

Vascular calcification: When should we interfere in chronic kidney disease patients and how?

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Abstract

Chronic kidney disease (CKD) patients are endangered with the highest mortality rate compared to other chronic diseases. Cardiovascular events account for up to 60% of the fatalities. Cardiovascular calcifications affect most of the CKD patients. Most of this calcification is related to disturbed renal phosphate handling. Fibroblast growth factor 23 and klotho deficiency were incriminated in the pathogenesis of vascular calcification through different mechanisms including their effects on endothelium and arterial wall smooth muscle cells. In addition, deficient klotho gene expression, a constant feature of CKD, promotes vascular pathology and shares in progression of the CKD. The role of gut in the etio-pathogenesis of systemic inflammation and vascular calcification is a newly discovered mechanism. This review will cover the medical history, prevalence, pathogenesis, clinical relevance, different tools used to diagnose, the ideal timing to prevent or to withhold the progression of vascular calcification and the different medications and medical procedures that can help to prolong the survival of CKD patients.

Key words: Chronic kidney disease; Uremia; Calcification; Sevelamer; Calcific uremic arteriopathy; Fibroblast growth factor 23; Klotho; Phosphate binders; Kidney transplantation

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Core tip: The last 2 decades witnessed the failure of all intervention studies targeting different risk factors of vascular calcification in chronic kidney disease (CKD) patients on regular hemodialysis. The main aim of all these studies was to decrease cardiovascular morbidity and mortality among such patients. These disappointing results criticized the value of such interventions in clinical practice. On the other hand, when similar trials were run on patients at an earlier stage of CKD, most of these

trials showed a significant impact on patient survival and/or cardiovascular morbidity. Such discrepancy indicates the value of timing of interference. We are trying in this review to develop the ideal strategy that would optimize the management of CKD patients to avoid the devastating vascular calcification, highlighting the value of different medicines used in this plan. Meanwhile we are showing the update in guidelines concerned with this issue.

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INTRODUCTION

Vascular calcification (VC) affects either the arterial tree or cardiac valves. Deposits of hydroxyapatite in the arterial wall occur within either tunica intima or tunica media. VC is a strong predictor of increased cardiovascular mortality among chronic kidney disease (CKD) patients. However, the different clinical studies that tried to manipulate the different risk factors of VC in dialysis patients failed to show a significant impact on patient survival. On the other hand, when pre-dialysis patients underwent similar studies, there was a significant decrease of cardiovascular and overall mortality rates, beside a comparable effect on vascular calcification progress rate. These results have probably two explanations. Dialysis patients might have advanced VC rendering their arteries permanently and irreversibly damaged [approaching end stage arterial damage (ESAD^[1])] or they might have additional pathologic problems exceeding in their survival impact the VC. The authors of this review are inclined towards the 1st possibility and will try to outline the best way to tackle this devastating pathology.

HISTORY

In 1855, "metastatic calcification" was described in three patients with renal disease^[2]. Eight years later, Virchow^[3] reported that this calcification is a definite ossification.

The first reported VC in infants was probably that of Durante^[4] describing aortic and pulmonary artery calcification. Calcification of peripheral vessels has been described in a few children with CKD as early as 1942^[5,6].

VC affected humans in ancient history. The most ancient calcification so far reported is 5000 years ago, "identified in the recently discovered ice man"^[7]. On the other hand, the earliest coronary calcification reported is that of an Egyptian mummy who was living 4000 years ago^[8].

VC IN CKD PATIENTS

A high percentage of CKD patients show VC. The prevalence among predialysis CKD G3-5 patients was 79% of cases in one study^[9]. It might approach 100% in patients starting dialysis^[10]. VC significantly contributes to morbidity and mortality of CKD^[11-13]. Up to 3- to 4-fold increase in VC has been reported in the earliest phases of CKD^[14].

CKD patients show VC in almost all arteries whether large, medium or small-sized vessels, including the coronary arteries^[10,15-17]. VC can affect the tunica intima and/or the tunica media of the arterial wall^[18]. Intimal calcification is mainly a feature of atherosclerosis^[19]. CKD patients can have intimal and medial calcification. Medial calcification is reported in CKD of any age^[20,21]. When epigastric arteries of patients with end-stage renal disease (ESRD) were examined at the time of kidney transplantation, vessel calcification was detected regardless of patient age and/or the presence of other risk factors for atherosclerosis^[22]. In one study, hemodialysis (HD) patients have higher calcification scores than either peritoneal dialysis (PD) or CKD G4. More heavily calcified patients were significantly older and mostly male^[23]. In HD patients, coronary calcification progresses steadily^[24]. High serum phosphate concentration was a strong independent risk factor only in non-diabetic patients. Diabetic patients lack similar association^[25].

Fifty percent of CKD patients die out of cardiovascular events^[26]. Cardiovascular mortality is 20- to 30-times of controls matching in age, race and gender^[27]. Patients starting dialysis at age of 25-29 years have a median life expectancy of 18.5 years. This means that their survival is 33 years less than normal personnel^[28]. Arterial calcification is one of the predictors of this increased cardiovascular mortality^[28]. Patients with CKD should, therefore, receive aggressive preventive measures to reduce this cardiovascular disaster^[29].

Coronary artery calcification (CAC) is common among CKD patients whether adolescents, adults or old aged, starting in early stages of CKD and steadily progressing in HD patients^[30-32]. Postmortem study of atheromatous lesions in ESRD patients found more intense calcification of such lesions compared to age- and sex- matched controls^[33].

Calcification of the internal iliac arteries in CKD patients was greater compared with controls^[34].

Large vessel disease is associated with decreased arterial compliance as detected by ultrasound and accounts for the increased mortality^[35,36].

Calcific uremic arteriolopathy (CUA), also called calciphylaxis is an obliterative vasculopathy affecting cutaneous arterioles. It occurs almost exclusively in ESRD patients. Affected arterioles show medial calcification^[37]. Ischemia and necrosis of the skin, subcutaneous fat, visceral organs and skeletal muscles eventually ensues. The skin



Figure 1 Male patient, 36-year-old, on regular hemodialysis for 8 years, presenting with multiple skin ulcers affecting both legs. A: His corrected serum calcium is 10.28 mg/dL and serum phosphorus 8 mg/dL. Serum PTH is 2588 pg/mL. He initially experienced itching papules that eventually ulcerated; B: Another ulcer with necrotic floor in the same patient. PTH: Parathyroid hormone.

manifests by necrotic foci and painful ulcers (Figure 1)^[38].

VC IN KIDNEY TRANSPLANT RECIPIENTS

Death with a functioning graft is one of the major causes of graft loss (accounting for 42% of graft loss) in kidney transplant recipients (KTRs). Cardiovascular events are the first cause of death in this population affecting 36% to 55% of patients. The impact of VC on morbidity and mortality of KTRs is not appreciated enough^[39-41]. Three point five percent to five percent of KTRs experience fatal or non-fatal cardiovascular events annually. This rate is much higher than in the general population. The prevalence of coronary artery calcification (CAC) in KTRs is higher (61%-75%) than that assessed in stage 3 CKD^[42-44] and lower than that found in HD patients^[45]. Moe *et al.*^[37] did not observe CAC progression after a successful kidney transplant. On the other hand, Oschatz *et al.*^[46] observed a significant progression within the first 6 mo, but no significant change between months 6 and 12 after a kidney transplant. All these trials were short term. When longer-term follow-up trials were performed, kidney transplant was found to favorably affects but does not halt CAC progression, with an annual rate of CAC progression ranging between 11% and 12.5%^[47-49]. The risk of progression was higher in Caucasian race, with increased body mass index, higher baseline CAC score, higher diastolic blood pressure and lower glomerular filtration rate 3 mo after transplantation^[50]. Other risk factors included inflammation, hyperparathyroidism and dialysis duration^[47,51,52]. CAC score was significantly lower in KTR who had a pre-emptive transplant in comparison to those who underwent dialysis before transplantation (3.7 vs 102.9, $P < 0.001$)^[52]. According to these studies, it seems that pre-emptive kidney transplant gives ESRD patients their best chance to avoid progressive VC.

PATHOGENESIS OF VC

Many factors summate the pathogenesis of VC in CKD. Such factors are either traditional or CKD related. The factors related to CKD include high serum calcium

and phosphorus, increased dialysis vintage, increased duration of uremia^[53], low serum fetuin-A level^[53], and high serum level of fibroblast growth factor 23 (FGF23)^[10,54-63]. Dialysis vintage, disturbed mineral metabolism and FGF23 are the most relevant factors having impact in the VC of CKD^[37]. There is an association between VC and indices of low bone turnover in dialysis patients^[64].

Is VC an active process?

More than 150 years ago, Virchow^[2] was the first to report that vascular calcium deposits were real ossification. In CUA, vascular smooth muscle cells express osteopontin, bone sialoprotein, and osteonectin^[37,65]. In non-calcified arteries in the same skin biopsy section, osteopontin or other bone proteins were not observed^[65]. It seems that the deposition of these proteins predispose calcification^[37,66].

Role of phosphorus

Vascular smooth muscle cells and osteoblasts originate from the same mesenchymal cell. Core binding factor α -1 (Cbfa1) turns the mesenchymal cell into osteoblast^[37,67]. β -glycerophosphate is a phosphate donor. Vascular smooth muscle cells mineralize in the presence of this phosphate donor and increased Cbfa1 activation^[37,68]. Calcific arterial lesions in patients devoid of CKD showed increased expression of Cbfa1 while normal arteries failed to show similar finding^[37,69]. The findings of Cbfa1 in both CKD vascular lesions and non-CKD arterial disease might denote a common pathogenesis of VC. A significant relationship between increased serum phosphorus and obstructive atherosclerotic coronary artery disease was observed in non-CKD patients^[37,70,71].

Bone morphogenetic protein-2

When bovine vascular smooth muscle cells (BVSMCs) were incubated in uremic serum and healthy control serum, upregulation of Cbfa1 was significantly higher with uremic serum. When β -glycerophosphate was added to increase the inorganic phosphorus within culture media, Cbfa1 significantly increased in normal control serum culture and

the significant difference in Cbfa1 was muffled^[72]. This increase in Cbfa1 was completely inhibited after addition of foscarnet (an inhibitor of sodium/phosphate co-transport) to the normal serum. In case of uremic serum, inhibition was partial, denoting other factors might have an action on Cbfa1 beside hyperphosphatemia^[37]. Bone morphogenic protein-2 (BMP-2) concentration is doubled in CKD serum. BMP-2 was detected in human calcified arteries^[37,73-75] and human uremic serum can induce *in vitro* calcification that increases as the CKD advances^[37,76].

Fibroblast growth factor 23 - klotho axis

Fibroblast growth factor 23 (FGF23) was isolated 16 years ago^[77]. FGF23 is responsible for autosomal dominant hypophosphataemic rickets (ADHR) in humans^[78] and is the humoral factor secreted by tumors inducing hypophosphatemia and osteomalacia (TIO)^[79]. FGF23 plays an important role in the regulation of serum phosphate level. FGF23 is secreted by osteocytes in bone^[80]. Other sites might share in FGF23 synthesis, including bone marrow, thalamus, lymph nodes and thymus^[81]. The serum levels of FGF23 are derived mainly from bone^[82]. FGF23 exerts its hypophosphatemic effect through inhibition of phosphate reabsorption by proximal tubular epithelial cells. It down-regulates the luminal sodium-phosphate co-transporters. FGF23 also inhibits 1 α hydroxylase^[83]. It was not clear if FGF23 stimulates secretion of parathyroid hormone (PTH)^[82] or PTH stimulates FGF23 secretion. Klotho acts as a co-receptor for FGF23 by markedly increasing the affinity of FGF23 for ubiquitous FGF receptors (FGFR)^[84]. Klotho, is highly expressed in the kidney and the parathyroid glands^[84,85].

Klotho is an anti-senescence protein^[86]. It exists in 2 forms: The transmembrane and the soluble secreted form^[87,88]. Klotho is detected as soluble protein in body fluids including blood, urine^[89-91] and cerebrospinal fluid^[89].

The highest expression of Klotho is in kidney and brain^[86,90,91], but it is also expressed in parathyroid gland^[92,93] and heart^[94] with less abundance.

The similarity of the phenotypes between *Kl*^{-/-} mice^[86] and *Fgf23*^{-/-} mice is striking^[95], which strongly suggests a common signaling pathway shared by these molecules^[96,97]. Now it is well documented that membrane Klotho functions as the coreceptor for FGF23, which amplifies and confers specificity of FGF23 action^[84,85,98,99].

In contrast, soluble Klotho protein functions independently of FGF23^[91] and plays an important role in modulation of ion transporters or channels^[91,100], antioxidation^[101] and anti senescence^[102,103], in addition to simply supporting FGF23 action^[104]. The protective effect of Klotho against soft tissue calcification is mediated by at least 3 mechanisms: Increasing urine phosphate excretion, renal protection and inhibition of phosphate uptake by vascular smooth muscle cells (VSMCs) and their dedifferentiation^[104].

Klotho and FGF23 are likely responsible for calcium and phosphate homeostasis^[105,106]. *In vitro* PTH secretion

and mRNA transcription are inhibited by FGF23^[107]. On the contrary, primary hyperparathyroidism in rodents is associated with increased FGF23 levels that are reduced by parathyroidectomy. PTH stimulates osteocytes to secrete FGF23^[108]. In physiological settings in which there are normal Klotho and FGFR expression, FGF23 decreases PTH production, increases expression of both the parathyroid Ca-sensing receptor and the vitamin D receptor, and decreases cell proliferation^[92].

In Klotho mutant mice, the different pathologic manifestations could be reversed when deficient Klotho is replaced^[109-111]. Exogenous klotho was found to ameliorate kidney injury and renal fibrosis in a rat model of CKD^[112]. It can also ameliorate endothelial cell senescence and muffles the binding of NF κ B to nuclear DNA^[113].

Patients with stages 3b-5 CKD and dialysis patients often develop high serum FGF23^[114]. This elevation can even occur as early as stage 2 CKD, long before any changes in calcium, phosphate, or PTH are apparent^[115]. Elevation in FGF23 stimulates the excretion of phosphorus by surviving nephrons. This would prevent the early onset of hyperphosphatemia in spite of increased bone turnover and the progressive decline in functioning nephrons. Development of CKD is associated with significant decline of Klotho mRNA expression^[116]. This deficiency might explain the increased serum FGF23 levels in CKD as a result of end-organ resistance to the action of FGF23. By the time the patients reach ESRD, FGF-23 concentrations are often 100- to 1000- fold above the normal range^[117], and moreover, circulating FGF-23 in ESRD patients is mostly intact and biologically active^[118]. Three possible explanations could account for such elevation. First, increased secretion into and decreased removal of FGF23 from the circulation. Treatment with corticosteroids could activate osteocytes in pediatric CKD patients, and then significantly stimulate FGF-23 synthesis^[119]. FGF-23 levels and estimated glomerular filtration rate (eGFR) were inversely correlating among individuals with CKD stage G4-5^[120]. Second, the other cause of increased levels of FGF-23 may be related to decreased klotho and end organ resistance to FGF23 action in CKD^[121]. Treatment of CKD patients with vitamin D may be the third cause. In 5/6 nephrectomized rats, intravenous administration of 1,25-(OH)2D, three times a week increased serum FGF-23^[122].

The first report of a positive correlation between FGF23 and VC among HD patients was 6 years ago^[10]. Similar results were reported in cases with CKD stages 2-5D. Patients with higher aortic and coronary calcification scores had elevated FGF23 levels^[62]. Similar results were found in healthy older men irrespective of traditional risk factors^[123]. Pediatric studies confirmed the same results in children with CKD^[124]. The same association was recorded in patients kept on HD for more than one year^[125].

Klotho deficiency in CKD vessels likely potentiates the development of accelerated calcification^[126]. Restoration of Klotho and FGFRs by vitamin D receptor activators

renders human vascular smooth muscle cells FGF23-responsive, and that may be the mechanism of their anti-calcific effects^[126].

Increased FGF23 level is associated with increased risk for mortality among incident HD patients, during their first year of treatment^[127]. This association was also confirmed in prevalent dialysis patients^[128]. Neutralization of FGF23 in CKD rats was found to accelerate VC and increases mortality^[129].

Inflammation

Atherosclerosis and VC accelerate in states of chronic inflammation. The later is one of the hallmarks of uremia. Uremic status was incriminated in the pathogenesis of chronic inflammation, however, the exact pathogenesis was not fully understood. Altered gut microbiome might affect the integrity of the intestinal barrier leading to facilitated blood translocation of bacteria and uremic toxins^[130]. Inflammation also results from multiple co-morbid conditions activating inflammation (like infections and autoimmune systemic diseases)^[131]. Many of the inflammatory markers and mediators are found to promote VC in CKD patients. These factors include interleukin 1 (IL-1), IL-6, C-reactive protein and tumor necrosis factor alpha (TNF α)^[132-137].

The association between FGF-23 and vascular calcification was mitigated when corrected for inflammation markers^[138]. In spite of this important role of inflammation that might underlie the role of Klotho-FGF23 axis, no intervention studies to target inflammation to prevent or stop VC progression in CKD were done.

Inhibitors of vascular calcification

All CKD patients are exposed to the uremic environment, however, not all of them will develop VC, suggesting that protective mechanisms also exist^[139].

Fetuin-A inhibits precipitation of calcium-phosphate^[140]. Fetuin-A synthesis is mainly hepatic. Its serum concentration falls with activation of cell mediated immunity^[141]. Fetuin-A calcium phosphate complex is called calciprotein particles (CPP). In comparison to hydroxyapatite, CPP induce significantly less cytokine secretion when macrophages are exposed to equimolar concentrations of hydroxyapatite and CPP^[142]. Mice deficient in fetuin-A develop extensive renal, myocardial, pulmonary, lingual and cutaneous calcifications^[140]. CKD patients with fetuin-A deficiency develop increased cardiovascular mortality^[140].

Matrix G1a protein (MGP) is a vitamin K dependent protein, synthesized in the bone^[143]. MGP has an inhibitory role in VC^[144,145]. MGP inhibits the formation of calcium crystal^[73]. CKD is associated with decreased uncarboxylated MGP level with subsequent increased rate of VC and atherosclerosis^[146].

Osteoprotegerin (OPG) is another anti-calcific agent. High OPG level is reported in patients with vascular calcification^[147,148]. Increase in OPG level may be a self-defensive mechanism against factors promoting VC^[148].

Vitamin K likely prevents post-menopausal fractures^[149]. Vitamin K deficiency increases the chance of

severe aortic calcification^[150]. Treatment of rodent with vitamin K2 reduced VC^[151]. Treatment of HD patients with vitamin K increases serum MPG and osteocalcin levels^[140]. Dietary menaquinone might be more effective compared to phyloquinone, in prevention of the progression of vascular calcification. Studies linking vitamin K status to calcification outcomes in CKD are needed to determine the therapeutic value in such cases^[152].

Pyrophosphate (PPi) directly blocks hydroxyapatite formation. PPi is synthesized in VSMCs^[153]. PPi deficiency results in excessive arterial calcification^[154]. Plasma PPi is deficient in HD patients, and is negatively correlating with VC^[155,156].

Vitamin D deficient mice develop excessive VC^[157]. Vitamin D deficiency is frequent among CKD patients. Decreased dietary intake, decreased synthesis in the skin and decreased 1 α -hydroxylase activity in the failing kidney are the main causes. Further inhibition of 1 α -hydroxylase ensues when serum FGF23 rises^[158]. In CKD G 3-4, CAC was elevated in both the mild and severe vitamin D deficient cases^[159]. Serum levels of 25(OH)D is negatively associated with VC in CKD G4-5^[160]. Low plasma level of 25-hydroxy - vitamin D is associated with increased mortality in different stages of CKD. Progression to ESRD was accelerated in vitamin D deficient patients^[161-163]. At therapeutic dosages sufficient to correct secondary hyperparathyroidism, VDR activator (VDRA) treatment of mouse model of CKD protected the vasculature from calcifying, but higher doses stimulated aortic calcification^[164]. The latter was probably caused by indirect, endocrine VDRA effects resulting in hyperphosphatemia and hypercalcemia. Organ cultures of human arteries from patients with CKD exhibited significant upregulation of Klotho mRNA levels following 48 h of calcitriol or paricalcitol treatment. This treatment effect was not observed in arteries from healthy individuals. Therapeutic dosages of VDRA were also found to reduce VSMC phenotype transformation in the aorta^[124].

To sum up, it seems clear that VC is triggered by different promoting factors that increase in CKD together with the deficiency of different protective factors. In other words, VC in CKD patients is the result of the interaction of this collection of offenders and inhibitors^[165].

CLINICAL RELEVANCE OF VC

Sudden cardiac death, arrhythmia, congestive heart failure, or stroke are the major causes of death in patients with VC^[166,167]. Most of the data on prognostic value of VC are extrapolated from studies in patients with normal kidney function. CKD patients still need prospective clinical trials evaluating the prognostic impact of aortic, coronary and carotid calcification in different CKD stages^[168]. The European Renal Best Practice (ERBP) work group recommends screening of incident dialysis patients^[169], whereas some national guidelines dictated the screening of any CKD patient^[170]. KDIGO guidelines, issued during 2009, considered that patients with CKD stages 3-5D and with known VC as



Figure 2 Plain X-ray of the pelvis in hemodialysis patient for 52 mo showing extensive calcification of the right common and external iliac arteries (arrows).

highest vascular risk and that this information should guide the management^[171]. On the other hand, Zoccali *et al.*^[172] denied VC as a risk factor for ongoing vascular disease. Their opinion relies on many studies, one of them is the recent meta-analysis of different clinical trials on the impact of different phosphate binders on mortality in CKD^[173], the ADVANCE trial^[174] and the EVOLVE trial^[175]. In addition, Wanner^[176] criticized any effort offered for diagnosis or treatment of VC as long as all the last mentioned trials failed to change the prognosis in HD patients.

In our opinion, the medical practitioners should do their best effort to prevent this devastating pathology in every CKD patient and not to wait to diagnose its end stage in the dialysis population. This means energetic preventive measures should be offered to every CKD patient all through different stages.

IMAGING OF VC

In 2009, the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines did not recommend the routine screening of VC as long as there is no clear clinical utility^[177]. However, in some cases, imaging of VC might help to guide the treatment plan^[178]. The gold standard for the quantification of calcification in different vessels is by computed tomography imaging. Plain X-rays can help to identify aortic and peripheral arterial calcifications (Figure 2); Doppler ultrasound is helpful in imaging the carotid, femoral and popliteal arteries and the aorta (Figure 3); echocardiography is valuable tool for visualizing valvular calcification and mammography for breast arterial calcification (BAC). BAC is a useful radiologic sign. It indicates tunica media calcification commonly encountered in CKD^[179].

Quantification of VC is achieved using either the Kauppila score, the Adragao scores, the Agatston score, the volume score or the mass score. The Kauppila scores are used to quantify calcification of abdominal aorta, an indicator of intimal calcification^[180,181]. The Adragao score is used to quantify VC in the iliac, femoral, radial, and digital arteries. Adragao score reflects me-

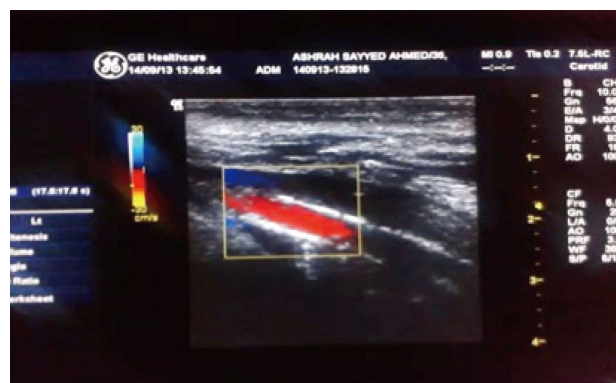


Figure 3 Doppler study of popliteal artery, the vessel wall shows linear calcification.

dial calcification^[182]. The volume and mass scores are quantitative and more reproducible measurements (mm³ or mg, respectively)^[183-185], in addition to being more appropriate for use with modern CT scanners than the Agatston score^[186]. However, the Agatston score (semiquantitative) is the most frequently used and reported method in the medical literature so far.

WHEN TO INTERFERE?

Interference for the traditional risk factors must start very early while the patient is still in stage G1. For nontraditional risk factors, we should start in the very early days of stage G2. The severity of arterial stiffness (as an index of atherosclerosis and VC) was found to increase steadily with more advanced CKD from stages 1 to 5^[187]. The different factors concerned with VC begin very early when renal damage is still trivial and before hyperphosphatemia ensues. Therefore, the earlier the intervention the better is the impact on morbidity and mortality^[188]. The changes in these factors are sequential. FGF23 is the earliest starting during stage G2. Decline of serum calcitriol follows when GFR falls below 60-70 mL/min per 1.73 m². PTH elevation follows in the late phase of stage G3a while changes in serum phosphate occur in stage G3b^[189]. We would like to emphasize that this sequence of events is triggered by the decreased capability of the injured kidney to manipulate phosphate excretion. FGF23 triggers the increase in the fractional excretion of phosphorus by the surviving nephrons. FGF23 inhibits 1- α hydroxylase enzyme, with subsequent decrease in synthesis of 1 α calcidol. Decreased calcitriol synthesis will result in the decline of its serum level, and later in stimulation of parathormone synthesis and secretion. Being the earliest sign of disturbed renal handling of phosphorus, interference should start as soon as FGF23 starts to rise, at a much earlier stage than we do in the time-being^[81,190-196].

HOW TO MANAGE?

VC management aims at improvement of survival and

morbidity in the CKD population^[197]. However, there is a lack of data to guide management strategies in these patients based on CAC scores^[198]. KDOQI guidelines recommend special care of CKD patient if VC is detected in more than one site^[199]. VC is not reversible, so far. Accordingly, the successful management is based on how to prevent or to stabilize existent lesions^[200].

Management of traditional risk factors among dialysis patients still faces concern about its value. Such factors were found correlating with better survival^[201]. Initially, treatment of different traditional risk factors in pre-dialysis CKD patients was based on studies mainly done in cohorts without renal disease, many trials tackling many of such factors in CKD patients have evolved but are still limited^[202].

The strict control of blood sugar carries little benefit, if any, to CKD G5D patients with or without diabetes mellitus^[203]. However, such control has a positive impact on survival of pre-dialysis diabetic CKD patients. Glycemic control might also delay CKD progression and postpones the need for dialysis^[204,205].

Blood pressure control muffles the rate of decline in GFR in pre-dialysis CKD patients^[206]. Hypertensive CKD patients should be treated according to KDIGO guidelines^[207]. The problem is much debatable when discussing hypertension control in dialysis patients^[208]. Home BP carries better prognostic impact when compared to recordings in the dialysis unit. Systolic home BP of 115-145 mmHg is associated with the best prognosis in HD patients^[209]. Renin-Angiotensin-system (RAS) blockers stimulate Klotho gene expression in CKD patients. This novel mechanism might clarify the vascular, cardiac and renal protective benefits of such agents^[210,211]. The RAS mediated renal damage might be through Klotho gene manipulation^[212]. Through their manipulation of Klotho gene, RAS blockers can add a new exciting mechanism for their cardiovascular and renal protective effect.

Aldosterone might induce vascular calcification. We are still waiting for clinical studies to evaluate if there is a protective effect of aldosterone antagonists^[213].

CKD patients frequently develop dyslipidemia. Treatment with statins to lower LDL cholesterol is recommended by KDOQI and KDIGO in all adult patients with diabetic CKD and in hypercholesterolemic non-diabetic CKD patient. Such treatment can reduce different cardiovascular events complicating atherosclerosis. However, this treatment does not impact overall mortality in these patients^[214,215]. Many trials targeting CKD patients were done using different statins or statin-ezetimibe combination. In CKD G3 patients, pravastatin treatment was associated with significant reduction of coronary events^[216]. However, another trial using the same statin failed to show any significant impact on 2nd prevention in patients with early CKD^[217]. When statins are used for primary prevention, instead, they reduced the risk of cardiovascular events in stages 1-3 CKD by 41%^[218]. On the other hand, all trials comparing statins with placebo in HD patients failed to demonstrate any significant impact

on clinical outcome or overall mortality. These trials used atorvastatin, 20 mg daily, in the 4D study, rosuvastatin, 10 mg daily, in the AURORA trial and simvastatin, 20 mg plus ezetimibe 10 mg, in the SHARP study^[219-221].

Lifestyle modifications including regular muscle exercise, salt restriction, decrease of calorie intake, and smoking cessation carry significant cardiovascular benefits in the general population. However, we lack data supporting such interventions at all CKD stages^[202].

The very early elevation of FGF23 during CKD G2 should stimulate the attending physicians to reduce phosphorus intake in CKD patients starting in the early days of stage 2^[222]. Phosphate binders, whether calcium containing or calcium-free, should be avoided in this early stage as long as serum phosphorus level is normal or near normal. The very early use of the phosphate binders might be associated with progression of VC while lowering serum phosphorus and attenuating the progression of secondary hyperparathyroidism^[223].

Calcium-based phosphate binders are still very useful to control hyperphosphatemia, but can lead to hypercalcemia and/or positive calcium balance and cardiovascular calcification^[224].

Sevelamer hydrochloride and carbonate are resin-based binders that appear to have profiles that would prevent or muffle VC^[224]. Treatment of non-diabetic stage 3 CKD patients that have normal serum phosphorus with sevelamer did not lower cardiovascular-related outcomes^[225]. These findings reinforce the trend to avoid phosphate binders in early stages of CKD where the serum phosphorus is still normal. On the other hand, when sevelamer was used in hyperphosphatemic stage 3-4 CKD patients, a significant impact on all-cause mortality and the need of dialysis was observed in comparison to calcium carbonate^[226]. The main drawback of all calcium-containing phosphate binders is the tendency to increase serum calcium level. The higher the dose ingested the greater the extent of VC^[227,228]. Thus their use in cases suffering VC, hypercalcemia, low level of parathormone (PTH) and/or adynamic bone disease has to be restricted^[229]. In the US Sevelamer is mainly used in dialysis patients to decrease progression of coronary artery and aortic calcifications^[230-235]. On the other hand, the European Medicines Agency recommended its use in hyperphosphatemic patients with CKD not yet on dialysis^[236-238]. When incident HD patients were assigned to either calcium-based phosphate binders or sevelamer, and were followed for 44 mo, all-cause mortality was lower in subjects assigned to sevelamer compared to patients assigned to calcium-based binders. However, results were of borderline statistical significance. Another important finding in this study is the significant predictive value of baseline CAC score concerning all-cause mortality^[239]. In the "Treat to Goal Study", coronary and aortic calcification progressed in dialysis patients receiving calcium-containing phosphate binders while those receiving sevelamer did not show progression^[232]. On the other hand, sevelamer failed to improve mortality rate among prevalent HD

patients when compared to calcium-based binders in the multicenter, randomized trial “the DCOR”^[240].

We like to emphasize that while the hyperphosphatemic stage 3-4 CKD patients showed benefits in all-cause mortality^[226], and the incident HD showed borderline significantly lower mortality after sevelamer use^[239], the same agent failed to show a similar benefit in prevalent HD subjects^[240]. We should remember that these different groups are in different stages of evolution as regards VC^[9,10,160] and that the baseline score of coronary calcification is a strong predictor of all-cause mortality^[239]. This confirms that the earlier the approach the better would be the impact on CKD patient survival.

Sevelamer is not just a calcium-free phosphate binder, but also has additional pleiotropic effects such as correcting certain abnormalities of lipid metabolism^[241], significant decrease in inflammatory parameters including IL-6, sCD14 and hs-CRP^[242,243], reduction of serum uric acid concentration^[244], decrease of serum FGF23^[123,245,246], increase of serum level of fetuin-A^[236,247] and Klotho^[246]. Compared to calcium based phosphate binders, sevelamer improves endothelial function in CKD patients^[248]. These results suggest that sevelamer has, beside its hypophosphatemic and calcemic actions, important metabolic, and anti-inflammatory actions that help in decreasing uremic vasculopathy. Sevelamer is more expensive compared to calcium-based phosphate binders^[249]. The significant reduction in all-cause mortality and the significantly fewer hospitalizations in the sevelamer group can offset the higher acquisition cost for sevelamer^[250].

Lanthanum carbonate (LC) is another non-calcium based phosphate binder. It was reported to improve aortic VC progression^[251]. There are no trials studying the effect of LC on either coronary or valve calcification^[252]. LC had no impact on over all mortality in CKD patients^[251,253]. However, the mortality was significantly lower in patients above 65 years in the LC treatment group compared with calcium based phosphate binders. A similar observation was reported in patients receiving sevelamer in the DCOR study^[240,254]. In the only trial looking for the impact of LC on the incidence of cardiovascular events, it failed to show any significant difference compared with calcium-based compounds^[251].

Contrary to sevelamer, lanthanum carbonate does not have a consistent effect on FGF23. LC failed to cause reductions in iFGF23 in patients with CKD stage G3-4^[255,256]. On the other hand, other studies showed that LC was effective in reducing FGF23 levels in CKD G3^[257] and CKD G4 - 5 patients^[258]. None of the trials on Lanthanum reported any effect on inflammation or inflammatory biomarkers. Although LC is cheaper and more compliant (Table 1) compared to either sevelamer hydrochloride or sevelamer carbonate^[259], our target is not just to control phosphorus level. Sevelamer compounds have got more comprehensive trials that showed significant impact on patient mortality during predialysis stages and in incident HD. No similar trials could be encountered for lanthanum. We are still waiting for such studies to assure non-inferiority of Lanthanum in this

field.

The value of nicotinamide (NAM) in phosphate control (as well as its effects on lipid levels) in dialysis patients was explored in some short-term trials^[260-262]. However, such trials did not look for either pharmacokinetics or safety. None of these trials studied the impact on VC, FGF23, Klotho or inflammatory mediators.

Iron compounds represent the new class of phosphate binders. Ferric Citrate, Sucroferric oxyhydroxide, and Fermagate (iron-magnesium hydroxycarbonate) were tested in some clinical trials^[263]. Most of the clinical studies done so far were using ferric citrate, stressing on phosphate binding and ferrokinetics after short periods of trial. So far, no trials have studied the impact on VC^[264-272]. A single study looked for non-inferiority of Sucroferric oxyhydroxide (PA21) compared to sevelamer carbonate concerning phosphate binding^[273].

Bixalomer is novel non-calcium, amine-functional polymer that binds phosphate in the gastrointestinal tract and inhibits its absorption. It was approved as hypophosphatemic agent in Japan by June 2012. It proved non-inferiority with much lower adverse effects relative to sevelamer hydrochloride^[274].

Salivary phosphorus binding is another approach to reduce serum phosphate level. Chitosan-loaded chewing gum, chewed during fasting periods, may be a valuable add-on to phosphate binders that can lead to a better control of hyperphosphatemia^[275].

The possible beneficial effect of bisphosphonates on VC has evolved during the 1970s when their administration was found associated with decreased calcification of soft tissue in animal and clinical trials^[276,277]. These observations are probably explained by the paradoxical relation between bone mineral density (BMD) and VC^[276-278]. That effect might also be related to the stimulatory action of bisphosphonates on fetuin-matrix Gla protein-mineral complex^[279] and their possible inhibitory action on IL-6. Transformation of VSMCs to osteoblasts and calcification of intimal atheromatous lesions might be triggered by IL-6^[280]. Bisphosphonates were found to inhibit vascular arterial and cardiac valvular calcifications that develop in rats treated with warfarin^[281]. When different members of bisphosphonates were tried in chronic HD patients their anti-calcific effect was favorable in some studies^[282-284] and failed in other more recent one^[285]. In addition, alendronate failed to withhold the progression of VC in G3-4 CKD patients when compared with placebo for 18 mo^[286]. Bisphosphonates are not safe in patients suffering advanced CKD. They can aggravate hyperparathyroidism. They can also lead to adynamic bone disease, osteomalacia or mixed uremic osteodystrophy^[287]. All the trials of bisphosphonates studied their impact on VC. Only one trial studied the impact of bisphosphonate treatment on cardiovascular outcomes in female CKD patients. This study was retrospective^[288].

In the EVOLVE Trial, cinacalcet was tested in chronic HD patients suffering moderate-to-severe 2ry hyperparathyroidism. Inspite of the favorable effects of

Table 1 Different therapeutic interventions used to prevent or withhold vascular calcification progression

CKD stage	Risk factor	Type off interference	Outcome	Ref.
Traditional Risk factors				
G1-G5	Cigarette smoking	Cessation	No evidence	[202]
G1-G5	Overweight	Decrease calorie intake	No evidence	[202]
G1-G5	Sedentary life	Muscle exercise	No evidence	[202]
G1-G5	Diabetes mellitus	Blood sugar control	Improves survival	[204]
			Delays CKD progression	[205]
G1-G5	Systemic hypertension	Blood pressure control	Delays CKD progression	[206]
G1-G5	Dyslipidemia	Statins	Decreased CV morbidity	[221]
CKD Related Risk factors				
G2-G5	↑	Dietary phosphate restriction	↓ FGF23	[222]
G3b-G4	Hyperphosphatemia	Sevelamer	↓ VC, ↓ mortality	[226]
G5		Preemptive kidney Tx	↓ VC, ↓ mortality	[52,295]
Incident G5D	Hyperphosphatemia	Sevelamer	↓ VC, ↓ mortality (borderline)	[231]
Prevalent G5D	Hyperphosphatemia	Sevelamer or L.C.	↓ VC	[232,240,251]
Prevalent G5D > 65 yr	Hyperphosphatemia	Sevelamer or L.C.	↓ VC, ↓ mortality	[240,251]

CKD: Chronic kidney disease.

cinacalcet on serum calcium, it failed to decrease the mortality rate or the major cardiovascular events in such patients^[175].

We recommend small dose of vitamin D or vitamin D analogues to be given daily as prophylaxis against VC in spite of the lack of clinical trials favoring the use of either native or active vitamin D analogues to prevent VC progression. The rarity of vitamin D toxicity in general and the privileged survival benefits offered by VDRAs administered in small doses even in cases suffering hyperparathyroidism and/or increased calcium and phosphorus levels supports this concept. Some studies reported the association of low vitamin D serum level with extensive VC^[289,290]. Vitamin D inhibits renin activity, inflammation, suppresses stimulators of VC and stimulates inhibitors of VC in the uremic milieu^[291].

We are still looking for the possible role of vitamin K supplementation in management of VC^[292]. Treatment of CKD rats with vitamin K1 suppressed the development of VC^[293]. A prospective trial is going on in RDT patients suffering coronary calcification. The effect of vitamin K1 supplementation on the calcification progression in the thoracic aorta and coronary artery will be addressed. All-cause mortality is a secondary end-point. This study may offer an inexpensive agent to treat or prevent VC^[294].

Once the patient proceeds to stage 5, pre-emptive kidney transplantation is the best option to improve patient and graft survival in comparison to patients admitted to dialysis or to patients transplanted after starting dialysis^[295-298]. In patients starting dialysis, the shorter the dialysis vintage the better is the post-transplant survival^[299]. The survival benefit of transplantation compared to dialysis is most probably related to the decreased rate of VC post-transplant compared to the accelerated progress in VC observed in dialysis. To further decrease the rate of calcification progression after transplantation, perioperative vascular imaging and analysis of serum FGF23 might help in appointing patients more likely to have progression of VC. Such patients should continue the anti-calcific measures

applied to CKD G3 patients. This advice is based on the previous observation of the strong association between baseline CAC score and CAC progression^[39,300] and on the recent finding of high serum level FGF23 in KTR even when they have normal graft function^[301]. This disturbance of FGF23 appeared to be related to the endothelial cell injury in KTR^[302]. Elevated levels of FGF23 may predict increased risks of death and allograft loss^[303].

Since the pathogenesis of CUA is not fully elucidated, its treatment is still not uniform^[304]. Cinacalcet appeared to reduce the incidence of CUA in HD recipients who have moderate to severe secondary hyperparathyroidism^[305]. Sodium thiosulphate^[38,304] is used successfully in treatment. Bisphosphonates may be also used^[306,307].

CONCLUSION

The new definition and staging for CKD suggested by the NKF-KDOQI in 2002 aimed at stimulation and increased awareness of the medical community to early diagnose CKD^[308]. Early diagnosis of CKD gives a great chance to delay the progression of such disease, and to have better chance to deal with the different complications. VC has evolved as the most serious complication in CKD patients endangering their life. The only successful treatment for VC is preventive. This treatment should start as early as the early days of stage G1. Control of blood sugar in diabetic pre-dialysis CKD patients is a mandate. Recommended hemoglobin A(1c) level should be around 7%. Hypertensive CKD patients should be treated according to KDIGO guidelines. Statin treatment should be prescribed according to KDIGO guidelines.

Screening for FGF23 would pick up CKD patients requiring phosphorus handling at much earlier stage when they benefit maximally. However, we are still waiting for epidemiologic studies that would determine normal and target levels of FGF23 and the ideal method of assay.

In these early days, moderation of dietary phosphate intake might suffice. If Serum PTH level is high, we

should measure serum 25-hydroxy vitamin D level^[309]. If such level is below 30 ng/mL the patient should be prescribed either vitamin D2 or D3. We are waiting for prospective clinical trials studying the value of recombinant Klotho treatment in normalization of serum FGF23 level and preventing the development or progression of VC. Regular estimation of serum calcium, phosphorus, Ca x p byproduct and PTH should be performed with the frequency recommended by guidelines^[310]. Once serum phosphorus starts to rise above normal, strict restriction of dietary phosphorus and prescription of sevelamer should ensue. Other phosphate binders could be used, however, the lack of clear evidence for their effect on Klotho and on cardiovascular morbidity and mortality would postpone their use in the time being till we have strong evidence for these effects. A small dose of vitamin D analogues should be added to all patients passing to stage 3 and beyond. Vitamin K looks promising in preventing or slowing the progression of VC, however, we are still waiting for the results of the ongoing study looking for its efficacy. Once the patient proceeds to stage 5, pre-emptive kidney transplantation is the best option to improve patient and graft survival in comparison to patients admitted to dialysis or to patients transplanted after starting dialysis. In patients starting dialysis, the shorter the dialysis vintage the better is the post-transplant survival. To further decrease the rate of calcification progression after transplantation, perioperative vascular imaging and analysis of serum FGF23 might help in appointing patients more likely to have progression of VC. Such patients should continue the anti-calcific measures applied to CKD G3 patients.

In patients maintained on dialysis, non-calcium phosphate binders still carry the privilege of decreased progression of vascular calcification in spite of their failure to impact either cardiovascular morbidity or mortality. HD patients above 65 years of age showed survival benefit after use of sevelamer or LC, the latter is preferred in this age group based on patient compliance and cost of treatment.

Finally we have to emphasize that huge effort is still needed to support many of the above suggestions by well-designed prospective controlled studies to evaluate either efficacy, safety of such interventions beside the precise definition of optimum dosage and frequency of every individual therapeutic modality.

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