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REVIEW

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Role of vascular calcification inhibitors in preventing vascular dysfunction and mortality in hemodialysis patients

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ABSTRACT

Cardiovascular events make up the primary cause of death in hemodialysis patients, and the risk for cardiovascular mortality is significantly increased by vascular calcification, a condition observed frequently in this patient population. The mechanisms underlying the pathogenesis of vascular calcification are complex, and many factors facilitate or hinder the development of calcification. In this review, we first summarize the main factors contributing to the pathogenesis of vascular calcification in patients with end-stage renal disease. We then explore the role of calcification inhibitors in the calcification process, as well as their effect on vascular dysfunction and mortality in hemodialysis patients.

1 | INTRODUCTION

The prevalence of cardiovascular diseases is high among patients with chronic kidney disease (CKD),[1] which increases morbidity and mortality in this population and represents a significant financial burden for both the patients and the healthcare systems. Compared to patients with preserved renal function, CKD patients with a glomerular filtration rate (GFR) <45 mL/min/1.73 m^2 have higher risk for cardiovascular disease.[2] Indeed, the cardiovascular mortality rate among 25-year-old patients with pre-dialysis end-stage renal disease (CKD stage 5) appears to be nearly equivalent to that of 75-85-year-old individuals.[3] Many cardiovascular risk factors are recognized in CKD patients, including hypertension, dyslipidemia, diabetes, and obesity. Additional cardiovascular risk factors potentially related to uremia are also common, such as anemia, hyperparathyroidism, carnitine deficiency, hyperhomocysteinemia, low vitamin C levels, high lipoprotein (a) levels, and small apolipoprotein (a) isoform sizes.[4]

Similarly, other systems such as bone mineral metabolism are influenced by the disease state in CKD. Decreased GFR results in diminished renal phosphorus excretion[5] which, in combination with the reduced levels of vitamin D, eventually lead to hypocalcemia, hyperphosphatemia, and hyperparathyroidism; detrimental effects follow, especially on bone and the vascular system.[6] The secondary and tertiary hyperparathyroidism observed in CKD patients is associated with an increased risk of high-turnover bone disease, adynamic bone disease, vascular and valvular calcification, calciphylaxis, metastatic calcification, and mortality, depending on the nature of the hyperparathyroidism.[7,8]

2 | GENERAL CONSIDERATIONS ON VASCULAR CALCIFICATION

Vascular calcification (VC) is associated with increased morbidity and mortality even in younger patients, and is observed frequently in diseases such as diabetes, hypertension, and atherosclerosis, where progression involves endothelial damage.[9] VC risk is higher in patients with CKD than in healthy individuals.[10] Epidemiologic studies of CKD patients have reported a VC incidence of 30% and 50% in the age groups of 15-30 and 40-50 years, respectively.[11]

Vascular calcification is frequently observed in dialysis patients, where it may occur in the intima and media layers of the blood vessels and in the cardiac valves.[12] The prevalence of coronary artery calcification is high among dialysis patients; specifically, some degree of coronary artery calcification is observed in 54%-100% of patients, well above the prevalence in the general population.[13] Older age, male sex, long duration of dialysis, diabetes, hypertension, smoking, alcohol consumption, hyperphosphatemia, hypercalcemia,

hyperparathyroidism, use of high-dose vitamin D, inflammation, and hypoalbuminemia represent known risk factors for VC development in dialysis patients.[14]

Many noninvasive methods have been developed to detect VC and quantitate its severity. Plain radiography, the simplest technique,[15,16] does not provide sufficient sensitivity and is not used for determining the amount of calcification. Sensitive methods for accurate assessment of calcification, especially in the coronary artery, include electron-beam computerized tomography and multislice spiral computed tomography, the latter of which is fairly newer.[17] Although not clinically applicable, the gold standard for detection, evaluation, and quantitation of VC is the histological examination of postmortem samples of arterial tissue.[18]

Vascular calcification in hemodialysis patients is associated with vascular stiffness, which increases ventricular load and causes left ventricular hypertrophy.[19] In addition, myocardial fibrosis and arrhythmia may develop because of tissue calcification. The presence of VC increases mortality.[20]

3 | PATHOGENESIS OF VC

Vascular calcification represents a pathological process characterized by loss of vessel elasticity and vessel wall thickening as a result of accumulation of minerals in the media and/or intima layers of the arterial wall.[21] Intimal calcification occurs typically in the aorta, coronary artery, and major arteries, and is recognized as an indicator of atherosclerosis progression. On the other hand, arteriosclerosis develops as a result of medial calcification.[9] It is now commonly believed that VC is not a passive and degenerative event developing in the artery intima or media layer, but it is an active and programmed process.[22] Chronic inflammation regulates the mechanisms that cause both atherosclerosis and VC.[23] Studies conducted so far have shown the importance of angiogenesis in the development of VC, and have revealed the role of osteoblasts and osteoclasts.[24]

It appears that opposing mechanisms influence and determine VC either by increasing or inhibiting the process; inhibitors help prevent VC. Many factors play a role in the pathogenesis of VC, and these will be reviewed briefly here with an emphasis on VC inhibitors, the main focus of this review. An overview of the pathogenesis of VC is provided in Figure 1.

3.1 | Factors involved in the pathogenesis of VC in end-stage renal disease

3.1.1 | Apoptosis

Apoptosis represents a complex mechanism contributing to the onset of VC. Specifically, it is believed that apoptotic formations (stemming from the vascular smooth muscle cells) act as a matrix sac that promotes the formation of calcium crystals, thereby initiating calcification.[25]

3.1.2 | Elastin degradation

The degradation of elastin plays an important role in the onset and progression of VC as elastin degraded by proteases has high affinity for calcium, facilitating the formation of hydroxyapatite along the elastic lamella.[26]

3.1.3 | Inflammation

It is already known that CKD patients have increased microinflammation. Some pro-inflammatory cytokines such as interleukin 1 (IL-1), interleukin 6 (IL-6), and tumor necrosis factor α (TNF-α) bind enzymatically to particles containing low-density lipoprotein cholesterol in reduced form, which results in their accumulation between the intima and media, activation of the complement system, and attraction of monocytes to the atherosclerotic lesions. TNF-α increases the activity of alkaline phosphatase and promotes matrix mineralization in bovine aortic smooth muscle cells.[23]

3.1.4 | Oxidative stress

Although the role of oxidative stress in the pathogenesis of VC has not been fully clarified to date, it is known that oxidative stress decreases the levels of nitric oxide, which results in retention of uremic toxins and further potentiates oxidative stress in vascular structures.[27]

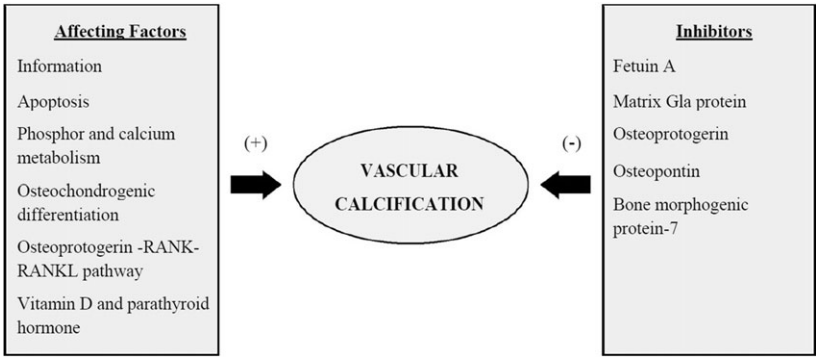

FIGURE 1 Pathogenesis of vascular calcification

3.1.5 | Phosphorus and calcium metabolism

Hypercalcemia and hyperphosphatemia contribute passively to the development of VC by promoting the precipitation of calcium and phosphorus complexes in the blood vessels, and by increasing bone-related gene expression in vascular smooth muscle cells.[28] Phosphorus is the best known stimulant of osteochondrogenic differentiation and apoptosis of vascular smooth muscle cells, which is also related to upregulation of the expression of the growth arrest-specific gene 6 product and its receptor.[29]

3.1.6 | Vitamin D and parathyroid hormone levels

While the role of the parathyroid hormone in VC remains unclear, the general viewpoint is that the parathyroid hormone might help-protect against VC, and that low parathyroid hormone levels (with its associated adynamic bone disease) might promote VC.[30] Regarding the complex role of vitamin D and its derivatives, several viewpoints have been expressed.[31] Although vitamin D deficiency increases the risk of cardiovascular disease in dialysis patients,[32] animal studies have reported that treatments using vitamin D supplementation may increase the prevalence of VC. Specifically, high-dose calcitriol treatment leads to the conversion of the osteoblast to the osteoclast phenotype in arterial smooth muscle cells.[33] There are as yet no clinical data assessing the therapeutic effects of native vitamin D3, D2, or active vitamin D derivatives in pharmacological doses on the progression of VC in dialysis patients.

3.1.7 | Fibroblast growth factor 23 and Klotho

Fibroblast growth factor 23 (FGF-23) is produced by osteocytes and osteoblasts and acts physiologically in the kidney to induce phosphaturia and inhibit the synthesis of 1,25-dihydroxyvitamin D3.[34] Klotho increases the sensitivity of FGF-23 to its receptor, acting as a co-factor for FGF-23-receptor binding. Therefore, FGF-23 and Klotho play important roles in the regulation of phosphorus and vitamin D levels.[35] In dialysis patients, serum FGF-23 levels are increased, while Klotho levels are decreased.[35] VC is enhanced in rats that do not have the *klotho* gene,[36] while overexpression of Klotho inhibits VC. Currently, available data on FGF-23 are insufficient to clarify its specific role in VC development.

3.1.8 | Osteochondrogenic differentiation

A recent study by Tang et al. claimed that multipotent vascular smooth muscle cells respond to vascular damage by being converted into osteochondrogenic cells, which represents the onset of VC.[37] Examination of calcified vessels from human subjects revealed the absence of chondrogenic factors. Arterial smooth muscle cells are converted into osteochondrogenic cells, which synthesize bone-related proteins and promote calcification because the presence of collagen fibrils on the cell surface and accumulation of apatite in the matrix supports crystal formation and storage.[37]

3.1.9 | Osteoprotegerin-RANK-RANKL pathway

The discovery of osteoprotegerin (OPG), the receptor activator of nuclear factor kappa B (RANK), and the RANK ligand (RANKL), followed by determination of their roles in osteoclastogenesis, contributed greatly to the understanding of VC.[38] RANKL binding to RANK stimulates preosteoclast differentiation into osteoclasts.[38] On the other hand, OPG recruits RANKL, thereby inhibiting bone resorption. OPG synthesis occurs in the media of major arteries and in various blood vessel cell types including coronary artery smooth muscle and endothelial cells, suggesting that OPG plays a role in the function or structure of the vascular bed.[39] Rats that lack OPG develop osteoporosis as well as calcification of the major arteries with intimal and medial proliferation, which shows that OPG protects major arteries against medial calcification.[40]

4 | CALCIFICATION INHIBITORS

Vascular calcification is not uniform, and some patients seem to be spared. One study found that 17% of dialysis patients showed no calcification at baseline and fewer findings indicative of new calcification during follow-up.[41] Calcification inhibitors, compounds that inhibit VC, were discovered as a result of efforts to explain why some patients are spared. It was found that certain proteins (e.g., fetuin-A, osteopontin, osteoprotegerin) inhibit calcification in dialysis patients. We further provide an overview of known calcification inhibitors, describe the regulatory mechanisms involved, and discuss the implications of their influence on VC development in hemodialysis patients.

4.1 | Fetuin-A

In 1944, Pedersen first purified fetuin-A from fetal bovine serum. The homologue of this protein in humans was discovered in 1961 by Heremans, Schmid, and Burgi. Fetuin-A, also known as α-2 Heremans Schmid Glycoprotein, is a 59-kD protein with a serum concentration of 0.5-1 g/L. In adults, fetuin-A is secreted mainly in the liver,[42] but is also expressed in the kidneys and choroid plexus. Fetuin-A is the major component of the bone matrix during fetal life.[42]

Fetuin-A acts as a negative acute phase reactant, and serum levels of fetuin-A are decreased in patients with inflammation, trauma, acute and chronic hepatitis, primary biliary cirrhosis, and hepatocellular carcinoma.[43,44] It has been determined that, in dialysis patients, there is a decrease both in the activity level and in the serum level of fetuin-A.[45] In addition, fetuin-A is a systemic calcification inhibitor, well-known to inhibit vascular and valvular calcification.

The levels of fetuin-A are higher in the serum than in tissues, and it is considered that fetuin-A is responsible for 50% of the calcification inhibition capacity available in human plasma.[46] The transforming growth factor-beta (TGF-beta) plays a critical role in bone

remodeling by stimulating matrix protein synthesis, with dramatic effects on the bone cells responsible for bone formation and resorption. Feutin-A contributes to the growth and reshaping of the bones by antagonizing the effect of TGF-beta.[47]

Fetuin-A inhibits calcium and phosphate precipitation. Incubation of fetuin-A with calcium and phosphorus at physiologic pH prevents crystallization for over 9 days, whereas, in the absence of fetuin-A, crystalization occurs within hours. Fetuin-A also binds hydroxyapatite crystals forming calciprotein particles, which can be cleared from the circulation.[48] Fetuin-A inhibits both the calcification of matrix vesicles inside vascular smooth muscle cells and the effects of TGF-beta and bone morphogenetic protein-2 (BMP-2), which facilitate valvular calcification. Fetuin-A may also suppress the excretion of TNF-α, which is a potent regulator of both valvular calcification and VC.[49,50]

The serum levels of fetuin A are lower in hemodialysis patients than in healthy individuals, and significant effort has been spent to gauge the significance of this finding with the prevalence of VC, valvular calcification, atherosclerosis, arterial stiffness, and mortality.[51,52] In a plain radiography study involving 50 hemodialysis patients, diabetes and low fetuin-A levels were independent risk factors for VC development.[53] A comparative study involving 70 hemodialysis patients and 20 healthy controls reported an association between serum fetuin-A levels and the incidence of VC, valvular calcification, and inflammation.[54] Similarly, an electron-beam computerized tomography study involving 68 hemodialysis patients found a negative relation between fetuin-A levels and coronary artery calcium scores.[55] The conclusion of many studies conducted so far (Table 1) is that, in hemodialysis patients, decreased fetuin-A levels are associated with increased incidence of VC and valvular calcification.

Medial calcification (arteriosclerosis) leads to loss of aortic wall elasticity via an active cellular process regulated by inducers and inhibitors of calcification. The relation between fetuin-A levels and arterial stiffness was first investigated by Hermans et al., wherein 131 patients (98 undergoing hemodialysis, 33 undergoing peritoneal dialysis) were examined; decreased fetuin-A levels were nonindependent predictors of arterial stiffness indices.[56] Another study involving 81 chronic hemodialysis patients found that fetuin-A levels independently predicted carotid-femoral pulse wave velocity, and that low fetuin-A levels were associated with increased carotid intima-media thickness, although this relation was not independent.[57]

Once it became clear that fetuin-A played a role in the mechanisms underlying calcification, atherosclerosis, and arterial stiffness, further investigations aimed to determine whether fetuin-A levels are related to mortality in dialysis patients (Table 2). In a study involving 312 hemodialysis patients followed up for nearly 32 months, low fetuin-A levels were, indeed, associated with cardiovascular and all-cause mortality.[58] Similarly, another study involving 222 hemodialysis patients followed up for an average of 42 months found that low fetuin-A and increased inflammation were additive predictors of increased mortality.[59]

After fetuin-A was confirmed as a VC inhibitor, its therapeutic role in the prevention of calcificaiton was assessed. Using simulated body fluid, fetuin-A was shown to surround nanoparticles of $CaCO_3$, changing their shape from cubic to spherical, which prevents further calcification.[60] In another report, increased fetuin-A levels inhibited atherosclerosis by preventing aggregation of mineral compounds.[61]

Based on the experimental data, the therapeutic strategy should be to increase fetuin-A levels in hemodialysis patients. Long-term (48 weeks) use of phosphate binders (sevelamer or CaCO3) decreased of fetuin-A levels.[62] A study involving 10 hemodialysis patients found a progressive increase in the levels of fetuin-A after 1, 4, and 8 weeks of treatment with paricalcitiol,[63] prompting the authors to advocate that vitamin D supplementation increases fetuin-A levels through activation of the hepatocyte receptor of vitamin D.[63] Other studies found that fetuin-A levels decrease during cinacalcet treatment, but the observed changes in osteoprotegerin and fetuin-A levels may have be attributable to the variations in the therapeutic approach rather than to cinacalcet itself.[64]

In summary, fetuin-A has been studied intensely and the highest-quality clinical evidence is available to support its role as a calcification inhibitor. The serum levels and activity of fetuin-A are

TABLE 1 Association between Feutin A levels with atherosclerosis and calcification

Author	Year	Patients no	Aim	Results
Odamaki	2005	141	Feutin A-atherosclerosis-calcification	Low fetuin-A level was associated with aortic calcification and atherosclerosis
Hermans	2006	131	Feutin A-arterial stiffness	Fetuin-A levels were inversely related to with arterial stiffness
Cozzolino	2006	115	Feutin A-vasculary calcification	Low fetuin-A level was associated with cardiovascular calcification
Pertosa	2009	174	Feutin A-atherosclerosis	Low levels of serum fetuin-A associated with progression of atherosclerosis
Porazko	2009	77	Feutin A-arterial stiffness	Fetuin-A levels were inversely related to with arterial stiffness
Kirkpantur	2009	72	Feutin A-vasculary calcification	Low fetuin-A level was associated with coronary calcification
El Shahaby	2010	70	Feutin A-vasculary calcification	Low fetuin-A level was associated with coronary and valvular calcification
Turkmen	2011	78	Feutin A-vasculary calcification	Low fetuin-A level was associated with coronary calcification
Mann	2016	40	Feutin A-vasculary calcification	Fetuin-A level was not associated with coronary calcification
Chen	2016	685	Feutin A-vasculary calcification	Low fetuin-A level was associated with coronary calcification

TABLE 2 Association between Feutin A levels and mortality

Author	Year	Patients number	Aim	Results
Ketleler	2003	312	Feutin A levels-mortality	Low levels of serum fetuin-A are associated with mortality
Stenvinkel	2005	258	Feutin A levels-mortality	Low levels of serum fetuin-A are associated with mortality
Honda	2006	176	Feutin A levels-mortality	Low levels of serum fetuin-A are associated with mortality
Hermans	2006	664	Feutin A levels-mortality	Low levels of serum fetuin-A are associated with mortality
Metry	2008	222	Feutin A levels-mortality	Low levels of serum fetuin-A are associated with mortality
Pertosa	2009	174	Feutin A-mortality	Low levels of serum fetuin-A associated with mortality
Blaha et	2009	67	Feutin A levels-mortality	Low levels of serum fetuin-A are associated with early mortality
Pecovnik	2010	106	Feutin A levels-mortality	Low levels of serum fetuin-A are associated with mortality
Scialla	2014	602	Feutin A levels-mortality	Lower fetuin-A levels were associated with higher mortality
Chen	2014	131	Feutin A levels-mortality	Low fetuin-A levels were not associated with mortality

decreased in dialysis patients, which is likely related to the increased VC, valvular calcification, atherosclerosis, arterial stiffness, and mortality in this population.

4.2 | Matrix gamma-carboxyglutamic acid protein

Matrix gamma-carboxyglutamic acid protein (MGP) is an important extracellular matrix protein with a wide tissue distribution. It has a molecular weight of 10 kDa and consists of 84 amino acid residues.[65] MGP was first isolated from bovine bone extract in 1983, and was described in humans in 1988.[65] It is believed that the basic function of MGP is inhibition of medial calcification of arteries.[66] MPG binds tightly to the crystal nucleus, preventing further growth of the crystal and inhibiting the conversion of vascular smooth muscle cells into chondrocyte- and osteoblast-like cells.[67]

Serum MPG levels of hemodialysis patients are lower than those in healthy individuals.[68] A study involving 49 dialysis patients and 51 transplant patients did not find any relation between serum MGP levels and coronary artery calcium scores.[69] On the other hand, a study involving 40 dialysis patients found that undercarboxylation of MGP is a predictor of coronary artery calcification.[70] Other studies reported that systemic MGP levels do not have any correlation with the presence of arterial calcification, suggesting that the calcification-inhibiting effect of MGP is not systemic, but local; indeed, no relation between MGP levels and vascular stiffness was found.[68,71] With respect to vascular stiffness, a study involving 120 dialysis patients found a negative relationship between MGP and the augmentation index, but did not detect any relationship with pulse wave velocity.[68] The studies on this topic are summarized in Table 3.

MPG gene polymorphism is associated with increased cardiovascular mortality risk in hemodialysis patients.[72] A report on 188 hemodialysis patients showed that a low level of dephosphocarboxylated MGP predicted cardiovascular and all-cause mortality.[73]Another study, in 387 hemodialysis patients, found that calcimimetic and calcium-based phosphorus-binding agents increased MGP levels, while vitamin D analogs had no effect.[74] The observed effect of calcimimetics on MGP levels is consistent with in vitro studies in bovine and rat smooth muscle cells.[75]

In summary, MGP seems to act as a local inhibitor of VC, but further studies are needed to clarify its effects on VC, vascular stiffness, and mortality in dialysis patients.

4.3 | Osteoprotegerin

Osteoprotegerin (OPG) is a member of the TNF receptor super family and consists of 380 aminoacids. It is synthesized in osteoblasts, hematopoietic, and immune cells, as well as in many tissues including the cardiovascular system, kidneys, liver, spleen, brain, lungs, and bone marrow.[76,77] While TGF-α, TGF-β, IL-1α, IL-18, BMPs, and 17β-estradiol promote OPG synthesis, other factors such as cyclosporine A, parathyroid hormone, prostaglandin E2, and FGF-2 inhibit its synthesis.[38] OPG consists of seven structural domains; the 1st and 4th domains inhibit osteoclastogenesis, while the 4th, 5th, and 6th domains are involved in the transmission of apoptotic signals, potentially inhibiting cell death.[38] It inhibits bone destruction performed by osteoclasts, exerting hypocalcemic and antiresorptive effects. OPG binds to RANKL, preventing the binding of RANK, which results in inhibition of osteoclast differentiation and activation, and prevention of RANKL-mediated bone resorption.[78]

Osteoprotegerin synthesis occurs in different blood vessel types including the media of the major arteries and in the coronary artery smooth muscle and endothelial cells, suggesting a role in the function or structure of the vascular bed.[79] It has been reported that OPG acts as an autocrine liveliness factor in endothelial cells.[79] Rats lacking OPG develop osteoporosis as a result of increased osteoclast activation.[80] Meanwhile, calcification in major arteries, proliferation in the intima and media, and aortic dissection were observed in the absence of OPG, suggesting that OPG protects major arteries against medial calcification.[81]

Surprisingly, high OPG levels were associated with coronary and aortic calcification in cross-sectional and follow-up studies conducted in humans.[82,83] High serum OPG levels predicted the progression of aortic calcification in hemodialysis patients. The discrepancy between experimental and human observational data may be related to the fact that high OPG levels might represent an incomplete defense mechanism against atherosclerosis-promoting

TABLE 3 Association between matrix GLA protein with calcification and mortality

Author	Year	Patients no	Aim	Results
Brancaccio	2005	99	Matrix GLA protein gene polymorphisms-mortality	Altered MGP gene polymorphism a negative prognostic factor for cardiovascular events
Hermans	2007	120	Undercarboxylated matrix GLA protein (uc MGP)-arterial stiffness	ucMGP levels were inversely associated with the aortic augmentation index
Cranenburg	2008	52	Uc-MGP-vascular calcification	ucMGP as a biomarker for cardiovascular calcification
Cranenburg	2009	40	Uc-MGP-coronary artery calcification	ucMGP is associated with coronary artery calcification
Schlieper	2011	188	Matrix gla-mortality	Nonphosphorylated carboxylated matrix gla protein predicts survival
Yoshikawa	2013	134	Matrix GLA protein gene polymorphisms- vascular calcification	Polymorphism in the human matrix Gla protein gene is associated with the progression of vascular calcification

TABLE 4 Association between osteoprotegerin with atherosclerosis, calcification, and mortality

Author	Year	Patients no	Aim	Results
Nitta	2003	26	Osteoprotegerin (OPG)-vascular calcification	Serum OPG levels were independently associated with vascular calcification
Nitta	2004	102	OPG-vascular calcification	OPG levels are associated with the extent of vascular calcification
Barreto	2005	101	OPG-vascular calcification	Higher OPG is independently associated with coronary artery calcification
Morena	2006	185	OPG-mortality	OPG levels strong predictors of mortality
Schlieper	2007	97	OPG-arterial stifness	OPG not correlated with arterial stifness
Speer	2008	98	OPG-arterial stifness and mortality	OPG is strongly related to arterial stifness and cardiovascular mortality
Shroff	2008	61	OPG-arterial stifness and calcification	OPG is associated with increased vascular stiffness and calcification
Nishiura	2009	99	OPG-mortality	Elevated levels of serum OPG may predict subsequent cardiovascular events
Cianciolo	2010	253	OPG-coronary calcification	OPG levels are associated with coronary calcification
Nakashima	2011	151	OPG-arterial stifness and mortality	OPG is strongly related to arterial stifness and mortality
Kurnatowska	2011	47	OPG-atherosclerosis and calcification	OPG could serve as a surrogate marker of atherosclerosis and calcification
Ozkok	2012	78	OPG-coronary calcification	OPG levels were significantly associated with progression of coronary calcification
Lee	2013	81	OPG-vascular and valvular calcification	OPG levels are associated with vascular calcification
Winther	2013	206	OPG-mortality	High level of OPG was an independent risk marker of all-cause mortality

factors and arterial calcification or other ongoing attempts of arterial smooth muscle cells to remodel and calcify.

In a study involving 102 hemodialysis patients, a positive relationship was noted between serum OPG levels and aortic calcification; OPG levels were independent predictors of aortic calcification.[82] A prospective study involving 78 patients found that high OPG levels at baseline predicted progression of coronary artery calcification.[83] Two independent studies on hemodialysis patients[84,85] reported that increased OPG levels were independent predictors of pulse wave velocity. Another study involving 185 hemodialysis patients reported that increased OPG levels at baseline were predictors of mortality.[86] Finally, another study involving 99 hemodialysis patients reported that increased OPG levels predicted cardiovascular death.[87] The studies conducted on OPG are listed in Table 4.

Phosphorus binding agents, vitamin D, and cinacalcet may have different effects on OPG levels. In the CALMAG study, subjects taking sevalamer showed increased levels of OPG.[88] Administration or paricalcitol was effective in increasing OPG levels in 10 healthy subjects.[89] Cinacalcet treatment also increases OPG levels.[64] Nevertheless, further studies are warranted to fully clarify the effect of such compounds on OPG levels.

In summary, although OPG is an important calcification inhibitor, clinical studies have surprisingly found that OPG levels are positively

correlated with VC, vascular stiffness, and mortality in dialysis patients. Further study is warranted before a sound hypothesis for this seeming contradiction can be estabished.

4.4 | Osteopontin

Osteopontin (OPN), first described by Young et al. (1990), is an acidic, negatively charged, and hydrophilic molecule consisting of 314 amino acid residues. OPN is also known as bone sialoprotein I, early T-lymphocyte activation 1, or urinary stone protein.[90] OPN, which is mainly found in bones, is synthesized by osteoblasts and osteoclasts but is also secreted by macrophages, endothelial cells, smooth muscle cells, active T lymphocytes, natural killer cells, epithelial cells, and tumor cells.[91] Cytokines such as IL-1, IL-2, and TNF-α regulate the expression of protein kinase C and promote OPN transcription. Since it is secreted by many cell types, OPN plays an active role in many physiologic and pathologic processes including cell adhesion, angiogenesis, apoptosis, inflammatory response, ectopic calcification, and tumor metastasis.[92,93] OPN is an important anti-apoptotic factor in smooth muscle, endothelial, epithelial, and pro-B cells. OPN may act as a pro- or anti-inflammatory factor, being expressed in macrophages, T cells, B cells, neutrophils, dendritic cells, natural killer cells, and fibroblasts; OPN expression is upregulated in all organs in response to inflammation.[94]

In bone, OPN interacts with integrin, CD44, and hyaluronic acid receptors, facilitating the binding of osteoclasts to the bone matrix. OPN regulates the size and growth of apatite crystals by binding to the crystal surface.[94] In addition, OPN has a regulatory effect on osteoclast differentiation and bone resorption as it can inhibit the growth of calcium-phosphorus crystals and regulate mineralization by inducing osteoclast function.[94]

Osteopontin is expressed in smooth muscle cells, angiogenic endothelial cells in atherosclerotic lesions, and in macrophages, thereby modulating the proliferation, migration, and accumulation of such cells during the repair and remodeling of the vasculature.[95] OPN may represent an important regulator of arterial mineral deposition during injury and disease. Indeed, its expression in atherosclerotic plaques correlates with the severity of atherosclerosis and calcification.[96] OPN-mediated inhibition of calcification in artery smooth muscle cells requires phosphorylation of OPN, which varies with tissue type; specifically, high levels of phosphorylated OPN are noted in bones and milk, while tumor cells have been found to exhibit significantly reduced OPN phosphorylation levels.[97]

Unfortunately, few studies have investigated the relationship between OPN and VC-related mortality in hemodialysis patients. A study involving 30 patients found that radial artery calcification was associated with OPN up-regulation and diminished expression of alpha-smooth muscle actin.[98] In another study, involving 36 hemodialysis patients, OPN concentration was positively correlated with the aortic calcification index.[99]

While no in vivo studies have been reported, OPN was found to inhibit ectopic calcification, when implanted in OPN-deficient mice. In addition, phosphorus binding agents including CaCO3 increased OPN levels in atherosclerotic lesions in rats.[100] Similarly, 1,25-dihydroxyvitamin D3 increased OPN production in rat kidneys[101]; no such study has evaluated calcimimetics.

To summarize, OPN inhibits calcification, but there are insufficient data regarding its levels hemodialysis patients. Available evidence from two studies indicates that the increase, and not the decrease, in OPN levels is associated with increased calcification, in a manner similar to the effect of OPG. Further studies are warranted to clarify this unexpected effect.

4.5 | Bone morphogenic protein-7

So far, nearly 15 types of BMP have been defined. Except for BMP-1, which is a metalloproteinase, all known BMPs are members of the TGF-beta super family.[102] In adults, BMPs are synthesized by osteoblasts and osteocytes, and accumulate primarily in bone tissue and dentine. They are mostly expressed during embryonic development and play important roles in the development of bones, cartilage, eyes, kidneys, and the cardiovascular system. Several BMPs (2, 3, 4, 6, and 7) and osteogenic protein-1 have osteoinductive activity, while other BMPs (5, 8, and 9 through 15) do not.[103] In vitro studies conducted on cell cultures showed that BMPs have important effects on osteoblastic growth and differentiation. Specifically, BMP-2, BMP-4, and BMP-6 stimulate osteoblast differentiation in rats and mouse cells while BMP-2 and BMP-7 stimulate the differentiation of human bone marrow osteoprogenitors and bone-derived osteoblasts.[104,105]

Of note, BMP-7 also stimulates osteoblastic differentiation as well as alkaline phosphatase activity, collagen and osteocalcin synthesis, as well as mineralization in rat calvarial cells and in mouse and human bone marrow stromal cells.[105] Recent evidence indicates that recombinant BMP-7 prevents VC and renal osteodystrophy in CKD.[106] In addition, BMP-7 effectively prevented VC in a uremic mouse model of atherosclerosis and VC involving low-density lipoprotein receptor double-knockout animals.[107] These animals had adynamic bone disorder and hyperphosphatemia; BMP-7 stimulated bone formation, corrected hyperphosphatemia, and prevented VC.[107] The protective effect of BMP-7 was partly based on its ability to correct hyperphosphatemia and act directly on the vascular smooth muscle cells.[108] Unfortunately, the relation between BMP-7 and VC has not been investigated in hemodialysis patients. There is a strong need for human studies with such a focus. There is currently little knowledge regarding the effect of phosphorus binders agents, Vitamin D or calcimimetics drugs on BMP-7 levels.

5 | CONCLUSION

Vascular calcification is clearly a process with complex pathogenesis. Calcification inhibitors can influence this process via different mechanisms, and may help reduce the progression of vascular damage. Although some studies have been conducted on this topic in dialysis patients, further investigation is warranted to clarify the therapeutic

mechanisms underlying the effect of calcification inihibitors on the progression of VC and to develop optimal therapeutic strategies to increase this effect.

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CONFLICT OF INTEREST

The authors declare they have no conflict of interests.

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