VASCULAR CALCIFICATION: PATHOGENESIS, EPIDEMIOLOGY AND CLINICAL IMPACT

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ABSTRACT

Several studies suggest that vascular calcifications play a main role in the cardiovascular disease, which is one of the main causes of mortality in CKD patients. Vascular calcification is determined by prevalent traditional, uraemia-related and non-traditional risk factors such as cardiovascular disease or pro-inflammatory molecules and occurs mainly in the arteries, which are classified in three types according to their size and structural characteristics.

Several epidemiological studies have linked vascular calcifications to bone loss and fractures in chronic kidney disease patients and also in the general population, stressing the fact that both can share pathogenetic pathways. The mechanisms behind vascular calcification are complex and not yet fully understood. Phosphorus plays a main role, while other elements related to bone formation have been recently identified, including the BMP-Wnt-Msx-2 axis.

The strategies to control vascular calcifications involve several measures, chief among them the control of hyperphosphatemia. Furthermore, it has been recently described that strategies focusing on both reducing bone resorption and increasing bone mineralization may decrease the risk of vascular calcifications.

Vascular calcification in chronic kidney disease: types and risk factors

Over the last years, the main cause of morbidity and mortality in chronic kidney disease (CKD) patients has been adjudicated to cardiovascular disease. Recent studies suggest that vascular calcifications play a main role in the cardiovascular disease in dialysis patients. CKD is now defined following the recommendations of the "Kidney Disease: Improving Global Outcomes Foundation" (KDIGO) (1,2). Kidney damage is defined as structural or functional kidney abnormalities, with or without a decrease in the glomerular filtration rate (GFR), which can lead to a decrease in GFR, together with other abnormalities such as vascular calcification, bone loss and secondary hyperparathyroidism. Nowadays, all these are combined and known as “chronic kidney disease - bone and mineral disorders” (CKD-MBD) (2). The evolution of CKD is subdivided into five stages; marked differences exist between the initial and final periods.

The predisposition of patients with CKD towards developing vascular calcifications was mentioned for the first time back in the 19th century; since then, many studies have addressed this matter. Vascular calcification occurs mainly in the arteries, which can be classified characteristics in three types according to their size and structure: elastic or large-caliber arteries, muscular or medium-caliber arteries, and small caliber arteries.

Elastic or large-caliber arteries show a relatively thin wall in proportion to their diameter. The tunica media is rather thick and it contains more elastic fibers than smooth muscle; the adventitia tends to be fairly thin. Through the elastic arteries, blood is conducted from the heart to the distribution arteries. Large vessels like the aorta, subclavia and common carotid arteries are included in this group.

Muscular or medium caliber arteries have a tunica media which contains a great proportion of smooth muscle fibers; they are capable of withstanding further vasodilatation

and vasoconstriction to adjust the volume of blood to accommodate perfusion requirements. Medium caliber arteries include the axillary, brachial, radial, coronary, femoral and tibial arteries.

Finally, small caliber arteries are less than 2 mm thick and their tunica media contains only smooth muscle fibers. In these vessels, luminal size variations, caused by vasoconstriction and vasodilatation of smooth muscle cells, are responsible for regulating the local blood flow and perfusion pressure. This group includes the palmar arch and the digital arteries, among others.

The classical description of arterial calcification specifies it may occur in two locations: the intima and the media layers (3). Nevertheless, this classical concept is not fully accepted by all authors (4,5).

Intimal calcification begins and progresses under the influence of both genetic and lifestyle circumstances throughout a person's lifetime. Intimal calcification is associated with a sequence of atherosclerotic events that include endothelial dysfunction, intimal edema, lipid cell formation and the migration of leukocytes and macrophages that can in turn cause a plaque rupture, thus leading to the formation of the thrombus (6). Atherosclerotic lesions have a patchy distribution along the length of the artery and may cause local stenoses and occlusions. Furthermore, it is characterized by chronic arterial inflammation exacerbated by alterations in lipid metabolism (7) and other well-characterized risk factors, including hypertension, diabetes, hypercholesterolemia (8,9), obesity, smoking and a family history of heart disease.

Calcification of the media occurs in the elastic lamina of large-caliber and medium-small size arteries; it seems to be independent of atherosclerosis, but can coexist with it. This type of calcification was known initially as "Monckeberg sclerosis", and it can be seen radiographically as railroads (10). It typically affects arteries that are less likely to develop atherosclerosis, such as visceral abdominal, thyroid, lung (10), limb and femoral arteries (11), but it is also extremely common in the aorta. Calcification of the media increases

linearly with age. It is frequently observed in patients with metabolic abnormalities such as hypervitaminosis D, CKD and diabetes (12).

Table 1 summarizes the most prevalent traditional, uraemia-related and non-traditional risk factors for vascular calcification in CKD patients. Just as in the general population, traditional cardiovascular risk factors, present in a large proportion of patients with CKD, are responsible to a great extent of the progression of vascular calcifications. Among non-traditional cardiovascular risk factors, including uraemia-related risk factors, time on dialysis and hyperphosphatemia, are the risk factors more strongly associated with increased vascular calcifications and mortality (13). Elevated CRP and IL-6, as expression of chronic inflammations, have been also frequently associated with vascular calcifications.

Clinical impact of vascular calcification in CKD patients and in the general population

As previously mentioned, CKD patients exhibit a very high percentage of vascular calcifications (14-17), leading to cardiovascular disease, decreased life expectancy and mortality (18). A high prevalence of vascular calcifications has been also demonstrated in the earliest phases of CKD; Russo et al. showed that 40% of patients with CKD (mean GFR 33 ml/min) suffered from calcification of the coronary arteries compared with a 13% of the control subjects within a similar age range and normal renal function (19). Krammer et al. found a significant positive association between the presence of coronary calcifications and renal failure, an association which increased dramatically in CKD-diabetic patients (20).

However, vascular calcification is not exclusively related to CKD patients. In a study carried out in a subgroup of a normal, randomly selected European population (Vertebral Osteoporosis Study [EVOS]), aortic calcification was observed in 54.2% of men and 43.1% of women older than 50 years (21, 22).

Depending on the type of population, there are several risk factors which exert a different impact on thel localization, rate, extension and severity of the vascular calcifications.

CKD patients develop vascular calcifications even at early ages (17), and almost in all localizations compared to the general population. They are frequent in high-caliber arteries, such as the aorta (79%); medium arteries (70.5%), including the coronary (12); and also in small calibre arteries (20.2%) (23). These differences may reflect the heterogeneity of the three categories of arteries studied, which also imply relevant functional changes in the vasculature (24). Not only is calcification present in the arteries, calcification of the cardiac valves represents a high risk of cardiovascular dysfunction (25) in both the general and haemodialysis (HD) populations.

In a recent study, prevalent aortic calcifications were significantly higher in HD patients (79%) than in a random-based general population of the same age, sex and region (37.5%) (23). Other reports have shown similar results for HD patients (26); in them, age was positively associated with vascular calcifications in large and medium calibre arteries, reinforcing the role of age as a risk factor for both atherosclerosis and arteriosclerosis. Time on HD and total time on renal replacement therapy have been also positively associated with vascular calcifications, particularly in medium calibre arteries: each new year on renal replacement therapy increased the risk of having vascular calcifications by ~15% (27), a finding in agreement with other studies that have identified time spent on dialysis as an important risk factor, mainly for medial but also for intima arterial calcifications in CKD patients (28).

The Framminghan study has shown that vascular calcification is also an independent predictor of vascular morbidity and mortality in the general population (29). The number and severity of vascular calcifications are associated with mortality (30), mainly in CKD patients, in which the latter is up to 10 to 30 times higher (31) than in the general population. Women on HD showed an increased risk of severe aortic calcifications compared with women from the general population, probably due to a combination of atherosclerosis and arteriosclerosis (23). Furthermore, women on HD showed a positive association between severe vascular calcifications and mortality.

Cardiovascular risk factors may have a different impact according to sex; for example, in the general population, cholesterol is more important for cardiovascular risk in men than in postmenopausal women, in whom hypertension, diabetes and their combined effects play a major role (32).

Links between vascular calcification and bone

Vascular calcifications, bone loss and increase in fragility fractures are very common disorders associated with ageing, both in patients with CKD (17, 33, 34) and in the general population (35-38). In recent years, several epidemiological studies have drawn attention to the relationship between vascular calcifications (37-40) and bone metabolism. Even though the pathogenetic factors linking vascular calcifications and bone fragility are not fully understood, at least two studies have shown that vascular calcifications in some localizations were associated with an increased risk of fragility fractures in both general (41) and HD populations (23). Furthermore, recent studies suggest that severe vascular calcifications can be positively associated with an increase in both the incidence and prevalence of any kind of fragility fractures in the general population (42). Similarly, a recent study in HD patients has found a positive association between vascular calcifications in some large and medium calibre arteries and vertebral fractures (23). In agreement with these results, other authors have also found a positive relationship between large-size arteries (aorta) (41) and osteoporotic fractures in the general population.

Pathogenesis of vascular calcification

Until recent years, vascular calcification was considered the result of a simple precipitation of the circulating calcium and phosphate. However, the mechanism by which the process of vascular calcification is produced is complex; it does not consist in a simple precipitation of calcium and phosphate, but requires an active and modifiable process that will be discussed later on this review. The mechanism of vascular calcification development involves a combination of physical and biological processes, in which the final result is a calcification inside the artery wall with a structure similar to bone tissue (43, 44). This regulated process involves not only a release of mineral content from the bone, but other changes as well, such as the loss of vascular calcification inhibitors (45) and the formation of calcification vesicles (46), which end up inducing a cellular phenotypic change: vascular smooth muscle cells (VSMCs) become bone-like cells (47, 48). Interestingly enough, the increase of bone-like cells in the vessels has been reported to be associated to a decrease in bone mass and mineralization in bone tissue (12 ,21, 42), favouring bone fractures.

Thanks to the advances in molecular biology, the vascular calcification mechanisms have been extensively studied and several inhibitors and promoters of vascular calcification have been described (Figure 1). Among the latter, phosphorus and calcium play a relevant role in the pathogenesis of vascular calcifications. However, in humans and other mammals, serum concentrations of calcium and phosphate exceed the calcium-phosphate solubility product; thus, the likelihood of precipitation is high. Nevertheless, in both young and adult populations, intravessel precipitation is uncommon, clearly stressing the important role played by several vascular calcification inhibitors present in the serum, which prevent calcium/phosphate precipitation and deposition.

Promoters of vascular calcification: Phosphorus, BMP-MSx-2-Wnt axis, Inflammation and Oxidative Stress

High serum phosphorus is the most important uremia-related, non-traditional risk factor associated to vascular calcification in CKD patients and in the general population (18). It is well known that high serum phosphorus levels aggravate secondary hyperparathyroidism and also lower the activity of 1-alpha-hydroxilase, which in turn decreases serum calcitriol levels. Between 30 and 50% of patients undergoing dialysis still feature high levels of phosphorus, which has been involved in the high prevalence of vascular calcifications and cardiovascular mortality (49). An important question that must be answered is how the increments in serum phosphorus trigger several mechanisms in the vessels that lead to a high prevalence of vascular calcifications.

Phosphorus, apart from being a simple extracellular mineral element, has been also described as an important intracellular player in VSMC cells (50). Not only does it collaborate with calcium in the formation of the mineralized matrix but it is also capable of acting as a "secondary intracellular messenger", activating several molecular pathways related to bone formation. It gets into the cells via a specific Na-dependent channel called Pit-1 and exerts some interesting actions; in fact, blocking Pit-1 prevents vascular calcification in an *in vitro* model (51).

In vitro experiments have demonstrated that elevated intracellular phosphate levels may act directly on the transcription of bone-related genes, such as Cbfa-1 and osteocalcin, resulting in the activation of several osteogenic pathways in the VSMCs, leading to phenotypic changes from VSMC into bone-like cells (52). In addition, in uremic rats with high serum phosphorus, medial layer vascular calcification has been suggested to be caused, at least in part, by increments in the vascular forms of Cbfa-1 and Pit-1 (53).

Cbfa-1 promotes the expression of one of the most important families of proteins involved in vascular calcifications: the bone morphogenetic proteins (BMPs). This family is composed of several members, but BMP-2, 4 and 7 are the ones which have received the most attention.

The role of BMP-2 in vascular calcification is not completely understood; recently, it has been proposed that BMP-2 can increase phosphorus uptake (54). In addition, BMP-2 has

been demonstrated to induce apoptosis of VSMCs (55), a process that is critical in the onset of vascular calcification (56). Moreover, *in vitro* studies with high phosphorus demonstrated that BMP-2 stimulates the expression of the transcription factor Msx-2 (57, 58), another bone-related gene, in the vasculature. The "BMP-Msx-2" axis also recruits other family of proteins such as the Winngless/ints proteins (Wnt's) (59) which has been associated with bone formation. Recently, the Wnt signalling pathway has been also added to the long lists of the paracrine "vascular calcification promoters" (60).

BMP-7 has also been suggested as an important player in the development of vascular calcification; the experimental use of BMP-7 in CKD mice has been able to inhibit the expression of osteocalcin in VSMCs (61).

Inflammation has been widely described as one component of atherosclerosis and medial vascular calcification. Towler and collaborators showed that when the inflammatory molecule "tumour necrosis factor alpha" (TNF-alpha) was overexpressed in the vessels, mice showed vascular calcification, with a higher activation of Wnt in their VSMCs (62, 63), suggesting that inflammation may promote vascular calcification, probably via the Wnt signalling pathway. These experiments support the idea that vascular calcification can be mediated by new players that could act upstream in the cascade of events that promotes vascular calcification.

Oxidative stress has been also related to the BMP-Msx-Wnt axis, inflammation, and vascular calcification. VSMCs cultured with H_2O_2 developed calcification via stimulation of Cbfa-1 (64), demonstrating that oxidative stress can act as a promoter of vascular calcification. In addition, *in vivo* studies have established that some antioxidants can prevent vascular calcifications (65). In agreement with this experimental analyses, clinical studies have shown that serum levels of oxidized LDL, advanced oxidation protein products and urine levels of F-2 isosprostanes (biomarkers of oxidative stress) may all be considered as risk factors for vascular and valvular calcifications (28,66).

Inhibitors of vascular calcification: Pyrophosphates, Fetuin A and OPG

Interestingly, not all dialysis patients develop arterial calcifications despite them being exposed to similar risk factors (67). This fact suggests that protective factors against vascular calcification might exist either in the vessels or in the blood stream. In fact, if human serum is added to a calcifying media, *in vitro* calcification is inhibited.

Pyrophosphates (PPi) are located in the vascular matrix and they are supposed to preserve the aortic vascular smooth muscle cell (VSMC) phenotype thanks to the inhibition of calcium carbonate formation, hence inhibiting calcium phosphate crystal formation; PPi inhibits the change of VSMCs into bone-like cells. PPi are processed by an ecto enzyme called NPP1. NPP1 K.O. mice exhibit medial artery and ligamentous calcifications (68). Deficiency in ectonucleotide pyrophosphatase/ phosphodiesterase I (NPP1) in humans causes widespread vascular calcification (69). Bisphosphonates, used in the treatment of bone diseases, are pyrophosphate analogues with effects at the tissue, cellular, and molecular levels. The key pharmacological action of bisphosphonates is the inhibition of bone resorption, which will be discussed later in this review (70).

In serum, the most abundant inhibitors of vascular calcification are fetuin-A (alpha2-Heremans-Schmid glycoprotein), osteoprotegerin (OPG) and matrix-gla protein. Fetuin-A is a known inhibitor of osteogenesis (71), capable of inhibiting vascular calcification (72). Fetuin-A knockout mice spontaneously develop widespread soft tissue calcification, including significant myocardial calcification. In this mice, vascular calcification was associated to the upregulation of the pro-fibrotic factor TGF-Beta (73).

OPG inhibits osteoclast differentiation, modulating bone resorption through its action as a decoy receptor of RANKL. OPG-null mice develop early onset osteoporosis and severe medial layer calcification (74), suggesting that OPG acts as an inhibitor of *in vivo* vascular calcification. OPG was shown to inhibit ALP activity in aortic tissue and prevent the progression of medial layer vascular calcification (75). The importance of the OPG/RANKL axis in vascular calcification has been recently shown in an *in vivo* model, in which the increase in vascular calcium content was parallel to an increase in the RANKL and BMP4 expression (76).

Other players

Klotho is a correceptor of the fibroblast growth factor 23 (FGF-23), a known phosphaturic hormone, and it controls phosphorus excretion (77, 78), among other functions. K.O mice for Klotho gene showed accelerating aging with widespread ectopic calcification, including vascular calcifications. The mechanisms by which FGF-23/Klotho affect vascular calcifications are not fully understood. Recent studies suggest that this axis controls phosphate excretion and homeostasis directly, and other important steps of the Vitamin D and PTH metabolism indirectly, which, in turn, can be also responsible of the vascular effect. Defects in both FGF-23 and Klotho genes lead to several disturbances, including vascular calcification and bone loss (79-82).

Advanced glycation end products (AGEs) are chemical modifications of proteins and lipids that become non-enzimatically glycated after contact with carbohydrates (83). The generation of AGEs is a continous *in vivo* process and their accumulation increases with aging and diseases, specially diabetes (84). AGEs accumulate in the vessel's wall and contribute to the development of atherosclerosis through the formation of cross-links between molecules in the basement membrane of the extracellular matrix, altering tisular structure, perturbing endothelial cells, VSMCs and macrophages, mainly through the interaction of AGEs with different cell surface receptors, especially RAGE (85). The result is an increased stiffness of the vascular wall, a procoagulant endothelium, foam cell transformation of macrophages and reduced bioavailability and activity of NO, all of them critical factors for atherogenesis. Furthermore, recent studies have shown a correlation between the accumulation of AGEs in bone and increased fracture risk, even with normal bone mineral density (86-88). This fact may be related with the abnormal cross-links induced by the AGEs in collagen proteins, which may increase bone fragility by modifying the biomechanical properties (89,90). Furthermore, it has been observed that AGEs alter the function of the osteoblasts and increase the activity of the osteoclasts (91), adding a complementary

explanation for the development of the bone disease; these findings all suggest that AGEs might be yet another likely link between vascular calcifications and osteoporotic fractures.

Strategies to reduce vascular calcifications

Any strategy designed to reduce the impact of vascular calcifications has to begin with primary prevention measures to control cardiovascular risk factors. In the particular case of CKD, it is imperative to avoid further kidney damage. In this respect, it is crucial to promote a healthy lifestyle, with a balanced diet, regular physical exercise, smoking abstinence and a low alcohol intake. Once vascular calcifications appear, secondary prevention must aim to reduce their complications, intensifying previous measures and initiating the appropriate drug therapy. Particular aspects of the pharmacological approach are discussed below.

Theoretically, any kind of intervention aiming to reduce vascular calcification should curtail the influence of factors that promote calcifications and/or augment the effects of factors that may inhibit calcifications (92). Most strategies to reduce vascular calcifications have focused on the most common modifiable risk factors such as hyperphosphatemia, hypercalcemia, the CaxP product, hyperparathyroidism, smoking, hyperlipemia and hypertension.

Control of hyperphosphataemia, hypercalcemia and CaxP product.

Disturbances in serum phosphorus, calcium and the calcium-phosphorus product are frequently seen in CKD patients and are implicated in the promotion of vascular calcification as well as in an increased death risk (92). Because dietary restriction of phosphorus and intermittent dialysis are not usually effective in controlling serum phosphorus, most patients with CKD stage 5 show a high prevalence of hyperphosphatemia with its known implications in the pathogenesis of secondary hyperparathyroidism, cardiovascular alterations and mortality. As mentioned before*, in vivo* and *in vitro* studies shed light on the role of

phosphorus as promoter of vascular calcification, demonstrating that the control of phosphorus should be a priority in clinical practice.

Calcium phosphate binders such as calcium acetate and calcium carbonate have replaced aluminium hydroxide as the most widely prescribed phosphate binders. The possible negative role of calcium loading from these binders on the progression of vascular calcifications has led to the abandonment of calcium- and aluminium-based phosphate-binders in favour of new calcium- or aluminium-free phosphate binders (sevelamer hydrochloride and lanthanum carbonate). These changes in the treatment have reduced hypercalcemic adverse events in comparison to calcium-based binders (93).

An experimental study demonstrated that treatment with sevelamer in rats decreased renal calcification compared to rats that received calcium carbonate or untreated rats (94). In addition, a clinical trial showed that sevelamer reduced the progression of both coronary and aortic calcifications compared to calcium carbonate (95). However, the mechanism of the beneficial effect of sevelamer on the progression of calcification is still not fully understood. One possible mechanism is based on the reduction of the calcium load; however, reduced vascular calcifications may also result from reductions in total and LDL cholesterol, which occur during treatment with sevelamer (93).

Control of Secondary Hyperparathyroidism: Vitamin D and Calcimimetics

The use of Vitamin D metabolites is a challenging subject that still remains controversial. The current treatment of secondary hyperparathyroidism in dialysis patients includes suppression of PTH with supraphysiologic doses of vitamin D or its analogues. Although it is widely known that a high dosage of vitamin D metabolites favours the onset and progression of vascular calcifications, several studies have paradoxically demonstrated a long-term beneficial effect of vitamin D on vascular calcifications. Low vitamin D status is associated with a higher prevalence of vascular calcifications, bone and mineral disturbances, susceptibility to some infections, higher risk of autoimmune diseases, some malignancies, and many other complications (96).

Observational studies in patients on HD and in the general population have also demonstrated a lower morbidity and a cardiovascular survival advantage in patients who are treated with vitamin D receptor activators (97, 98).

A major breakthrough in the management of the calcium phosphate metabolism of dialysis patients was achieved recently with the introduction of calcimimetics. These compounds were the first agents introduced to lower PTH with advantageous effects on serum calcium and phosphate. It has been demonstrated experimentally that the calcimimetic R568 reduces aortic calcifications and mortality in rats in which aortic calcifications were induced using a high dose of calcitriol (99). Moreover, another experimental study showed that calcimimetics may even favour the regression of vascular calcification (100).

Control of dyslipidemia

Hyperlipidemia, particularly increased LDL-cholesterol, has been implicated in the progression of vascular calcifications. In addition, in the general population, the beneficial effect of lowering LDL cholesterol levels on the progression of calcification has been reported by several groups (101, 102). As mentioned previously, patients who were treated with sevelamer showed a significant decrease in LDL cholesterol levels (95), which may explain the beneficial effects in the progression of cardiovascular calcification. It is known that the rapid progression of coronary arterial calcification in haemodialysis patients is associated with higher triglycerides and lower HDL cholesterol levels (103).

Control of blood pressure

Hypertension is a modifiable risk factor for vascular calcifications in both general population and CKD patients. Several studies n ESRD and essential hypertension have shown that arterial stiffening is an independent predictor of mortality. As arteries become stiffer, the pulse wave velocity increases and it is responsible for a rapid return of wave reflections from the periphery to the ascending aorta during systole, which causes an

abnormal rise of aortic systolic blood pressure with decreased diastolic blood pressure and high pulse pressure. Increased wave reflections and high pulse pressure are independent risk factors for mortality of ESRD patients (104).

Diabetes

Diabetes is a disease that is known to be complicated by heterogeneous metabolic risk factors, such as hyperglycemia, hyperlipidemia, insulin resistance, glycation, oxidative and carbonic stress, and tissue hypoxia. In the non-uremic population, vascular calcification occurs more frequently in diabetics. In CKD patients, vascular calcification in diabetics has been reported to be more prevalent and more advanced than in non-diabetics (105). Several studies emphasize the importance of glycemic control in the prevention of the development and progression of vascular calcification in diabetic CKD patients (106).

Factors that inhibit vascular calcification

Although vascular calcification is very common in patients with CKD, it is absent in a non-negligible percentage of patients close to 20%, despite a similar exposure to the known factors that promote calcification (67). As mentioned before, inhibitors of the precipitation of calcium and phosphate must be playing a major role in preventing extraosseous calcification. Unfortunately, the therapeutic potential of these inhibitors of calcification has not been explored in clinical trials. Because MGP requires vitamin K for γ-carboxylation, an acquired vitamin K deficiency and the use of warfarin may predispose towards vascular calcification (107).

Clinical and experimental studies have consistently established a positive association between arterial calcification and bone resorption (108, 109). Consequently, it can be hypothesized that treatment strategies that simultaneously reduce bone resorption and increase bone mineralization may decrease the risk of vascular calcifications.

Bisphosphonates, used as standard therapy for osteoporosis, inhibit the experimentally induced vascular calcification, offering perspectives for the treatment of

vascular calcification. The exact mechanism by which bisphosphonates inhibit the arterial calcification is not entirely understood. One possibility is an indirect effect through inhibition of bone resorption, which would reduce the efflux of calcium and phosphate out of the bone, resulting in a decreased performance of the substrates required to form hydroxyapatite in the arterial wall (110).

Bisphosphonates have been demonstrated to reduce vascular calcifications in experimental models (111), but also in CKD in a reduced group of HD patients (112). Nevertheless, the use of bisphosphonates, particularly in CKD patients with underlying renal osteodystrophy, should be carefully considered as they are still in the research phase (110).

Even though new strategies may improve the management of vascular diseases and, more specifically, may have a positive impact on the high prevalence of vascular calcifications, the more effective approach is still that involving the best possible control of the mineral and bone metabolism and the inflammatory parameters (12).

We need more experimental, epidemiological and randomised clinical studies designed to ascertain the effects of the newly available “bone-vascular active drugs” on the bone and cardiovascular systems.

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Table and Figure Legends

Table 1. *Risk factors associated to vascular calcification in CKD patients*

Table 2. *Strategies to reduce vascular calcification*

Figure 1*.*

Promoters and inhibitors of vascular calcification

Figure 2

Severe aortic calcifications (black arrows) and vertebral fracture (red arrow)

Table 1

Traditional risk factors:

- Hypertension
- Dyslipidemia
- Diabetes mellitus
- Smoking
- Older age
- Family history of premature coronary heart disease

Uraemia-related and non-traditional risk factors:

- Time on dialysis
- Hyperphosphatemia
- High Calcium-phosphorus product
- Hyperparathyroidism and hypoparathyroidism
- High dosage of vitamin D metabolites
- Low fetuin-A
- Anaemia
- Poor nutrition (low albumin)
- Chronic Inflammation (CRP, IL-1, IL-6, TNFα)*
- Hyperhomocysteinemia
- Advanced glycated end products

* CRP: C reactive protein; IL-1: interleukin 1 ; IL-6: interleukin 6 ; TNFα: tumoral necrosis factor α.

Table 2

- Balanced diet, with low salt and saturated fats intake
- Regular physical exercise
- Smoking abstinence
- Low alcohol intake
- Control of serum phosphorus and calcium levels
- Use of physiologic doses of vitamin D
- Treatment of secondary hyperparathyroidism
- Lipid-lowering therapy with statins
- Treatment of hypertension
- Rigorous control of diabetes mellitus
- Caution with acenocumarol or warfarin treatments

Figure 1

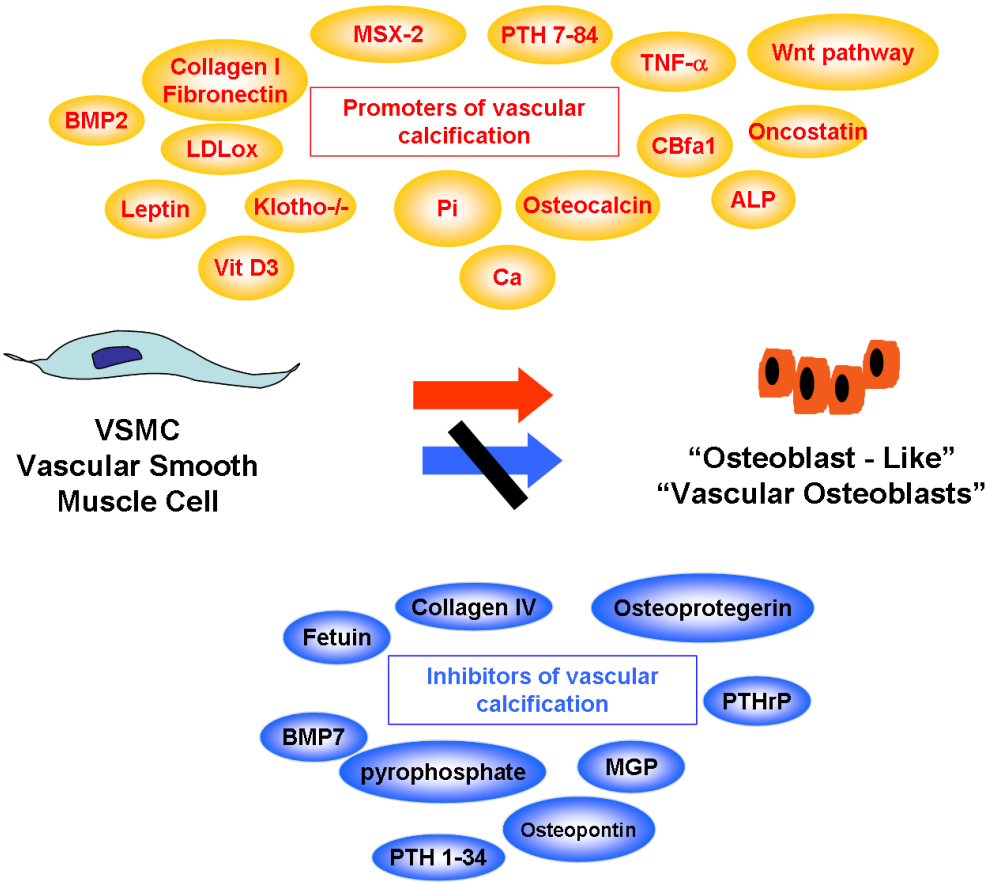
MSX-2
PTH 7-84
TNF-α
Wnt pathway
Collagen I
Fibronectin
BMP2
Promoters of vascular calcification
LDLox
CBfa1
Oncostatin
Leptin
Klotho-/-
Pi
Osteocalcin
ALP
Vit D3
Ca
VSMC
Vascular Smooth
Muscle Cell
"Osteoblast - Like"
"Vascular Osteoblasts"
Collagen IV
Osteoprotegerin
Fetuin
Inhibitors of vascular calcification
PTHrP
BMP7
pyrophosphate
MGP
Osteopontin
PTH 1-34

Figure 2