A decade of progression in understanding vascular calcification in CKD patients*

Year	
2000	Coronary artery calcification is highly prevalent in young end-stage renal disease (ESRD) adults.
	Phosphate directly promotes vascular smooth muscle cell calcification (VSMC) and induces osteogenic transdifferentiation of VSMC.
2001	Vascular calcification directly and independently impairs survival in ESRD.
	Sevelamer attenuates vascular calcification in ESRD patients.
2002	Low serum fetuin-A is associated with reduced survival in ESRD.
	Survival of dialysis patients is different depending on vitamin D receptor (VDR) activators.
2003	KDOQI Guidelines.
	Complex influence of mineral metabolism upon outcome in ESRD.
2004	Calcium, phosphate, and PTH levels influence survival in ESRD.
2005	High phosphate decreases survival in CKD patients not on dialysis.
	FGF-23/Klotho interaction regulates phosphate and vitamin D metabolism
2006	Cinacalcet decreases vascular calcification *in vivo*.
	Sevelamer not superior to calcium-based binders in terms of survival.
2007	Vitamin K has anticalcification properties.
	Different VDR activators influence vascular calcification differently.
2008	Adynamic bone disease is associated with vascular calcification.
	Phosphate has negative effects on vascular health.
2009	High phosphate, high calcium, and the uremic milieu directly promote vascular calcification.
	KDIGO Guidelines.
2010	Bone and vascular health are closely related: bone–vascular axis.

The progressive loss of kidney function in chronic kidney disease (CKD) contributes to a decreased production of 1-alpha-(OH)$_2$-D3 (1,25-dihydroxy-vitamin D; calcitriol) that leads to a mineral-bone metabolism disorder associating abnormal serum calcium (Ca) and phosphorus (P) levels, and parathyroid hormone (PTH) levels, respectively [51–54]. According to some studies, only the activation of vitamin D receptors (VDRs) has some beneficial extraskeletal effects [51, 55, 56]. The development of secondary hyperparathyroidism (SHPT) may be influenced by different factors: increased PTH levels, hypocalcemia, calcitriol and vitamin D deficiency, P retention, fibroblast growth factor (FGF)-23 and various receptors (VDR, Ca-sensing receptor, FGF-23/Klotho) dysregulation [51, 52, 57, 58]. Even more, nowadays, it is worldwide accepted the positive association between mineral-bone metabolism disorders different pathological conditions, such as vascular calcifications, fractures, renal impairment progression and cardiovascular diseases. [51, 59, 60].

Because of the multifactorial involvement and severe systemic consequences, the new term CKD–mineral and bone disorder (MBD) has been proposed [51, 61] and it reflects: (a) Ca, P, PTH, or vitamin D metabolism disorders; (b) abnormalities in bone turnover, mineralization, volume, linear growth, or strength; and/or (c) vascular or other soft-tissue calcifications [51, 59–62]. This syndrome consists in six recognized types of bone disorders. First type, hyperparathyroid bone disease is characterized by high turnover, normal mineralization and any bone volume [51, 59, 63]. Mixed bone disease, the second form, consists in high turnover with mineralization defect, but with normal bone volume [51, 59, 63]. Osteomalacia presents low turnover with abnormal mineralization and low-to-medium bone volume and the adynamic bone disease is characterized by low turnover with normal mineralization and low or normal bone volume [51, 59, 63]. The last two types are amyloid bone disease and aluminum bone disease [51, 59, 63].

Summarizing, impaired VDR activation leads to cellular injury, that determines neoplasic diseases development, cell differentiation, infection, diabetes, arterial dysfunction, and vascular calcification [55, 56, 64]. Therefore, VDR activators should be included in the therapy scheme in CKD patients with vascular calcifications [61].

Recently, some studies suggested that excessive calcium intake might contribute to vascular and other extraskeletal calcification genesis [5, 65, 66]. For this reason, NKF–KDOQI Guidelines [60] recommends the use of non-calcium, non-magnesium, non-aluminum phosphate in RRT patients associating low parathyroid hormone, because these patients often present low-turnover bone disease, and are predisposed to extra-skeletal calcification [67].

It is essential to emphasize the idea that calcium-based phosphate binders should not be used in patients with hypercalcemia or with severe vascular calcification and a non-calcium, non-magnesium, non-aluminum phosphate binder (Sevelamer/Lantanum) could be a reliable option.

Takei T *et al.* [68] experimental study noticed that Sevelamer allows a better serum phosphorus control compared with calcium-based phosphate binder, reducing aortic calcification progression in HD individuals. Their findings showed a decrease of serum phosphorus values (from 6.7±0.7 to 6.2±0.5 mg/dL), of total cholesterol (from 158.5± 20.7 to 146.2±24.1 mg/dL) and of serum C-reactive protein (from 0.14± 0.13 to 0.08±0.11 mg/dL) in the Sevelamer group compared to calcium group. They also observed that in the Sevelamer group the mean changes of the aortic calcification index was significantly lower than in the calcium group.

In concordance with different trials, Sevelamer (available as Sevelamer carbonate – 800 mg tablet and Sevelamer hydrochloride – 400 mg or 800 mg tablet) should be used according to the following therapeutic schemes:

▪ Initial Sevelamer carbonate and hydrochloride dosage in patients not currently receiving a phosphate binder depends on serum phosphorus concentrations (Table 2) [69, 70].

Table 2 – *Initial Sevelamer carbonate and hydro-chloride dosage in patients not currently receiving a phosphate binder*

Serum phosphorus concentration [mg/dL]	Initial Sevelamer carbonate dosage	Initial Sevelamer hydrochloride dosage
>5.5 and <7.5	800 mg three times daily.	800 mg three times daily.
≥7.5 and <9	1.6 g three times daily.	1.2 g or 1.6 g three times daily.
≥9	1.6 g three times daily.	1.6 g three times daily.

▪ Initial dosage in patients being transferred to Sevelamer from calcium acetate therapy depends on current calcium acetate dosage (Table 3) [69, 70].

Table 3 – *Initial dosage in patients being transferred to Sevelamer from calcium acetate therapy*

Calcium acetate dosage	Initial Sevelamer carbonate dosage	Initial Sevelamer hydrochloride dosage
667 mg three times daily.	800 mg three times daily.	800 mg three times daily.
1.334 g three times daily.	1.6 g three times daily.	1.2 g or 1.6 g three times daily.
2.001 g three times daily.	2.4 g three times daily.	2 g or 2.4 g three times daily.

▪ Sevelamer hydrochloride dosage for all dialyzed patients depends on serum phosphorus concentrations (Table 4) [70].

Table 4 – *Sevelamer hydrochloride dosage for all dialyzed patients*

Serum phosphorus concentration [mg/dL]	Initial Sevelamer hydrochloride dosage
<3.5	Decrease dosage by one tablet (400 mg or 800 mg) per meal.
3.5–5.5	Maintain current dosage.
>5.5	Increase dosage by one tablet (400 mg or 800 mg) per meal.

Initially, Lantanum carbonate is recommended in a daily dose of 1500 mg and dosage titrate should be performed every 2–3 weeks until the serum phosphate wanted level is reached. Generally, the required total daily dose, to reduce phosphate values below 6 mg/dL, is between 1500 mg and 3000 mg.

Furthermore, according to NKF–KDOQI Guidelines [60] a 2 g/day calcium intake is sufficient in CKD patients and any supplementation may induce hyper-calcemia and consequent complications in almost 36% of individuals [71].

Although phosphate binders' administration may decrease vascular calcification progression, still their effect is not potent enough and at this moment, there are no specifically designed drugs in completely reversing vascular calcifications.

Murshed M *et al.* observed that pyrophosphate molecule (PPi), that inhibits hydroxyapatite formation and calcification process in soft tissues, is rapidly degraded by the tissue non-specific alkaline phosphatase (TNAP) and therefore it is not normally active in bone tissue [72].

Considering these data, Riser BL *et al.* study [73] proposed a new for of therapy by introducing PPi into peritoneal dialysis (PD) solution for preventing the VC progression linked to the patients' uremic condition. They provided a daily continuous administration of PPi in PD solution and observed that PPi intraperitoneum (IP) administration was completely absorbed, with minimal degradation at peritoneum level and, in addition, the maximum concentrations of PPi in plasma were lower and the time to reach these maximal values were prolonged compared to intravenous (IV) administration. Consequently, detectable levels of PPi remained in plasma following IP delivery even after eight hours post-administration, whereas after 1 hour PPi levels were not longer detected following IV administration. They concluded when PPi is delivered daily (six times per week) in a PD solution, it can prevent the development of aortic calcification and that a PD solution containing 150 μM PPi may inhibit aortic calcification. Additionally, they noticed when the PPi dose was reduced to the lower 30-μM concentration, reflecting a dose–response effect, the blockade of aortic calcification was no longer evident.

⊟ Conclusions and Future Perspectives

Chronic kidney disease patients could present various types of calcifications causing different pathological conditions that would contribute to the CKD progression and unfavorable outcome. Calcification may occur anywhere (vascular and valvular calcification, calcific uremic arteriolopathy (CUA; calciphylaxis), soft tissue and parenchymal organs, conjunctival and corneal calcification, peritoneal calcification). Frequently, metastatic, tumoral and soft tissue calcifications occur in the shoulder and hip region (*Teutschlander disease*), but there have been observed in other locations, too: hands, feet, nose, spinal canal. Unlike vascular calcifi-cations, the current international database reported just few information regarding the soft tissue calcifications incidence and clinical impact.

Extra-skeletal calcifications represent an often consequence of mineral bone disorders in CKD patients. Vascular calcifications represent a complex systemic manifestation influenced by phospho-calcium severe disorder, by the imbalance among promoters and inhibitors of calcification and the presence of other risk factors (Table 5) [74].

Table 5 – *Risk factors for vascular calcification in kidney disease*

Traditional risk factors	Non-traditional risk factors
Age	Renal impairment
Diabetes mellitus	Dialysis vintage
Hypertension	Disorders of mineral metabolism:
Dyslipidemia	▪ hyperphosphatemia; ▪ hyperparathyroidism;
Smoking	▪ changes in vitamin D metabolism; ▪ elevated FGF-23 levels.
	Inflammation and oxidative stress
	Osteogenesis factors (CBFA1/RUNX2)

Most of CKD patients present vascular calcification, but currently no effective treatment has been developed to stop the natural progression of the disease and therefore, future clinical controlled trials are needed. Before starting a suitable therapy scheme to delay vascular calcifications development, our recommendations are: (a) to perform lateral abdominal radiography or CT-based techniques in CKD stages 3–5 patients for an early vascular calcification detection, (b) to assess thoroughly patients presenting hyperphosphatemia, hyperparathyroidism, vitamin D deficiency and (c) to understand clearly the pathophysiology of arterial calcification and calciphylaxis.

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Corresponding author

Ionel Alexandru Checheriță, Assistant Lecturer, MD, PhD, 13 Vitan–Bârzeşti Highroad, 4th Sector, 042122 Bucharest, Romania; Phone +4021–334 50 75, Fax +4021–334 59 70, e-mail: fizij@yahoo.com