Aortic valve calcification in chronic kidney disease

Marcello Rattazzi¹, Elisa Bertacco¹, Antonio Del Vecchio², Massimo Puato¹, Elisabetta Faggin¹ and Paolo Pauletto¹

¹Department of Medicine, University of Padova, Padova, Italy and ²Unit of Nephrology and Dialysis, Monselice Hospital, Padova, Italy

Correspondence and offprint requests to: Marcello Rattazzi; E-mail: mrattazzi@ulss.tv.it

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Several clinical studies reported an increased prevalence and accelerated progression of aortic valve calcification among patients with end-stage renal disease when compared with subjects with normal kidney function. Recently, mechanisms of calcific valve degeneration have been further elucidated and many of the pathways involved could be amplified in patients with decreased renal function. In particular, calcium-
phosphate balance, MGP metabolism, OPG/RANK/RANKL triad, fetuin-A mineral complexes and FGF-23/Klotho axis have been shown to be impaired among patients with advanced chronic kidney disease and could play a role during vascular/valve calcification. The scope of the present review is to summarize the clinical data and the pathophysiological mechanisms potentially involved in the link between renal function decline and the progression of aortic valve disease.

**INTRODUCTION**

Several clinical studies conducted in the last two decades clearly demonstrated that patients with chronic kidney disease (CKD) harbour a significant increase in the risk of cardiovascular (CV) events, including coronary artery disease (CAD), heart failure and stroke [1]. The burden of arterial calcification and the associated increase in vascular stiffness observed during renal function decline are now considered as important contributors to the onset of CV complications [1, 2]. Of note, dialysed patients showed increased calcium deposition within the cardiac valve apparatus, namely aortic and mitral valves [3]. As a matter of fact, haemodynamically significant aortic valve stenosis is more prevalent and accelerated in end-stage renal disease (ESRD) patients when compared with subjects with normal kidney function [4].

Kidney function decline induces the ‘perfect storm’ for vascular/valve calcification initiation and progression. This is mainly due to alteration in calcium-phosphate (Pi) homeostasis, inflammation, pathological bone remodelling and reduced vascular and systemic levels of calcification inhibitors [2]. The scope of this review is to summarize the clinical evidence and the pathophysiological mechanisms potentially involved in the link between CKD and the progression of calcific aortic stenosis (AS).

**AORTIC VALVE CALCIFICATION IN CKD PATIENTS**

In the last two decades, a series of population-based studies demonstrated an increased prevalence of aortic valve calcification among dialysed patients (Table 1). Results of these investigations showed a prevalence of calcific abnormalities ranging from 28 to 85% of the patients, whereas severe AS was observed in 6–13% of the subjects undergoing haemodialysis (HD) [3, 5–14]. This prevalence is significantly higher than findings in the general population, where aortic sclerosis is observed in about 25% of people over 65 years of age and severe AS is found in about 3% of the subjects over 75 years of age [15]. While most of the researchers were concordant about the importance of aging and duration of dialysis in predicting the prevalence of aortic valve disease, the association with increased calcium and Pi levels has been documented only in a few cases [3]. Nevertheless, the studies agreed about the absence of an association between lipid disorders and the presence of AS in ESRD patients, while some investigations showed a correlation between valve disease and inflammatory markers. In particular, a significant increase in C-reactive protein (CRP) plasma levels was observed in a group of dialysed patients with haemodynamically significant AS, while no differences were observed between patients with sclerotic versus normal valve [10]. Another investigation conducted in 137 patients on continuous ambulatory peritoneal dialysis (PD) showed that increased levels of CRP, fibrinogen and lower albumin levels, together with hyperphosphatemia and

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Age</th>
<th>Time on dialysis (months)</th>
<th>Aortic valve abnormalities (%)</th>
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<tr>
<td>Maher et al. [3]</td>
<td>87</td>
<td>35–70</td>
<td>7.5 (0.5–19)</td>
<td>28</td>
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<tr>
<td>Straumann et al. [5]</td>
<td>62</td>
<td>55.2 ± 13.5</td>
<td>50.4 ± 46.1</td>
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<tr>
<td>Braun et al. [6]</td>
<td>49</td>
<td>55 ± 11</td>
<td>77 ± 70</td>
<td>55</td>
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<td>Ribeiro et al. [7]</td>
<td>92</td>
<td>60 ± 16</td>
<td>53 ± 46</td>
<td>52</td>
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<tr>
<td>Ventura et al. [8]</td>
<td>135</td>
<td>58 ± 17</td>
<td>80 ± 49</td>
<td>78</td>
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<td>Raggi et al. [9]</td>
<td>205</td>
<td>56.8 ± 14.9</td>
<td>36.8 (17.1–62.5)</td>
<td>34</td>
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<tr>
<td>Schönenerberger et al. [10]</td>
<td>55</td>
<td>60.3 ± 12.8</td>
<td>45 ± 34.9</td>
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<td>Tarras et al. [12]</td>
<td>90</td>
<td>45.6 ± 13.6</td>
<td>117.4 ± 50.3</td>
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<tr>
<td>Holden et al. [13]</td>
<td>108</td>
<td>63.2 ± 14.7</td>
<td>47.3 ± 44.4</td>
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<td>Ikee et al. [14]</td>
<td>112</td>
<td>67 ± 10</td>
<td>95 ± 67</td>
<td>75</td>
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*aAccording to the different studies includes aortic valve calcification, sclerosis and critical aortic stenosis.

*bYears.

*Aggregate time (years).
increase parathyroid hormone levels, were associated with increased calcification of both mitral and aortic valves [16].

Only a few studies have specifically investigated the prevalence of aortic valve calcification in non-dialysed patients with moderated kidney disease. In the Framingham Offspring study cohort, valvular calcification was more prevalent among individuals with advanced CKD. However, this association was significant only for mitral calcification (MAC), while aortic calcification was not increased in pre-dialysis CKD patients [17]. This intriguing observation was confirmed in a cohort of 67 subjects from the multi-ethnic study of atherosclerosis study [18], where in models adjusted for age, sex and race/ethnicity, reduction of kidney function was associated only marginally with AS. On the contrary, association of MAC with each measure of kidney function remained significant also in multivariable adjusted models, yet limited to diabetic subjects [18].

Data are available suggesting that ESRD patients suffer accelerated progression of calcific AS [4]. In a retrospective study of 110 HD patients, a 3.3% per year incidence of new cases of AS was observed after a 7-year follow-up [19]. Significant predictors for AS development were age, Pi levels, calcium × Pi product and vitamin D levels. The annual decrease in aortic valve area was 0.23 cm², even if a large individual variability was observed among patients [19]. A similar rate of annual change in valve area (~0.19 cm²/year) has been described in another group of HD patients [20]. Patients with faster progression of AS were older and showed a close-to-statistical significance higher Pi level (P = 0.09) [20]. Additional confirmation that AS is an accelerated process in ESRD was obtained in the same population after demonstration that within a time frame by which all ESRD patients had either undergone valve replacement or died, one-third of the control cohort remained free of either of these end points [4]. Of interest, the presence itself of calcium deposits within valve leaflet is able to predict the rapidity of AS progression. In fact, in a cohort of 55 HD patients followed for 1 year, it has been observed that progression of maximum aortic jet velocity and regression of aortic valve area were more rapid among patients with valve calcification than in those without calcium deposits [21].

It is well-known that in the general population, that aortic valve abnormalities are accompanied by detrimental effects on left ventricular (LV) remodelling, including the development of LV hypertrophy (LVH) [22]. Similar findings have been described in HD patients where the presence of aortic valve sclerosis, and calcification have been associated with a significant increase in LV mass and prevalence of LVH [8, 23], which are both recognized as strong predictors of CV mortality in HD subjects [24]. A number of studies specifically investigated the clinical predictive power of valve calcification on presence of CAD and the risk of future CV mortality. In particular, the presence of aortic valve calcification has been associated in HD patients with increased prevalence of CAD [11], coronary artery calcification [6, 25] and higher risk of atrial fibrillation [25, 26] and restenosis after placement of drug-eluting stents [28]. After a follow-up of 3.5 ± 3 years of 137 long-term HD patients, it was also observed that the presence of calcific aortic valve is accompanied by increased risk of all-cause mortality [11]. Similar findings were observed in a population of ambulatory PD patients followed-up for a mean of 17.9 months [29]. In this group of 192 patients, the presence of cardiac valve calcification was associated with all-cause and CV mortality independently from age, male gender, duration of dialysis, diabetes, the presence of atherosclerotic vascular disease and CRP levels [29]. The predictive power of heart valve calcification for all-cause and CV mortality was also confirmed in a cohort of 202 HD patients followed-up for an average of 44 ± 23 months, although this association was no longer present after adjustment for several confounders (including background CV complications, LVH and inflammatory markers) [30]. More recently Raggi et al. confirmed these data showing that the presence of valvular calcification was associated with all-cause mortality over 5 years of follow-up of 144 dialysis patients. However, only MAC maintained a predictive power after adjustment for age, gender, race, diabetes and CV history [31]. Another study conducted in 1290 HD patients followed up to 10 years showed that the risk of CV mortality was significantly increased in patients with two calcified valves and that the worse prognosis was observed among those having the highest CRP levels [32].

MECHANISMS OF AORTIC VALVE CALCIFICATION IN CKD

Histopathological analyses of aortic valve tissues, animal models studies, and in vitro data obtained from interstitial valve cells (VIC) cultures, suggested that ‘active’, cell-mediated processes can be of pathophysiological relevance for calcium deposition within valve leaflets [33]. The early stage of valve disease commonly starts on the aortic side of the leaflet and extends to the fibrosa/spongiosa layers [34]. This initial stage is described as a subendothelial thickening and is characterized by accumulation of modified/oxidized lipoproteins (oxLDL) [including Lp (a)], inflammatory cells (macrophages, lymphocytes, mast cells) and formation of calcified microscopic foci [22, 34]. Inflammatory cells are usually located near the surface of the lesion, while initial foci of calcification are deeper [34]. As described for atherogenesis, lipids infiltration beneath the lamina elastica and valvular endothelial cells damage/dysfunction represent initiating events of valve disease, which are followed by recruitment/migration of inflammatory cells within the leaflet [35]. In the advanced stages of aortic valve degeneration, calcium deposits can be identified in the form of different combination of calcium-Pi, including hydroxyapatite (HA), the form of mineral present in the bone. In addition, up to 13% of advanced calcified valves contain lamellar or endochondral bone tissue including, in some cases, haematoxyphilic marrow [36]. Moreover, several histological and gene expression analyses demonstrated the expression in the pathological valve of bone-related proteins, such as alkaline phosphatase (ALP), osteopontin (OPN), osteoclast (OC), bone morphogenic proteins (BMPs) and Runx2/Cbfal [22, 35, 36]. On the whole, these data suggest that active biological processes, resembling those happening during bone formation, can be involved in calcium accumulation inside the aortic valve. In particular VIC, stimulated with oxLDL,
Valve disease progression are known to be elevated/modi
called renal function decline and increased circulating levels of Pi are
potential involvement of these factors during the aortic valve
and neo-vasculogenesis [37].

As a matter of fact, some mediators implicated in aortic
valve disease progression are known to be elevated/modified
during kidney function decline. We will now focus on the
potential involvement of these factors during the aortic valve
degeneration associated with ESRD (Figure 1).

**Phosphate**

Studies on animal models of CKD clearly demonstrated that
renal function decline and increased circulating levels of Pi are
accompanied by appearance of ectopic calcification within the
arterial wall [2, 38, 39]. Some of these studies also reported signi-
nificant calcium deposition occurring within the valve appar-
atus. In particular, by using a model of adenine-induce renal
failure Shuvy et al. demonstrated that rats fed with a high Pi-
diet underwent significant calcification of the aortic valve, a
process characterized by development of cartilaginous meta-
plasia, increased expression of bone-related mediators (such as
OPN, OC, Runx2, RANKL) and recruitment of inflammatory
cells [38]. These changes were not observed in uraemic rats fed
with normal Pi diet. Aikawa et al. also demonstrated that the
expression of Cathepsin S and the release of elastin fragments
are of great relevance for vascular and valve calcification associ-
ated with renal function decline. Of note, these calcific phenomen-
a are amplified by using diet enriched in Pi [39].

In vitro studies with vascular smooth muscle cells (VSMC)
clearly demonstrated that Pi supplementation promotes matrix mineralization by the cells [40]. Similar findings have
been reported by VIC challenged with high-Pi conditions [41,
42]. In particular, Pi levels could be sensed by the cells
through the PiT-1 transporter that is in fact overexpressed
within human calcified valves and is able to drive Pi-driven
differentiation of human VIC towards an osteoblast-like profile [42]. We also observed that high Pi induces matrix
mineralization by VIC, and this is significantly amplified by
treatment of the cells with pro-inflammatory mediators, such
as endotoxin [41]. Hyperphosphatemia is also able to activate
apoptotic pathways in VIC, maybe through the mitochondrial
pathway and down-regulation of Akt-1 [42]. In fact, blockade
of Pi-induced VIC apoptotic cell death is accompanied by sig-
ificant reduction of calcium deposition. This possibility is in
line with a series of data showing increased apoptotic cell
death within the arterial wall of CKD animal models as well as
ESRD subjects [2].

**Matrix-GLA-protein**

Matrix-GLA-protein (MGP) is a γ-carboxylated protein ex-
pressed in cartilage, lung, heart, kidney and arteries that act as
an inhibitor of soft-tissue calcification [43]. Generation of bio-
logical active MGP depends on its γ-carboxylation and in fact
under-carboxylated MGP (ucMGP) has been shown to be less
effective than carboxylated MGP (cMGP) in preventing
calcium deposition [43]. This process, which happens locally
within the arterial wall, is vitamin K (VitK) dependent. Inter-
estingly, calcified arteries obtained from dialysed patients
demonstrated a significant decrease of the cMGP /ucMGP ratio
[44]. This relative increase of MGP with reduced anti-calci-
fic properties can be due to local dysfunction/apoptosis of vascu-
lar cells and/or systemic factors related to the uraemic milieu,
such as VitK deficiency. In fact, a number of clinical investi-
gations underscored a high prevalence of subclinical VitK
deficiency among both dialysed patients and subjects with
earlier stages of CKD [45]. The discovery of this biological
fundamental step for MGP anti-calci fic activity also raised
some issues about possible pro-calci fic effects of warfarin, a
well-known inhibitor of γ-carboxylation. In agreement with
this possibility, Holden et al. observed, in series of 108 dialysed
patients, that the long term use of warfarin was associated with
increased severity of aortic valve calcification [13]. This obser-
vation is in line with other retrospective studies in the general
population which demonstrated an increased risk of AS and
MAC in patients with atrial fibrillation assuming warfarin

![Figure 1](https://academic.oup.com/ndt/article-abstract/28/12/2968/1832832)

**FIGURE 1:** Pathways potentially involved in aortic valve calcific degeneration associated with CKD. Hyperphosphatemia, reactive oxygen
species production (ROS), increased asymmetric dimethyl arginine (ADMA), and augmented expression of RANKL could act as promoters of
calcific valve degeneration associated with advanced stages of CKD. In this clinical context, calcification could be also favoured by reduced circu-
lating levels of fetuin-A and valvular production/activation of matrix-Gla protein (MGP).
Unfortunately, information about the expression and metabolism of MGP within the normal/pathological aortic valve are limited. Further studies are needed to clarify these aspects and to delineate possible treatment strategies (such as VitK supplementation).

FGF-23/klotho axis

Fibroblast growth factor-23 (FGF-23) is a phosphaturic hormone produced in the bone which controls Pi excretion while Klotho is a protein responsible for the FGF-23 kidney-specific action. FGF-23 also controls vitamin D metabolism by reducing the circulating levels of its activated form [47]. Elevated FGF-23 plasma levels have been linked to the presence of vascular damage and increased risk of CV mortality among both dialysed patients [48] and subjects with normal kidney function [47]. Increased FGF-23 and reduced Klotho have also been associated with the extent of vascular calcification in CKD patients [49, 50]. Moreover, two recent studies showed that FGF-23 serum levels are increased among CKD/HD subjects with presence of aortic valve calcification [51, 52].

It is still unclear whether FGF-23 or Klotho might exert a direct effect on valve/vascular cell phenotype and/or modulate their transition towards osteogenic cells. Some evidence suggested that FGF-23 has no effect on Pi uptake or Pi-induced calcification by VSMC, even in the presence of soluble Klotho [53]. These findings are in agreement with another report showing that the FGF-23/Klotho signalling is absent in mouse arteries and that FGF-23 treatment did not modify calcification by VSMC [54]. Other studies suggest instead that Klotho is expressed by arterial cells and that CKD is associated with reduced expression of Klotho within the vascular wall [55]. Moreover, it has also been shown that Klotho could act as a calcification inhibitor and exerts its effects independently from its role as FGF-23 co-receptor. In fact, vascular deficiency of Klotho could promote calcification by increasing PiT-1-dependent Pi uptake by vascular cells, and treatment with Klotho was able to suppress Pi-driven VSMC differentiation into osteoblast-like cells [56]. Discrepancies about FGF-23/Klotho expression and function in vascular cells are difficult to interpret and might be explained by the different cell culture conditions and animal models. Nevertheless, data collected from mouse studies recognized the presence of hyperphosphatemia rather than FGF-23 levels as the major factor driving vascular calcification [47]. To date, no data are available about a potential role of FGF-23/Klotho axis in controlling VIC phenotype during aortic valve disease progression.

Fetuin-A

Fetuin-A is an inhibitor of calcium precipitation, which circulates in the blood in a complex with minerals forming the so-called calciproteins particle (CPP or fetuin-A mineral complexes, FMC) [57]. Reduced levels of fetuin-A have been associated with both increased prevalence of vascular calcification and mortality in subjects with CKD [58]. Some clinical data are also available about the association between fetuin-A and aortic valve calcification. In particular, a follow-up study performed in 238 patients undergoing PD showed that patients belonging to the lowest tertile of serum fetuin-A levels displayed the greater prevalence of valvular calcification and the higher risk of CV mortality [59]. An inverse relationship between fetuin-A and the presence of AS has been described among patients with normal kidney function [60], and low serum fetuin-A levels have also been linked to accelerated valve disease progression independently from renal function [61]. On these bases, fetuin-A metabolism and its relationship with circulating minerals is an increasing topic of interest in the context of vascular calcification. However, the physiological role/metabolism of the circulating CPP is still unclear. It has been postulated that fetuin-A can buffer the excess of circulating minerals and mediates their clearance in the form of CPP. The latter could be formed mainly during bone remodeling and removed from the circulation by the reticuloendothelial system cells through scavenger-A receptor [57]. More recently, using a sequential ultracentrifugation approach that estimates the presence of CPP/FMC, and not only fetuin-A levels, it has been shown that the calcific particles are increased in the bloodstream of CKD patients and that their levels are directly correlated with the presence of vascular calcification [62]. Additional studies about the clinical impact of CPP in different pathological conditions, including aortic valve calcification, might offer the opportunity to deepen our knowledge about the metabolism of these complexes and their utility as a therapeutic target.

Reactive oxygen species and ADMA

Vascular production of ROS is increased in CKD patients and is considered a major contributor to accelerated atherogenesis [1]. More recently, ROS have also been proposed as critical mediators of calcium deposition within valve apparatus. In fact, it has been shown that ROS generation is increased in human stenotic valve while antioxidant mechanisms (such as superoxide dismutase and catalase) are reduced within pathological valves [63]. Of interest, nitric oxide synthase (NOS) uncoupling can also contribute to ROS generation within the calcific leaflets [63]. Nevertheless, mechanisms whereby ROS enhance valve calcification are still poorly understood. A series of studies suggested that ROS can promote the expression of bone-related factors, such as BMP-2, ALP as well as Runx2/Cbfa-1, in vascular cells thus favouring the cellular transition towards an osteoblast-like profile [33]. Whether increased ROS generation by VIC is implicated in accelerated valve calcification during kidney function decline is currently unknown and deserves further investigation.

A number of clinical studies have shown that asymmetric dimethylarginine (ADMA) levels are increased in CKD patients and are strong predictors of future CV mortality [64]. ADMA is a well-known competitor of L-Arginine for NOS activity and reduces NO production [65]. We recently observed that VIC acquiring a calcifying profile shows reduced expression of DDAH -1 and -2, the enzymes that reduce ADMA intracellular levels [66]. It is known that in case of increased ADMA generation and decreased intracellular antioxidant defence, NOS may undergo enzymatic uncoupling, leading to reduced NO production and further increase in ROS release. So far, three clinical studies have been performed to investigate the link between ADMA levels and the
prevalence of calcific valve degeneration. Two of these investigations reported an association between ADMA circulating levels and the presence of aortic valve calcification [67, 68], while another study was not able to confirm these findings [69]. However, none of these studies specifically investigated the association between ADMA, decline of kidney function and the progression of valve disease.

**OPY/RANKL/RANKL triad**

In the bone, the RANKL (expressed by osteoblast)/RANK (expressed by monocytes) interaction promotes the complete development of multinucleated bone-resorptive osteoclasts. OPG acting as a decoy receptor and interacting with RANKL inhibits osteoclast’s differentiation and activation. Imbalances in the RANKL/OPG ratio and its effect on RANK signalling appear to underlie the pathology of bone diseases characterized by bone loss, such as osteoporosis [70]. Interestingly, mice deficient in OPG showed both the presence of osteoporosis and vascular medial calcification. This evidence has been confirmed in the setting of atherosclerosis by Bennett et al., showing that the OPG deficiency in ApoE double KO mice is associated with higher calcium deposition within the vasculature in comparison with the ApoE−/− control mice [71]. How OPG exerts its protective effects on calcium deposition within the arterial wall is not yet defined, albeit part of this could be due to the block of detrimental RANKL activities. In fact, the latter has been shown to promote the acquisition of an osteogenic phenotype both in vascular and valve cells [72, 73].

Studies conducted by measuring OPG and RANKL circulating levels in CKD and HD have, so far, yielded conflicting results. Nevertheless, most of the studies concur that OPG levels are elevated in HD patients and are directly correlated with the presence of vascular disease and the risk of CV mortality [74]. Conversely, data obtained with RANKL have, so far, been contradictory, with studies in CKD patients showing either increased [75] or identical [76] protein serum levels compared with controls. Some investigations showed that calcium deposition within the valve leaflets is associated with reduced OPG expression and increase RANKL production [72]. Whether these changes in OPG/RANKL ratio are amplified in CKD subjects is currently unknown. In line with this possibility, it has been demonstrated that uraemic rats placed on a high-Pi diet showed increased calcium deposition within valve leaflets together with higher expression of several osteoblast-like markers, including RANKL [38].

**THERAPEUTIC PERSPECTIVES**

To date, no effective medical treatment is available to either slow or prevent calcium accumulation within vascular and valve tissue. Data demonstrating lipids accumulation within the calcific valves offered the rationale for testing hypcholesterolemic drugs as a therapeutic strategy for slowing valve degeneration. However, the SEAS trial failed to show a significant effect of treatment with simvastatin + ezetimibe in preventing the valve disease progression [77]. The lack of efficacy of the lipid lowering strategy suggests that once mineral deposition in the leaflet is initiated, the calcium accrual might occur independently from further cholesterol accumulation in the valve. Efficacy of ACE-inhibitors on valve calcific degeneration has been investigated in animal studies, which showed some promising effects [78]. However, findings from large retrospective studies have been contradictory showing both protective and neutral effects ACE-inhibitors on the progression of calcific valve degeneration [79, 80]. Nevertheless, the use of ACE-inhibitors and sartans has been proven to increase survival and to reduce CV events among patients with AS, probably through a positive effect on ventricular remodelling [81]. Some observational, small-size studies also suggested that the use of bisphosphonates, the treatment of choice for osteoporosis, might carry some protective effects on aortic valve calcification. However, a recent retrospective analysis of 801 older females with a mean follow-up of 5.1 ± 2.4 years, showed that there were no differences in the progression of aortic valve disease based on the use of bisphosphonates [82].

Thus, it appears that innovative therapeutic strategies for the treatment of vascular/valve calcification are needed and could be based on some of the pathophysiological mechanisms listed above. A very simple strategy, which is worthwhile to be tested, is the use of VitK supplementation. As mentioned above, VitK is important for the anti-calcific effects of MGP [43], and several studies have shown that dietary VitK intake is compromised in CKD patients [45]. Thus, intervention trials testing the efficacy of VitK supplementation in the prevention of vascular/valve calcification carry both clinical and pathophysiologic valid background. Hyposphaturic strategies have shown some potentiality in preventing vascular calcification, although the clinical studies yielded conflicting results. Early intervention studies comparing sevelamer with calcium-based phosphorus binders showed that MAC, and combined mitral + aortic valve calcification were less in sevelamer-treated than in calcium-treated subjects, although the difference was not significant [83]. More recently, the ADVANCE study showed that compared with flexible doses of vitamin D, treatment for 52 weeks with Cinacalcet plus low-dose vitamin D was accompanied by significant reduction in calcium deposition within aortic valve leaflets [84]. In particular, the authors observed that the median difference between treatment groups in percentage change of Agatston score for the aortic valve was −44.7% [95% confidence interval (CI) −85.8%, −61.6%] in favour of the Cinacalcet group. Nevertheless, recent findings of the EVOLVE study demonstrated that treatment with Cinacalcet for up to 5 years did not significantly reduce the risk of death or major CV events in patients with moderate-to-severe secondary hyperparathyroidism undergoing HD. These data raised some doubts about the efficacy of vascular calcification blockade in reducing CV mortality. However, it should be underlined that so far, the EVOLVE trial did not furnish information about the effects of the treatment on progression of vascular/valvular calcification in the population under investigation. Interventional strategies based on FGF-23/Klotho levels have, so far, not been conducted and might represent an interesting option to be tested in future human studies. Denosumab, a monoclonal antibody anti-RANKL also used for the treatment of osteoporosis might...
harbour potential anti-calcific effects [85]. However, before testing this drug on such clinical ground, additional studies would be needed to clarify whether overexpression of RANKL is indeed causally associated with aortic valve degeneration in CKD patients.

There are not enough data to recommend that HD patients with aortic valve calcification should be screened and treated differently from what is currently indicated for the general population in the guidelines for valvular heart disease management [86]. Nevertheless, we believe that the clinical evidence summarized above and showing a high prevalence of aortic valve abnormalities among dialysed subjects suggests that every HD patient should undergo baseline echocardiographic evaluation of the valvular apparatus. In addition, as calcific degeneration is accelerated in this group of patients [4], we propose that dialysed subjects harbouring moderate-severe AS should undergo echocardiographic evaluation at least every 6 months, while patients with mild AS should be re-evaluated yearly (especially those with significant calcification).

As for treatment management, both surgical valve replacement and transcatheter aortic valve implantation (TAVI) have been shown to be feasible in HD subjects [87, 88]. Retrospective data about the outcome of HD patients undergoing surgical valve replacement suggest that these subjects can be treated just like non-dialysis patients [89]. In addition, although early reports raised some concerns about the use of bioprosthetic valves, following investigations provided evidence that tissue valves can be safely used in dialysed patients and that prosthesis selection should be made on individual basis [88]. TAVI is an emerging therapeutic option for patients at high risk for cardiac surgery, and only few studies have, so far, been conducted using this approach in dialysed patients. Nevertheless, the data available suggest that the endovascular approach is a safe procedure in patients on chronic HD and that dialytic treatment should not represent a contraindication for TAVI [87]. However, further clinical studies are needed to confirm these preliminary data.

CONCLUSIONS

Mechanisms of aortic valve calcification have recently become more elucidated and several of the pathways identified could be amplified in patients with decreased renal function. Of note, MGP metabolism, OPG/RANK/RANKL triad, fetuin-A mineral complexes and FGF-23/Klotho axis represent novel fields of investigation for the development of innovative therapeutic strategies. In fact, identification of treatments that are able to prevent/reduce calcium accumulation within valve leaflets may represent a priority for achieving a significant reduction in the CV risk of CKD patients.

CONFLICT OF INTEREST STATEMENT

The present paper has not been published previously in whole or part and is not under consideration in other journals. There are no conflict of interests.

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