REVIEW

Vascular calcification in chronic kidney disease

Adrian COVIC∗, Mehmet KANBAY†, Luminita VORONEANU∗, Faruk TURGUT†, Dragomir N. SERBAN‡§, Ionela Lacramioara SERBAN‡§ and David J. GOLDSMITH∥

∗Clinic of Nephrology, “C. I. Parhon” University Hospital, “Gr. T. Popa” University of Medicine and Pharmacy, Bd. Carol I, Nr. 50, Iasi 700503, Romania, †Section of Nephrology, Department of Internal Medicine, Fatih University School of Medicine, Bestepe/Cankaya, Ankara, Turkey, ‡Department of Physiology, “Gr. T. Popa” University of Medicine and Pharmacy, Str. Universitatii, Nr. 16, Iasi 700115, Romania, and §Unit of Cell Physiology and Pharmacology at Center for Study and Therapy of Pain, “Gr. T. Popa” University of Medicine and Pharmacy, Str. Mihail Kogalniceanu, Nr. 9, Iasi 700454, Romania, and ∥Renal Unit, Guy’s Hospital, Great Maze Pond, London SE1 9RT, U.K.

ABSTRACT

VC (vascular calcification) is highly prevalent in patients with CKD (chronic kidney disease), but its mechanism is multifactorial and incompletely understood. In addition to increased traditional risk factors, CKD patients also have a number of non-traditional cardiovascular risk factors, which may play a prominent role in the pathogenesis of arterial calcification, such as duration of dialysis and disorders of mineral metabolism. The transformation of vascular smooth muscle cells into chondrocytes or osteoblast-like cells seems to be a key element in VC pathogenesis, in the context of passive calcium and phosphate deposition due to abnormal bone metabolism and impaired renal excretion. The process may be favoured by the low levels of circulating and locally produced VC inhibitors. VC determines increased arterial stiffness, left ventricular hypertrophy, a decrease in coronary artery perfusion, myocardial ischaemia and increased cardiovascular morbidity and mortality. Although current therapeutic strategies focus on the correction of phosphate, calcium, parathyroid hormone or vitamin D, a better understanding of the mechanisms of abnormal tissue calcification may lead to development of new therapeutic agents, which could reduce VC and improve cardiovascular outcome in CKD patients. The present review summarizes the following aspects: (i) the pathophysiological mechanism responsible for VC and its promoters and inhibitors, (ii) the methods for detection of VC in patients with CKD, including evaluation of arterial stiffness, and (iii) the management of VC in CKD patients.

INTRODUCTION

VC (vascular calcification) is very common in CKD (chronic kidney disease), becoming more prevalent with the worsening of kidney function and with CKD duration. VC is associated with many adverse clinical outcomes, including ischaemic cardiac events and subsequent vascular mortality [1]. Pathogenesis of VC is complex, and it does not consist of a simple precipitation of calcium and phosphate, but is instead an active process in which VSMCs (vascular smooth muscle cells) undergo apoptosis and vesicle formation.

Key words: arterial stiffness, calcimimetic, haemodialysis, hyperphosphataemia, non-calcium phosphate binder, vitamin D.

Abbreviations: CAC, coronary arterial calcification; Ca×P, calcium-phosphate product; CBPB, calcium-based phosphate binder; CKD, chronic kidney disease; CT, computer tomography; CYP27B1, cytochrome P450, family 27, subfamily B, polypeptide 1; EBCT, electron beam CT; FGF-23, fibroblast growth factor-23; HD, haemodialysis; HDL, high-density lipoprotein; IS, indoxyl sulfate; LDL, low-density lipoprotein; MGP, matrix Gla protein; MSCT, multi-slice spiral CT; OPG, osteoprotegerin; PPi, pyrophosphate; PTH, parathyroid hormone; PWV, pulse wave velocity; Runx2, Runt-related transcription factor 2; SHPT, secondary hyperparathyroidism; TNS, tissue non-specific alkaline phosphatase; VC, vascular calcification; VDR, vitamin D receptor; VSMC, vascular smooth muscle cell.

Correspondence: Professor Adrian Covic (email adrianccovic@gmail.com).
and are transformed into osteoblast-like cells, inducing matrix formation and also attracting local factors that are involved in the mineralization process [2]. VC is usually seen in aging, after vascular injury and in various clinical conditions, such as diabetes, atherosclerosis and Monckeburg’s medial sclerosis. However, there is no doubt that CKD patients have a high risk for and a high prevalence of VC because of multiple risk factors that induce the phenotypic transformation of VSMCs into osteoblast-like cells capable of the tissue mineralization process [3]. VC has been associated with numerous ‘traditional’ risk factors such as aging, hypertension, diabetes or dyslipidaemia, as well as with ‘non-traditional’ risk factors, such as hyperphosphataemia, hyperparathyroidism, hypervitaminosis D or excess administration of calcium salts [4]. The haemodynamic consequences of VC include a loss of arterial elasticity, an increase in PWV (pulse wave velocity) [5], development of left ventricular hypertrophy [6], decrease in coronary artery perfusion and myocardial ischaemia. In addition, VC in iliac and femoral vessels can prejudice or compromise renal transplantation. At the site of vessel injury, such as needle sites in arteriovenous fistulae, VC can compromise patency and function. An example of dense concentric VC in all coronary artery territories of an 83-year-old Type 2 diabetic woman on long-term HD (haemodialysis) is shown in Figure 1. Current strategies employed towards delaying VC are focused on the correction of mineral metabolism markers of bone disease, such as phosphate, calcium, PTH (parathyroid hormone) and vitamin D. The use of agents such as bisphosphonates and cinacalcet show much initial promise, but further clinical data are urgently required ([7] and http://clinicaltrials.gov/ct2/show/NCT00379899). Cutting-edge scientific research on the mechanisms underlying VC is increasingly being undertaken and further insight into these mechanisms may lead to the development of several types of therapeutic agents, which could improve cardiovascular outcome in CKD patients. The present review will summarize current knowledge regarding the pathogenic determinants and inhibitors of VC, methods for assessing VC, and management of VC in CKD patients, all aimed at evaluating the potential therapeutic impact of recent progress in understanding VC.
PATHOPHYSIOLOGICAL MECHANISMS OF VC, ITS PROMOTERS AND INHIBITORS

The pathophysiology of vascular disease in CKD is increasingly recognized to be distinct from that related to atherosclerosis in the general population [8]. Initially, VC was viewed as a passive phenomenon; however, it has been subsequently recognized as an active cell-mediated process [9,10]. VC may occur in either the intimal layer or the medial layer of the vessel wall, e.g. Monckeberg’s sclerosis, which is very common in CKD patients [11]. It is not yet clear to what extent these two patterns of VC might overlap in terms of pathogenetic mechanism, but both are associated with increased mortality in CKD patients [12]. Intimal calcification is focal, associated with inflammation and the development of plaques and occlusive lesions, while adjacent regions of the vessel wall may remain remarkably normal. This form of calcification represents an advanced stage of atherosclerosis and is seen in the aorta, coronary arteries and other large vessels [9]. Medial calcification, characterized by diffuse mineral deposition throughout the vascular tree, can occur completely independent of atherosclerosis or alongside, and is commonly observed in muscle-type conduit arteries, such as femoral, tibial and uterine arteries [6,10]. The two forms of calcification may well co-exist in the same vessel, which could be even more detrimental.

The mechanisms underlying accelerated VC in CKD are not completely understood. It is well recognized that in patients with CKD changes in the arterial wall, fibro-elastic intimal thickening, calcification of elastic lamellae, increased extracellular matrix and more collagen deposition with relatively less elastic fibre content all cause arterial remodelling [13]. In this process, many bone-associated proteins [including osteocalcin, osteopontin and OPG (osteoprotegerin)] and many bone morphogenetic proteins are involved; they are expressed in calcified arterial lesions and are associated with VC [14]. VSMCs are the major component of the medial arterial layer and, in the setting of CKD, can differentiate into chondrocyte- or osteoblast-like cells, by up-regulation of transcription factors such as Runx2 (Runt-related transcription factor 2) and Msx2 (Msh homeobox 2), which are critical factors for normal bone development [15]. This phenotypic switch may lead to a calcified smooth muscle, in a process similar to bone formation. In other words, this pattern of VC is actually an ectopic ossification. Moreover, uraemia induces differentiation of VSMCs into an osteoblast-like phenotype, and also inhibits the differentiation of monocyte macrophages into osteoclasts [15]. Dialysis vessels also show increased alkaline phosphatase activity and Runx2 and Osx (Osterix) expression, indicative of VSMC osteogenic transformation [16]. Furthermore, chronic vascular injury secondary to chronic volume overload, high blood pressure and an overactive renin-angiotensin system may cause smooth muscle proliferation, medial hyperplasia and, eventually, the recruitment of osteoblast-like cells into the vessel walls in CKD patients.

Determinants of VC

Numerous risk factors have been reported for VC. Several are ‘traditional’, such as increasing age, hypertension, diabetes or dyslipidaemia; a number of other, ‘non-traditional’ factors, such as mineral metabolism abnormalities, extreme PTH serum levels, excess administration of calcium salts, inflammation, malnutrition and oxidative stress have been described in CKD patients [1].

Phosphate and calcium metabolism

Advanced CKD patients develop hyperphosphataemia due to impaired renal phosphate excretion [17]. There is strong evidence that VC is closely associated with serum levels of calcium, phosphate and Ca×P (calcium-phosphorus product) [6,18,19]. High serum phosphate levels might be considered as a ‘vascular toxin’ [20]. Clinical studies have shown that patients with the worst phosphate control have the most rapid progression of VC [21]. Two different mechanisms are proposed to explain the relationship between calcium and phosphate disorders and VC: (i) a passive one, the direct calcium-phosphate precipitation in the vasculature, and (ii) an active one, that induces the expression of bone-associated genes in VSMCs, which acquire the phenotype of bone-forming (osteoblast-like) cells (see above) [22]. Experimental studies have demonstrated that calcium plays a role in the development of VC by stimulating mineralization of VSMCs under normal phosphate conditions [22]. Furthermore, with elevated phosphate levels, this calcium-driven mineralization is accelerated synergistically [22,23]. Hyperphosphataemia may directly induce vascular injury and indirectly stimulates osteoblastic differentiation through a type III sodium-dependent phosphate co-transporter (PiT-1) [24]. Jono et al. [25] suggested that elevated intracellular phosphate may directly stimulate VSMCs to transform into calcifying cells by activating genes associated with osteoblastic functions [24]. Additionally, in an important recent paper [26], Giachelli’s group from Seattle reported a good animal model of CKD-related VC (calcification-prone DBA/2 mouse); using varying levels of renopreservation, this model then allowed the development of mild-to-severe VC as a result of different diets. The extensive arterial calcification only develops once the animals are on a high-phosphate diet, suggesting that hyperphosphataemia is a marked accelerator of this process. These findings provide strong evidence that hyperphosphataemia and calcium load are probably the most important pathogenetic factors in VC. Nevertheless,
a significant decrease in serum vitamin D is observed from the early stages of CKD [28] as result of renal and non-renal factors, including reduced sun exposure, impaired production of the 25-hydroxy vitamin D precursor molecule and reduced dietary intake [17,29]. As vitamin D deficiency progresses in CKD, the parathyroid glands are maximally stimulated, causing SHPT [17]. Recently, an association between vitamin D deficiency and increased cardiovascular morbidity and mortality, including increased VC and stiffness, was described [30]. Vitamin D increases the gastrointestinal absorption of calcium and phosphate, and also induces the proliferation and osteoblastic differentiation of VSMCs. Moreover, 1,25-dihydroxy vitamin D has been shown to operate as a negative hormonal regulator of the renin–angiotensin system, which plays an important role in the cardiovascular system by modulating volume and electrolyte homoeostasis [31]. Vitamin D deficiency might also be associated with blood levels of inflammatory factors, including TNF-α (tumour necrosis factor-α) and IL-10 ( interleukin-10) [32]. Although it has been reported that administration of supra-physiological doses of 1,25-dihydroxy vitamin D induces VC [33], physiological doses are protective against aortic calcification in animal models of CKD [34]. Schroff et al. [35] showed that the vitamin D level is the most important predictor of increased arterial thickness, stiffness and calcification in children on dialysis, a population where atherosclerotic lesions are minimal. VSMC drop out by apoptosis was also shown in the arteries of uraemic children [35].

**FGF-23 (fibroblast growth factor-23)**

FGF-23, a novel hormone produced by osteoblasts, is involved in the regulation of phosphate and vitamin D metabolism [36]. FGF-23 level rises in CKD from early stages and causes renal phosphate loss by inhibiting NPT2a (sodium/phosphate co-transporter type IIa) in the renal proximal tubule. It also suppresses the renal expression of CYP27B1 (cytochrome P450, family 27, subfamily B, polypeptide 1), resulting in the impairment of 1,25-dihydroxy vitamin D synthesis [37,38]. FGF-23 binds to its receptor via α-Klotho, a pleiotropic transmembrane protein expressed in the kidney [39]. There is also evidence that FGF-23 also controls bone mineralization independently of phosphate homeostasis [40]. Reduced FGF-23 activity is associated with vascular and soft tissue calcification in both experimental animals and human studies [41]. Extensive vascular and soft tissue calcification is observed in FGF-23-knockout mice by 6 weeks of age; small-and medium-sized arteries and the proximal tubules in the kidneys are the most extensively affected sites, in addition to the aorta [42]. In accordance with the animal studies, human diseases associated with inactivating mutations in either FGF-23 or Klotho gene express severe ectopic calcification. FGF-23 can reduce calcification by inhibiting vitamin D activity [43]. On the other hand, Cozzolino et al. [44] reported that, in CKD patients undergoing dialysis, extensive VC is present, despite their significantly high serum FGF-23 levels. Gutiérrez et al. [37] reported that increased FGF-23 levels are independently associated with mortality in newly started HD patients. Finally, in a recent study, Roos et al. [38] found no correlation between serum intact FGF-23 and coronary artery score in subjects with normal kidney function. These findings suggest that, under normal renal function, where the kidneys are effectively maintaining a normal phosphate balance, FGF-23 is not a suitable marker for coronary artery calcification. Further studies are needed to better understand the role of FGF-23 in vascular and soft tissue calcification under various pathological conditions.
mechanisms in endothelial cells [49]. Finally, it has been shown that serum IS levels increase as renal failure progresses, and they are closely associated with aortic calcification in CKD patients [49].

To summarize, there are many factors that play a role in the development of VC. Some of them are unique to dialysis patients, whereas some are also present in the general population. Current knowledge does not offer the answers to important questions: which is the most important contributing factor, how does each risk factor exactly work, how do they interact with each other, and at what stage can we stop the process?

Inhibitors of VC

Although VC is very common in CKD patients, not all patients will develop VC, despite similar exposure to the uraemic environment, suggesting that protective mechanisms also exist.

Extracellular calcium-regulatory proteins: fetuin-A and MGP (matrix Gla protein)

Fetuin-A is mostly synthesized in the liver, and circulating concentrations fall during the cellular immunity phase of inflammation [50]. Fetuin A is an extracellular calcium-regulatory protein acting as a potent inhibitor of calcium-phosphate precipitation [51], inhibits calcification by binding hydroxyapatite structures [52] and it protects VSMCs from the detrimental effects of calcium overload and subsequent calcification [53]. Thus fetuin-A inhibits VSMC apoptosis by perturbing death-signalling pathways: (i) it is internalized by VSMCs and concentrated in intracellular vesicles and it is secreted via vesicle release from apoptotic and viable VSMCs; (ii) the presence of fetuin-A in vesicles abrogates their ability to nucleate basic calcium phosphate; and (iii) in addition, fetuin-A enhances phagocytosis of vesicles by VSMCs. These observations provide evidence that the uptake of the serum protein fetuin-A by VSMCs is a key event in the inhibition of vesicle-mediated VSMC calcification [53]. In vitro, fetuin-A antagonizes the antiproliferative action of TGF-β1 (transforming growth factor-β1) and blocks osteogenesis and deposition of calcium-containing matrix in dexamethasone-treated rat bone marrow cells [51]. Fetuin-A-knockout mice develop extensive ectopic calcifications in the myocardium, kidney, lung, tongue and skin [51]. Ketteler et al. [51] showed that CKD patients with lower serum fetuin-A levels have increased mortality due to cardiovascular events, suggesting that fetuin-A is involved in preventing the accelerated extra-skeletal calcification.

MGP, a small ubiquitous matrix protein, initially isolated from bone [54], is a key regulator of VC. To achieve full biological activity, MPG needs to be activated and this depends on the availability of vitamin K [55]. Studies have demonstrated that MGP inhibits calcification of cartilage and blood vessels [56]. MGP exerts its effects on VC directly, via inhibition of calcium crystal formation, and indirectly, by influencing transcription factors that inhibit VSMC differentiation to the osteoblast-like phenotype [57]. MGP also appears to be an important factor in ensuring correct differentiation of VSMCs [56]. It has been shown that declining GFR (glomerular filtration rate) results in a decreased uncarboxylated MGP level which is associated with VC and atherosclerosis [58].

OPG

OPG forms a system with the receptor activator of NF-κB (nuclear factor κ-light-chain-enhancer of activated B-cells), called RANK, and the ligand of this receptor (e.g. RANKL). This system may play a role in bone–VC imbalance and could be a marker of VC extent and progression. In a recent study, Morena et al. [59] found that, in CKD patients, CAC (coronary arterial calcification) is strongly associated with plasma OPG: values of OPG >757.7 pg/ml were predictive of the presence of CAC in these patients. The mechanism by which OPG levels might be related to CAC is unknown. OPG is recognized as a protective factor for vascular calcium deposition in animal models [60]. Surprisingly, higher levels of OPG have been reported in patients with vascular damage [61], suggesting that an increase in OPG level may represent a compensatory self-defensive mechanism against factors promoting VC, atherosclerosis and other forms of vascular damage [61].

Vitamin K

Vitamin K is an essential nutrient and a cofactor in the production of coagulation factors, osteocalcin and MGP. Vitamin K contributes to bone health, probably through its role as a cofactor in the carboxylation of osteocalcin. The efficiency of vitamin K in preventing fractures is controversial, but it has proven to be effective in preventing fractures in postmenopausal women [62]. In a meta-analytical review, Iwamoto et al. [63] showed that vitamin K supplementation has inconsistent effects in serum total osteocalcin levels, with a modest increase through its role as a cofactor in the carboxylation of osteocalcin. Vitamin K is an essential nutrient and a cofactor in the production of coagulation factors, osteocalcin and MGP. Vitamin K contributes to bone health, probably through its role as a cofactor in the carboxylation of osteocalcin. The efficiency of vitamin K in preventing fractures is controversial, but it has proven to be effective in preventing fractures in postmenopausal women [62]. In a meta-analytical review, Iwamoto et al. [63] showed that vitamin K supplementation has inconsistent effects in serum total osteocalcin levels, with a modest increase
PP_1 (pyrophosphate)
PP_1 is a potent inhibitor of medial VC, directly blocking hydroxyapatite formation [66]. PP_1 is produced by arterial smooth muscle and its level is controlled by hydrolysis via a TNAP (tissue non-specific alkaline phosphatase), which hydrolyses PP_1 and generates phosphate [67]. A deficiency of the ectoenzyme that synthesizes extracellular PP_1 results in massive arterial calcification in mice and humans [68]. In HD patients, plasma PP_1 is deficient; these lower circulating levels of PP_1 are not understood, but could result from higher hydrolysis (an increase in TNAP activity and PP_1 hydrolysis was demonstrated in uraemic rats) [69] and from dialytic clearance (PP_1 is removed during the HD session). In a recent study, O’Neill et al. [70] found that plasma PP_1 is negatively associated with VC in end-stage renal disease. Taken together, these studies show an inhibitory effect of PP_1 on VC, but further studies are needed to establish a causal role.

METHODS FOR ASSESSING VC
A number of non-invasive imaging techniques are available to screen for the presence of VC: plain X-rays to identify macroscopic calcifications of aorta and peripheral arteries; two-dimensional ultrasound for calcification of carotid arteries, femoral arteries and aorta; echocardiography for assessment of valvular calcification; and, of course, CT (computer tomography) technologies that constitute the gold standard for quantification of coronary artery and aorta calcification.

EBCT (electron beam CT) and MSCT (multi-slice spiral CT)
EBCT and the newer MSCT are highly sensitive methods, assessing accurately and quantitatively, especially coronary artery calcification, by using an electrocardiographic trigger for heart imaging only in diastole, thus avoiding motion artifacts [71]. These methods could be successfully used to study prevalent calcifications, progressive VC and the impact of therapy on VC [72]. EBCT is not readily available in many hospitals. In contrast, almost every hospital has a multi-purpose spiral CT and, with software adjustments to allow gated imaging, the newer faster spiral CTs can assess VC. However, there are conflicting results about the correlation between the severity of CAC measured by EBCT and subsequent clinical cardiac events in dialysis patients [17,73,74]. This can be explained by the fact that the arterial calcification score generated by CT scanning is a composite of both medial and intimal calcification. This is a limitation of these CT-based imaging techniques, as they are unable to distinguish between the two predominant arterial calcification sites [17]. EBCT and MSCT could be also used for assessment of VC in the aorta [75].

Conventional CT
Conventional CT may be used to evaluate non-coronary VC, especially aortic calcifications. Measuring the proportion of aortic circumference showing calcification can generate an ACI (aortic calcification index). This method seems to be simple, relatively inexpensive and useful for an initial diagnosis of VC. Taniwaki et al. [76] used this method for the quantification of VC in HD patients with diabetes mellitus. Again, this method could not quantify the medial/intimal distribution of VC.

Laterto-abdominal plain radiography
Laterto-abdominal plain radiography is a valuable and inexpensive tool for the detection of VC in CKD patients, but the method is semi-quantitative, possibly missing subtle changes in the evolution of VC. It is the only technique for the detection of VC included in the K/DOQI (Kidney Disease: Improving Global Outcomes) guidelines for cardiovascular disease in dialysis patients [77]. The pattern of VC seen on plain radiographs may yield some information about the localization of calcification within the arterial wall (intima compared with media). Kauppila et al. [78] used lateral lumbar films to detect the presence of calcification in the abdominal aortic wall, in the region corresponding to the first to the fourth lumbar vertebrae. This semi-quantitative method is more widely available and less expensive for studying calcification and could be used for cardiovascular risk stratification.

Ultrasound-based methods
Ultrasound-based methods indirectly evaluate calcium content and are typically used to study carotid artery calcification. Ultrasound uses a universally available technology, is relatively inexpensive and does not require exposure to ionizing radiation. This method has two significant limitations: first, it is unable to differentiate medial from intimal calcification; and secondly, data derived from ultrasound are qualitative and are unlikely to detect small changes, at least over the shorter term. Using transthoracic echocardiography, the valvular calcium could be quantified. In a very recent study, Leskinen et al. [79] found that valvular calcification in CKD patients is associated with increased carotid intima-media thickness, carotid plaque, coronary artery disease and peripheral arterial disease.

Arterial stiffness
Arterial stiffness and increased PWV are induced by VC [80]. PWV measured in large elastic arteries could be another indirect method for the quantification of VC. A positive correlation between VC and arterial stiffness measured by PWV has been demonstrated in both
early CKD and HD patients [80–82]. Several possible mechanisms for the association between arterial stiffness and VC can be hypothesized. First, arterial calcification may induce arterial wall stiffness and increased PWV [81,83]. A previous study in adult HD patients reported an association between 25-hydroxy vitamin D deficiency and arterial stiffness [84]. Secondly, increased arterial stiffness may cause vessel wall damage and atherosclerosis [85]. Thirdly, changes in the intrinsic properties of arterial wall by arterial remodelling may contribute to both processes in CKD patients [14].

**MANAGEMENT OF VC**

**Non-calcium phosphate binders**

Hyperphosphataemia is involved in SHPT, vascular events, cardiovascular mortality and all-cause mortality. Phosphate binders currently used to manage hyperphosphataemia include sevelamer, lanthanum and the CBPBs (calcium-based phosphate binders) CaCO₃ and calcium acetate. Sevelamer is an aluminium- and calcium-free phosphate binder, which does not promote hypercalcaemia, allows a better serum phosphorus control compared with CBPBs, suppresses the progression of aortic calcification in HD patients and has favourable effects on the lipid profile, with an associated reduction in LDL (low-density lipoprotein)-cholesterol and an increase in HDL (high-density lipoprotein)-cholesterol [86]. In a comparative study including 200 HD patients, Chertow et al. [87] demonstrated that sevelamer attenuates the progression of coronary and aortic calcification better than CBPBs after 1 year. These findings were confirmed by Cozzolino et al. [88], who showed that treatment with sevelamer, when compared with CaCO₃, is associated with less VC within the myocardium, aorta and kidney. The probable mechanism consists of a strong phosphate-binding capacity in the intestine, without excessive calcium loading. In contrast, in the RIND (Renagel in New Dialysis) study, in patients with baseline CAC scores of 30 or higher, there was no significant difference in the rates of calcification progression between the patients treated with sevelamer and those treated with CBPBs, at any point up to 18 months of follow-up [89]. The improvement in lipid metabolism could be another factor contributing to decreased VC. *In vitro* studies have shown that acetylated LDL stimulates, whereas HDL inhibits, VSMC calcification [90]. In human studies, sevelamer has been shown to consistently reduce LDL and frequently increase HDL levels. Such an improved lipid profile could potentially play a role in the lower degree of VC seen after sevelamer treatment; however, in the CARE-2 (Calcium Acetate Renagel Evaluation-2) study, intensive LDL-cholesterol-lowering therapy with atorvastatin is associated with a similar progression of CAC in HD patients treated with either calcium acetate or sevelamer [91].

**VDR (vitamin D receptor) activators**

VDR activators are an essential part of treatment among stage 5 CKD patients. Different VDR activators exert differential effects on VC. Cardús et al. [92] showed in uremic rats that paricalcitol and calcitriol had differential effects on VC. Although both drugs raised serum calcium and Ca×P, only calcitriol caused an increase in the calcification of the abdominal aorta [92]. Hirata et al. [93] found similar results in 5/6 nephrectomized rats, and demonstrated that 1,25-dihydroxy vitamin D₃, but not 22-oxacalcitriol, induced the calcification of the aorta. Noonan et al. [94] found that paricalcitol and doxercalciferol display differential effects on aortic calcification *in vivo*, which is independent of serum calcium, phosphate and Ca×P. The mechanism by which VDR activation inhibits aortic calcification seems to be the inhibition of osteoblastic gene expression in the vessels. In addition, VDR activators stimulated osteoblast function instead of suppressing it and increased osteoblast surfaces and bone formation rates, contributing to their protection against aortic calcification [95,96].

**Calcimimetics**

Because calcimimetics reduce PTH levels without the induction of hypercalcaemia, it is likely that patients who are treated with a calcimimetic may show less risk for VC than patients who are treated with vitamin D sterols. In a rat model of SHPT (5/6 nephrectomy), Henley et al. [33] showed that calcitriol-treated rats have moderate-to-marked aortic calcification, whereas no significant calcification was observed in cinacalcet-treated groups. Lopez et al. [97] studied the effect of the calcimimetic R-568 alone or in combination with calcitriol on the development of VC and other soft tissue calcifications in a rat model of uraemia-associated SHPT. They showed that the calcimimetic R-568 reduces PTH levels without inducing VC and can also attenuate the calcitriol-induced calcifying effects on vascular tissue and decrease mortality associated with calcitriol. They concluded that, in uremic rats, R-568 reduces elevated PTH levels without inducing VC and prevents calcitriol-induced VC [97]. The most valid explanation is related to the control of PTH level without increasing Ca×P.

**Bisphosphonates**

Bisphosphonates may have a future role in the management of VC, as they have been shown to reduce VC in experimental models. Tamura et al. [98] showed in 5/6 nephrectomized rats that aortic calcification induced by calcitriol could be reduced by etidronate. Initially, they demonstrated that low-dose etidronate (2 mg/kg of body weight) was ineffective, but a dose of 5–10 mg/kg of body weight inhibited calcification. In another study
using BASMCs (bovine aortic smooth muscle cells), pamidronate inhibited arterial calcification [99]. In HD patients, etidronate reduced and even reversed the progression of CAC in some, but not all, of the patients after 6 months [100] and 12 months [101] of treatment. However, the mechanism is not clear. Bisphosphonates could inhibit bone resorption, with reduced efflux of calcium and phosphate, limiting their availability for deposition in the vasculature [102], or could influence the activity of the sodium/phosphate co-transporter in VSMCs. Alternatively, bisphosphonates may have direct effects on the vessel wall and, like pyrophosphate, on crystal formation [102].

CONCLUSIONS

Vascular disease is the most important cause of morbidity and mortality among patients with CKD, while VC is common and is nearly ubiquitous in these patients and progresses rapidly. It can severely prejudice therapeutic options for patients with CKD and is therefore something we cannot view with equanimity. VC is an active process, involving multiple risk factors with additive effects, which has a profound influence on arterial stiffness and cardiovascular function. Recent cell biology studies have provided novel findings about the important role of the VSMCs in the complex process of ectopic bone development (calcified matrix) in CKD patients. Plasma phosphate remains in our view the key clinical driver of the process. If this is valid, urgent efforts should be made to achieve rigorous phosphate control without compromising nutrition. New strategies may improve the management of vascular diseases, possibly with a specific positive impact on the high prevalence of VC in CKD. These are encouraging, but we need solid epidemiological and clinical data to underpin a better management of the bone–cardiovascular axis in CKD patients. The best therapeutic strategy available remains the control of altered bone metabolism and inflammation.

FUNDING

This work was supported by Romanian Ministry of Education and Research [grant number ID-1156; 2007-2010], via Consiliul National al Cercetarii Stiintifice din Invatamantul Superior (CNCISIS) and Unitatea Executiva pentru Finantarea Invatamantului Superior si a Cercetarii Stiintifice Universitare (UEFISCU) [plan PN2, program IDEI, section PCE].

REFERENCES


Vascular calcification in CKD


Received 3 December 2009/4 February 2010; accepted 2 March 2010
Published on the Internet 28 April 2010, doi:10.1042/CS20090631

© The Authors Journal compilation © 2010 Biochemical Society