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TOPIC HIGHLIGHT

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# Coronary artery calcification in chronic kidney disease: An update

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## Abstract

Arterial calcification is a well-recognized complication of advanced atherosclerosis. Chronic kidney disease (CKD) is characterized by significantly more pronounced, disseminated and fast-progressing calcification of the vascular system, including the coronary arteries. New computed tomography-based imaging techniques allow for the noninvasive assessment and monitoring of calcification in different vascular sites. Coronary artery calcification (CAC) develops early in the course of CKD and is tightly associated with mineral and bone disorders, which include but are not limited to secondary hyperparathyroidism. In this review, recent data on the pathogenesis of CAC development and progression are discussed, with a special emphasis on fibroblast growth factor 23 and its co-receptor, klotho. The prevalence, progression and prognostic significance of CAC are reviewed separately for patients with end-stage renal disease treated with dialysis, kidney transplant recipients and patients with earlier stages of CKD. In the last section, therapeutic considerations are discussed, with special attention paid to the importance of treatment that addresses mineral and bone disorders of CKD.



**Key words:** Chronic kidney disease; Dialysis; Kidney transplantation; Vascular calcification; Coronary artery calcification; Coronary artery calcification score; Agatston units

**Core tip:** Vascular calcification, a common feature of advanced atherosclerosis in the general population, is extremely advanced in patients with chronic kidney disease (CKD). CKD is associated with very fast progression of vascular (and in particular coronary) calcification. Pathogenetic aspects, clinical consequences and prognostic significance of coronary artery calcification in different CKD populations are discussed in this review. Therapeutic strategies used to limit the extent of vascular calcification and to improve the prognosis of patients with CKD are also discussed.

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## INTRODUCTION

The importance of pathological calcification of soft tissue in chronic uremia has been recognized for a long time. The new era of research is associated with the introduction of new tools, allowing for noninvasive, quantitative assessment of mineral depositions in soft tissues, and electron-beam computed tomography (CT) and multi-slice CT (MSCT). A milestone study in the field was published in 1996 by Braun *et al*[1] which documented an extremely high coronary artery calcium score (CACS) of 4290 ± 1509 Agatston units in patients on long-term hemodialysis (for comparison, a value of 400 Agatston units is associated with an extremely high risk of coronary artery disease in a general population). Many stud-

ies that followed this seminal paper reported advanced coronary and other cardiovascular calcification in patients with chronic kidney disease (CKD) in the pre-dialysis period, on hemodialysis, peritoneal dialysis and following kidney transplantation. Several studies also documented progression of arterial calcification in patients who remained on dialysis or progressed from earlier to more advanced stages of CKD. We were among the first who demonstrated such a progression in patients treated with peritoneal dialysis and attenuation of progression following kidney transplantation[2-4]. Several experimental and clinical studies attempted to highlight mechanisms of development and progression of vascular calcification under the setting of chronic uremia. In this review, the pathophysiological background of coronary artery calcification (CAC) is discussed and the recent literature in the field of CAC in CKD reviewed.

## CURRENT UNDERSTANDING OF PATHOPHYSIOLOGY OF CAC IN CKD

### *Calcium and phosphate*

Mineral and bone disorders of CKD (CKD-MBD) develop early in the course of CKD. The hallmark of these disorders is hyperphosphatemia; levels of calcium and parathyroid hormone (PTH) are variable, *i.e.,* decreased, normal or elevated. Phosphate plays two important roles in the development of artery mineralization. It certainly serves as a substrate that is deposited within the tunica media or intimal layer of the vessel. It also acts as a mediator activating transcription of certain genes in vascular smooth muscle cells (VSMC) and pericytes which results in their transformation into osteoblast-like cells. The term "ossification" used sometimes with regards to pathological calcification is fully justified since this is not just a passive deposition of minerals within the vessel wall, but a precisely regulated process that mirrors bone formation. Macrophages resembling osteoclasts can also be found in an area of vascular mineralization; they become silenced upon challenge with phosphates, so the process of "bone formation" within the blood vessel is not counterbalanced with "bone resorption"[5,6]. It should be emphasized that phosphate, considered a uremic toxin responsible for several adverse effects on cardiovascular system (CVS) in CKD, now has also been identified as such a toxin in the general population. Several population-based studies (such as the Framingham Offspring Study) showed that a high-normal serum phosphate level is also associated with a worse outcome and a higher risk of CV end-points[7-9]. Low normal serum phosphorus in patients with normal renal function is associated with less calcification within coronary arteries[10].

### *PTH*

Changes in plasma PTH are linked to poor survival of patients with CKD, although the normal PTH level for a given level of glomerular filtration rate (GFR) is the matter of ongoing debate. Although recently published Kidney Disease: Improving Global Outcomes (KDIGO) guidelines on CKD-MBD expanded the upper acceptable value in CKD stage 5 to as high as nine times above the reference value for normal subjects, recent studies indicate that mortality increases markedly when plasma PTH decreases below 150 or exceeds 300 pg/mL (according to most laboratories, the upper normal level for a healthy population oscillates around 70 pg/mL)[11,12]. It seems that low plasma PTH is even more significantly associated with progression of vascular calcification than high PTH. Low bone turnover resulting from low PTH leads to decreased ability of bone to uptake calcium and phosphate delivered with diet since renal function is severely compromised and there is no "safety valve" by means of hypercalciuria and hyperphosphaturia; excess minerals activate pathological calcification and serve as substrates to this process[13].

As in the case of phosphates, PTH is also considered cardiotoxic in uremia[14,15]. High-normal plasma PTH is also considered a risk factor for increased CV morbidity in patients with normal renal function[16,17].

### *Calcium sensing receptor*

The discovery of calcium sensing receptor (Ca-SR) allowed for a more precise understanding of regulation of PTH synthesis and release in the course of calcium-phosphate metabolism disorders. Although its expression was originally thought to be limited to parathyroid cells, now it has become apparent that Ca-SR is present in several cell types. These include endothelial cells, cardiomyocytes and VSMC. Stimulation of Ca-SR on parathyroid gland cells strongly suppresses PTH synthesis and release. Ca-SR located in cardiovascular (CVS) structures seems to protect against their pathological calcification, decreased expression of this receptor observed in chronic uremia promotes osteoblastic transformation of VSMC and accelerates vessel wall calcification. Drugs designed to sensitize Ca-SR (*i.e.,* to enhance the receptor response even in lower serum calcium level, calcimimetics) were demonstrated to limit development and progression of vascular calcification in several experiments[5,18-20]. This is in agreement with observations made in a general population suggesting that a high calcium diet is cardioprotective[20]. Two distinct protective mechanisms of these drugs can be considered: better control of hyperparathyroidism and direct interaction with the vessel wall. Data from clinical studies using calcimimetics to control secondary (renal) hyperparathyroidism are equivocal, although these drugs tend to slow down the progression of coronary artery and heart valve calcification[21].

### *Fibroblast growth factor 23 and klotho*

The current era of investigation on vascular mineralization can be called the "era of Fibroblast growth factor (FGF)23 and klotho". FGF23 was recently described as the hormone that acts as a strong phosphaturic agent in line with PTH. This protein is synthesized and released by osteocytes and represents the family of proteins re-

ferred to as phosphatonins. Both PTH and FGF23 are released upon stimulation by a high serum phosphate level. Although PTH and FGF23 act synergistically on the proximal tubular epithelial cells where they limit phosphate reabsorption (and thus enhance phosphaturia), their effects in other pathways is rather opposite. PTH enhances renal activation of active vitamin D (calcitriol) and thus increases intestinal absorption of calcium and phosphate; FGF23 decreases calcitriol synthesis and stimulates its degradation, in turn resulting in decreased GI absorption of calcium and phosphate[22,23].

FGF23 starts to increase much earlier than PTH in the course of CKD. Its increase can already be noticed when the GFR decreases from 90 to 60 mL/min per 1.73 $m^2$; thereafter, this increase is even steeper. Changes in serum calcitriol level follow FGF23. It starts to decrease when GFR falls below 60-70 mL/min per 1.73 $m^2$. PTH elevation is a rather late event; it occurs in the GFR range between 45 and 50 mL/min per 1.73 $m^2$. Increased serum phosphate can be noticed usually when GFR drops below 40 mL/min per 1.73 $m^2$[24]. This sequence of events indicates the efficacy of phosphaturic agents in elimination of phosphate *via* the kidney (they significantly increase single nephron phosphaturia which is sufficient to keep a normal serum phosphate level despite progressive loss of the total nephron number).

FGF23 has been identified as a very powerful predictor of poor prognosis, both all-cause and cardiovascular mortality. This predictive value applies to the whole population with CKD, including end-stage renal disease (ESRD), CKD stages 2-4 and kidney transplant recipients[24-30]. FGF23 remains an independent predictive factor after correction for possible confounders, such as plasma phosphate, calcitriol or PTH. As in the case of high normal phosphate and PTH, borderline elevated or high normal FGF23 is also associated with a worse CV prognosis (this has been demonstrated, for example, in the Heart and Soul Study)[31]. An association between CV outcome and plasma FGF23 can at least in part be explained by stimulation of vascular calcification; some data may indicate that this phosphatonin stimulates more tunica media calcification (Monckeberg calcification or arteriosclerosis that translates into increased arterial stiffness, left ventricular hypertrophy and heart failure) rather than intimal calcification (localized mostly within atherosclerotic lesions, atherosclerosis)[32-35]. A predominance of Monckeberg-like lesions may in general explain why advanced CAC does not directly translate into coronary events (linked rather to calcification of lumen-narrowing atherosclerotic plaques). FGF23 was found to predict the severity of coronary artery disease in a large group of 1263 males and 813 females patients subjected to coronary angiography due to an acute coronary syndrome. FGF23 was an independent and strong predictor of stenosis score (that combined both severity of stenosis of an individual vessel and the number of vessels involved) and was also correlated with the extent of atherosclerosis and plaque calcification, as assessed with IVUS and virtual histology. There were 368 patients with eGFR < 60 mL/min per 1.73 $m^2$. FGF23 appeared to predict the extent of stenosis and number of stenotic vessels (integrated together into stenosis score) in the whole study group and separately in patients with normal (> 60 mL/min per 1.73 $m^2$) and reduced eGFR. FGF23 was inversely correlated with eGFR, but remained an independent predictor of coronary artery disease severity on angiography and the extent of atherosclerosis and plaque calcification on IVUS and virtual histology[36].

Klotho is one of the most fascinating proteins discovered in relation to vascular calcification and FGF23 function. This protein is considered to have an important anti-aging potential and to protect against CVS disease[37,38]. Since klotho is expressed mostly in renal tubular cells and parathyroid glands, this emphasizes the paramount importance of phosphate balance for cardiovascular health. Klotho facilitates normal phosphaturic function of FGF23 in the kidney and acts as its co-receptor. In experimental models of klotho, knockout FGF23 loses its phosphaturic potential even if renal function is preserved. Renal content of klotho possibly decreases early in the course of CKD and triggers upregulation of FGF23, even when other abnormalities of mineral balance (such as hyperphosphaturia) are not yet apparent[39]. It is important to mention that several tissue receptors for FGF23 can be localized without klotho co-expression, possibly elevated FGF23 overstimulates these receptors leading to adverse CVS effects. Indeed, receptors for FGF23 can be found in cardiomyocytes and experimental studies demonstrate that FGF23 leads to left ventricular hypertrophy. This may suggest a direct cardiotoxic effect of FGF23[32,33]. Klotho deficiency leads to increased expression of sodium-phosphate co-transporters Pit1 and Pit2 which facilitate phosphate transport into VSMC and stimulate their osteoblastic transformation. Runx2, a transcription factor that governs this transformation, is also upregulated in klotho deficiency[40,41].

### *Vitamin D and vitamin K; matrix Gla protein*

In many experiments, very high doses of vitamin D were shown to induce disseminated vascular calcification; these doses are never used in humans[42]. Vitamin D receptor deficiency and a low vitamin D diet stimulate vascular calcification in mice[43]. Experiments also demonstrated that vitamin D analogues [vitamin D receptor agonists (VDRA) modified in order to decrease their hypercalcemic effect] may protect against pathological calcification. Patients with CKD (and especially those with end-stage renal disease) suffer from profound vitamin D deficiency. Dietary regimes, lack of skin exposure to sun, failure to hydroxylate vitamin D in 1$\alpha$-position in failing kidneys, as well as the impact of high serum FGF23 contribute to such a deficiency[44]. Low plasma level of 25-hydroxy-vitamin D is associated with poor survival in patients with ESRD and CKD, as well as with the risk of progression to ESRD[45-47]. An association between low vitamin D status and adverse outcome in CKD may possibly be

explained in part by the risk of vascular calcification, inversely associated with plasma vitamin D (calcidiol)[48]. Multiple clinical observational or registry studies demonstrated that supplementing 1α-hydroxy-vitamin D is beneficial for the outcome of patients with end-stage renal disease; even better results can be achieved with novel analogues, such as paricalcitol. Unfortunately, these trials do not allow a conclusion of what the impact of vitamin D and other VDRA on vascular calcification in the clinical setting is.

Disseminated calcification of microcirculation that leads to necrotic lesions of skin and subcutaneous tissue, and ultimately to a fatal outcome has been well documented in ESRD (mostly on the level of case reports or case series) and is called calciphylaxis or calcifying uremic arteriolopathy (CUA). This phenomenon was demonstrated mostly in patients using warfarin and other drugs that antagonize vitamin K[49,50]. Vitamin K is responsible for γ-carboxylation of several proteins, not only those of the clotting cascade. It contributes to post-translational modification of matrix Gla protein (MGP), a protein synthesized by VSMC which acts as a potent inhibitor of vascular calcification. This biochemical pathway was supposed to link development of CUA and the use of warfarin[51,52]. Based on these observations, it has been hypothesized that vitamin K may have certain cardioprotective effects. The data from observational studies suggested a relationship between a higher intake of vitamin K (or biochemical measures suggesting high intake of this vitamin) and better CVS outcome, although a direct cardioprotective effect of vitamin K has not been proven to date[53]. A high percentage of ESRD patients suffer from vitamin K deficiency; supplementing them with menaquinone 7 (vitamin K2) decreases the level of circulating uncarboxylated MGP. This observation may provide a rationale for the therapeutic use of vitamin K in order to prevent cardiovascular disease (possibly by limiting advancement of vascular calcification)[54]. Low levels of carboxylated MGP were shown to predict a poor outcome in patients on maintenance dialysis[55].

### Inflammation

Chronic inflammation is a well-recognized factor that accelerates atherosclerosis and vascular calcification. Chronic inflammation is one of the hallmarks of uremia. It is triggered by the uremic status itself but also results from multiple co-morbid conditions activating inflammation (such as periodontal disease, activity of autoimmune systemic diseases, infection of vascular access for hemodialysis, presence of other foci of infection, *etc.*)[56]. Several proinflammatory cytokines, such as interleukin 1, interleukin 6 or tumor necrosis factor alpha (TNFα), were shown to promote vascular calcification in experimental models of uremia and in uremic patients. C-reactive protein, the marker most commonly measured to assess inflammation, also correlated with the advancement of vascular and coronary calcification in patients with CKD[3,4,57-60].

The anti-inflammatory potential of human serum seems to be essential in protecting patients against vascular calcification. One of the best recognized protective mechanisms is serum fetuin A. This is a "negative" (anti-inflammatory) acute phase protein synthesized by hepatocytes. It was hypothesized some years ago that fetuin A prevents precipitation of calcium and phosphate in serum. Uremic serum is supersaturated with calcium and phosphate, which suggests their ability to precipitate spontaneously in the absence of inhibitors. Fetuin A forms colloidal complexes with calcium apatite and other crystals (called calciprotein particles), thus preventing from their precipitation within soft tissues[61]. Serum fetuin A was shown to predict prognosis in patients with advanced CKD; patient survival was inversely correlated with serum fetuin A[62]. Recent years have brought new insight into the role of fetuin A in vascular calcification. Data concerning the association between serum fetuin A and soft tissue calcification are equivocal: some studies reported such an association, whereas others failed to demonstrate it[63,64]. Hamano *et al*[65] found, in an animal model of uremia and in humans with CKD, that centrifugation of serum at 16000 *g* can separate fetuin A into two fractions: pellets in sediment, containing fetuin A, fibronectin-1, albumin, fibrinogen, Igκ light chains and Igμ heavy chains; and apolipoprotein A- I and "free" fetuin fraction in supernatant. The pellets are also enriched with calcium. The authors found that the serum level of fetuin A before centrifugation is higher compared to supernatant fetuin A after centrifugation in patients with different stages of CKD (including ESRD and dialysis); such a difference was not observed in healthy controls. CACS did not correlate with fetuin A; however, it was correlated with the reduction ratio of fetuin A (*i.e.,* reduction in fetuin A level in supernatant after sedimentation, reflecting the amount of fetuin complexed with calcium and other proteins in the calciprotein particle). These results were confirmed and extended by Smith *et al*[66], who also identified two fractions of fetuin in sera of patients with CKD, free and contributing to calciprotein particle formation. They found that high fetuin A in the calciprotein complex was positively associated with aortic pulse wave velocity, which reflects media calcification of arteries. In addition, they highlighted the importance of fetuin A molecule phosphorylation as a prerequisite to form calciprotein particles.

### Epicardial fat as a new factor regulating CAC

Obesity and body mass index (BMI) were identified as important predictors of CAC both in the general population and in patients with CKD. Several cytokines such as TNFα that were implied in the development of CAC can be synthesized in adipose tissue; in addition, adipose tissue may be the source of more specific mediators (adipocytokines). The most important include leptin, adiponectin, visfatin and resistin. They were also shown to correlate with the degree and progression of CAC[3,58,67]. Recently, a fascinating observation has been made, name-

ly, that similar to fat present in other body regions, epicardial fat is also characterized with certain metabolic and proinflammatory functions and the hormonal cross-talk between epicardial adipose tissue (EAT), myocardium and coronary artery exists[68-73]. It is important to emphasize that adipose tissue in this location can be assessed quantitatively using similar techniques that are used to identify CAC (for example MSCT). Studies revealed an association between the amount of epicardial fat and the presence of CAC in post-menopausal women[74]. Recently, the series of studies on such a link was published in CKD patients. Kerr *et al*[75] searched for a correlation between CAC and epicardial fat volume in 94 stage 4-5 (pre-dialysis) CKD patients and found that CAC strongly and independently correlates with epicardial fat volume in this patient group. In addition, the amount of EAT was correlated with plasma interleukin 6, which confirms its inflammatory activity. A similar association was found in ESRD patients. Recent publications from the Turkish study group indicated that both CAC and EAT deposits were significantly more prevalent and more advanced in patients on renal replacement therapy compared to controls. These studies revealed an independent relationship between EAT and advancement of malnutrition, inflammation, atherosclerosis-calcification (MIAC) syndrome. MIAC integrates signs of malnutrition, enhanced "non-specific" inflammation of uremia, accelerated atherosclerosis and the presence of arterial calcification in one score. It cannot be concluded from the manuscript if there was a correlation between the amount of EAT and CACS[76].

## PREVALENCE AND PROGRESSION OF CAC IN DIFFERENT GROUPS OF CKD PATIENTS AND ITS ASSOCIATION WITH OUTCOME

In this part of the review, the recent, most important publications dealing with CAC and its clinical and laboratory associations in different groups of renal patients are discussed.

### *Dialysis patients*

As mentioned previously, the phenomenon of an extremely advanced CAC was first identified and explored in patients treated with hemodialysis; these publications were followed by investigation in the field of peritoneal dialysis. In recent years, a series of publications were issued by the Italian independent study group. These authors aimed to analyze if randomization to different types of phosphate binders (sevelamer HCl *vs* aluminum or calcium-containing salts) have any impact on the progression of CAC. The study was performed in patients new to hemodialysis (which is important, since previously many were performed in prevalent patients, *i.e.,* with different dialysis vintage before inclusion). The 24 mo observation period was completed by 132 patients (23% diabetics); 70.4% had evidence of CAC at the study entry (although the initial CAC score was relatively low and equaled 286 ± 744 Agatston units). About 61% of patients experienced progression in CACS; it was independently and positively associated with the presence of diabetes, increasing serum LDL-cholesterol and C-reactive protein; randomization to sevelamer decreased the risk of progression by 34% ($P < 0.001$). This study also demonstrated that an increment in CACS correlates with progression of pulse wave velocity and worsening in cardiac repolarization, as measured with QT dispersion. As in most of the previous studies, it was also shown that baseline CACS is an important predictor of CACS progression; in contrast to several other studies, age did not predict the progression[77,78].

High prevalence and fast progression of CAC were also identified in children and young adults with advanced CKD[79,80]. This issue was analyzed recently by Srivaths *et al*[81], who examined the relationship between CAC and FGF23, discussed above as one of the key predictors of cardiovascular outcome in renal patients. Sixteen patients aged 16 ± 3.3 years were involved in this study; they were on dialysis for quite a long period of time given their young age, *i.e.,* for 27.3 ± 19.3 mo. Compared to earlier reports on young patients, CACS was relatively low (median, 19; range 1-49 Agatston units) and present in only 5. FGF23 and serum phosphate were identified as being independently associated with CACS, although the statistical power in this small sized study must be considered very low. It should be emphasized that mean serum FGF23 level equaled 4024 pg/mL (in one of the recently published studies, the lowest quartile of FGF23 in patients with normal renal function was as low as < 40 pg/mL)[36,81]. Pencak *et al*[82], who recently analyzed correlations between CAC and a broad spectrum of calcification and bone turnover parameters (including FGF23, osteocalcin, osteoprotegerin, MGP, fetuin A, C-reactive protein, interleukin 6 and TNFα) in a large group of patients on hemodialysis, failed to reveal any association between CAC and any of the listed markers. Multiple logistic regression analysis allowed identification only of "classical" risk factors, namely age and time, on HD as independent predictors of CAC. FGF23 was not associated with the risk of CAC in the group of CKD patients (in stages 1-5) included in a recent Turkish study, although phosphatonin was related to valvular (aortic valve) calcification[83].

The impact of CAC on survival was analyzed in hemodialysis patients included into the prospective Nutritional and Inflammatory Evaluation of Dialysis Patients study that comprised of 166 subjects on hemodialysis (51% diabetics) who were followed prospectively and all-cause mortality was analyzed according to baseline CACS. More than 80% of patients were Hispanic or black and the majority was dialyzed for more than 2 years. Patients were divided according to baseline CACS into four groups (0, 1-100, 101-400, 400+ Agatston units). There was a statistically significant trend towards increasing

age, percentage of diabetics and value of the Charlson Comorbidity score with increasing CACS category; no differences in serum calcium, phosphate, cytokine profile or BMI were observed between the groups. Fifty deaths occurred during follow-up: 30 in 400+ CACS group and only 2 in patients with CACS 0 at baseline. This translated into 88.9% event-free survival rate in patients without CACS compared to 58.3% in those with CACS 400+. Cox proportional regression analysis with adjustment for case-mix variables has shown that the hazard ratio of death in three CASC groups (1-100, 101-400 and 400+ Agatston units) equaled 2.9, 8.5 and 13.3 compared to the reference group (CACS = 0). This analysis also revealed that CACS measured for each coronary artery (individual CACS) was also predictive for all-cause mortality (with significance decreasing from the left main through left anterior and left circumflex to right coronary artery)[84].

The predictive value of CAC for survival was also analyzed by the Italian group led by Prof. Gorgio Coen. 81 patients on maintenance hemodialysis for a very long time (82.5 ± 99.5 mo) at the time of baseline CAC assessment were included. In most of them (71 out of 81) CAC was found at baseline; the median value increased after one year from 481 to 528 Agatston units. Age and dialysis vintage were found to predict baseline CAC. A strong positive association was found between the baseline CAC and CAC increment over 12-18 mo observation period. In addition, calcium and PTH predicted the increment in CAC over this period of time, whereas fetuin A was shown to be protective. A total of 11 patients died during follow-up; mortality among those who progressed in terms of CACS increment equaled 72.7%. Agatston score was found to predict mortality during the follow-up[85].

In many previously published studies, a fascinating link between CAC and bone turnover was postulated: in clinical circumstances with excess bone resorption, a certain amount of mineral content from the skeletal system may deposit within soft tissues, including the vessel wall. The inverse relationship between vascular calcification, vascular stiffness and bone mineral density was described in the general population[86]. In CKD, characterized with bone and mineral disorders that are far more complicated that in osteoporosis, such a relationship was also documented[87]. So called "adynamic" bone disease (low bone turnover) was postulated to be a form of bone mineral disorders that is frequently associated with advanced and progressing vascular calcification in CKD patients[88]. Osteoprotegerin/receptor activator of NF-κB ligand (OPG/RANKL) axis, crucial in regulation of bone resorption, was also postulated to be involved in pathological soft tissue calcification in uremia. The possible link between this axis and CAC was recently addressed in a group of 78 HD patients, 44 CKD stage 4 subjects and 42 healthy volunteers in a prospective manner. Serum OPG was significantly higher in HD patients compared to stage 4 CKD or healthy controls; an opposite trend could be seen for RANKL and resulted in a significantly higher osteoprotegerin/RANKL ratio in HD patients compared to CKD stage 4 and healthy controls. Serum OPG and OPG/RANKL ratio were correlated with CAC at baseline and after one year; patients who progressed in CAC after one year (at least 10% and 50 Agatston units *vs* baseline) were characterized with a higher baseline and follow-up OPG and an increase in OPG during the one year observation period. Multivariate analysis confirmed an independent relationship between CAC progression and increase in serum OPG; high baseline CAC was also identified as another significant predictor of CAC progression. In the cited study, femoral bone mineral density was also measured but no correlation of BMD with baseline CAC or CAC progression was found[89].

### *Pre-dialysis patients*

The burden of CAC in CKD subjects not yet on dialysis is also significant, although generally less advanced compared to dialysis patients. The prognostic significance of CAC in pre-dialysis, however, was not known until recently. Russo *et al*[90] analyzed the impact of baseline CAC and CAC progression on cardiac events in CKD patients not yet on dialysis (the study group comprised of the patients with CKD stages 2-5). They identified 181 patients with baseline CAC assessment who were followed prospectively and 54.7% of subjects were found to have CAC at baseline. The authors divided them into those with baseline CACS ≤ 100 and > 100 Agatston units and followed them until a cardiac event or end of the study, for a median period of 689 and 820 d, respectively (cardiac event was defined as cardiac death or myocardial infarction). Patients with higher baseline CACS were older, more frequently diabetic and had a longer duration of hypertension; interestingly, they did not differ in terms of GFR, mineral metabolism parameters, lipid profile or inflammatory markers. After adjustment for baseline differences, CACS > 100 Agatston units at the start of observation and accelerated progression of CAC (defined as annualized increment of CACS exceeding 75$^{th}$ percentile) were shown to predict cardiac events.

Another recent study addressed the issue of CAC progression in CKD patients not yet on dialysis. This study comprised of 103 CKD stage 3 and 4 patients with a baseline CAC assessment and who were then followed for 2 years. CAC was repeated after this period of time. Many other parameters, including a broad panel of biochemical markers and bone mineral density, were monitored. The study demonstrated that baseline CAC was higher in diabetic patients with CKD stage 3-4 compared to those without diabetes. Patients with diabetes were also more likely to progress in CAC compared to non-diabetics. The rate of progression was also faster among diabetics (although the increment in CAC was statistically significant within both groups). The prevalence of CAC greater than zero was also higher in diabetic CKD patients at baseline and follow-up (73% and 80%, respectively) compared to non-diabetics (46% and 60%). As in many previous reports, the most important predictors of

CAC progression were baseline CAC, BMI and serum phosphate level[91].

### Proteinuric patients

Proteinuria is considered a powerful predictor of cardiovascular events (CVEs) and mortality due to CVS disease. To the best of my knowledge, no study has been performed to analyze the prevalence or extent of CAC among patients with proteinuria in the course of primary kidney disease (primary glomerulopathy). However, a study was performed in diabetic patients with CKD and overt proteinuria (mean eGFR 52 ± 26 mL/min per 1.73 $m^2$ and median urine protein loss 2.7 g/g of creatinine, *i.e.,* close to nephrotic). No correlation was found between CAC and proteinuria, or eGFR; there was also no association between CAC and parameters of mineral metabolism, including calcium, phosphate, PTH or 25-hydroxyvitamin D. Only age, male gender and ethnicity (being non-Latino white) were independently associated with advancement of CAC. In this study that involved 225 patients, 54 deaths occurred over the period of 39 ± 25 mo. CAC was an independent predictor of death in different statistical models and the hazard ratio of death equaled 1.49, 2.2 and 4.32 in patients with baseline CACS of 1-99, 100-399 and ⩾ 400 Agatston units, respectively, compared to patients with CACS = 0[92,93].

### Renal transplant recipients

Several papers demonstrated that CAC is highly prevalent in transplant recipients and that successful kidney transplantation attenuates the rate of progression in CAC and mineralization within other vascular sites[2,4,94,95]. Papers that were published recently expand our knowledge of CAC after kidney transplantation.

Shu *et al*[96] analyzed the prevalence of CAC in a group of 99 renal transplant recipients from Taiwan. In 60% of patients CACS exceeded 10 Agatston units (mean and median values were not provided). CASC was independently associated with age and the presence of hypertension; female gender and high HDL-cholesterol were identified as protective factors in multivariate analysis.

Roe *et al*[97] were among the first who analyzed the impact of CAC on CVEs and mortality in renal transplant recipients. These authors selected a broad spectrum of inflammatory markers in addition to other "classical" clinical and biochemical risk factors of CVEs. The study group consisted of 112 renal transplant recipients (31.5% diabetics, 61% received kidney from a deceased donor) with age a mean 48.8 ± 12.5 years. Dialysis vintage before transplantation was relatively short (3 ± 2.7 years). Mean calcification score equaled 367.7 ± 682.3 Agatston units (median 70.5 units, no CAC found in 38 patients). These results correspond with values expected in wait-listed dialysis patients (usually healthier compared to non-selected dialysis population). The patients ($n$ = 87) had CAC assessment repeated after the median period of 1.7 years; in 25.9% CAC progression was noted and 95.1% of patients with CAC < 100 units survived, whereas survival rate among those with CAC > 100 units was 82.3% ($P$ = 0.03). The probability of remaining CVS event-free in respective CAC groups equaled 90.2% and 70.6%. Baseline CAC and CAC increments were shown to predict CVEs and mortality (depending on applied statistical approach, time spent on dialysis and if the presence of diabetes was predictive for CVS events or death).

Nguyen *et al*[98] recently published the observation of 281 renal transplant recipients in whom initial CAC and aortic calcification were measured and the predictive value of arterial calcification in these two localizations on development of CVE was analyzed. The patients had a very long history of ESRD since the main dialysis vintage before transplantation was 2.4 ± 2.4 years and the time between transplantation and baseline CAC analysis equaled 8.3 ± 6.9 years. They were much younger than an "average" dialysis cohort (53 ± 13 years). Higher CACS and previously experienced CVE were identified as independent predictors of future CVEs during the mean observation period of 2.3 ± 0.5 years. These two factors combined significantly decreased the chance of remaining CVE-free during the follow-up. Interestingly, in this study, "classical" factors such as age, male gender, obesity, lipid profile disorders and smoking, did not predict the onset of CVE.

Seyahi *et al*[99] analyzed the prevalence and progression of CAC in the group of renal transplant recipients a long time after transplantation (99.5 ± 54 mo) with well-preserved graft function (mean eGFR of 63.9 ± 18.1 mL/min per 1.73 $m^2$), who were earlier treated with dialysis for a mean period of two years. This Turkish population was much younger compared to an "average" Western dialysis or transplant cohort (38.7 ± 11.2 years) and, probably due to the young age, the prevalence and advancement of CAC was relatively low, despite a long history of renal replacement therapy (mean CACS 60 ± 174.8 Agatston units; median 0, range 0-1350; CAC present in 35.6% of patients). A very high percentage of patients (84%) received the kidney from a living donor. There were different methods of CAC progression defined in this study; depending on definition, progression in CAC was observed in 28%-38% of patients and prevalence of CAC-positive patients increased to 64.6% after 3 years. Baseline CAC and serum triglycerides were identified as independent predictors of CAC progression; in addition, bisphosphonate use was also independently associated with a 2.64-fold increased risk of CAC progression. The latter observation is very interesting and has been reported previously for other populations, for example, in a population-based Multi-Ethnic Study on Atherosclerosis. This study demonstrated that using bisphosphonates in post-menopausal osteoporotic women is associated with an increased risk of calcification in the aortic valve, aortic valve ring, mitral annulus, thoracic aorta and coronary arteries, especially in patients younger than 65 years[100].

One of the most interesting studies in the field is the paper reporting prevalence and progression of CAC in transplant recipients who were on dialysis due to lupus

nephritis. Systemic lupus erythematosus (SLE) is one of the most important causes of "secondary" glomerular diseases, especially among young females, and certain types of lupus nephritis are associated with poor renal outcome and a need for renal replacement therapy. SLE is a systemic inflammatory disease with a very high risk of atherosclerosis and CVS disease[101]. This includes a high prevalence of CAC in this patient group[102]. Patients with SLE on dialysis are excellent candidates for kidney transplantation (unless no disease activity is observed at the time of transplantation) and the outcome after transplantation is comparable with non-SLE subjects. Hence the importance of study performed by Norby *et al*[103] on CAC in renal transplant recipients should be acknowledged. These authors included 39 young renal transplant recipients with SLE (aged 34.1 ± 12.1 years, 74% female) in the study and identified a very high prevalence of CAC in MSCT (82%) and high mean and median CAC (894 ± 1679 and 135 Agatston units, respectively, with 36% of subjects with CAC exceeding 400 units). This important study identified the duration of SLE and BMI as independent predictors of CAC advancement; CAC was highly correlated with aortic pulse wave velocity (the measure of arterial stiffness and tunica media calcification). It should be emphasized that, in contrast to other papers in the field, the impact of dialysis on CAC in these patients was almost negligible: average time on dialysis was very short (13.2 ± 14.7 mo) and almost half of the recipients obtained a graft from a living donor[103]. Given the fact that CAC was shown to predict cardiovascular outcome in transplant patients, it is, however, sad to say that these young people (predominantly women) can be considered as high-risk patients.

## THERAPEUTIC PERSPECTIVE

There are only a few prospective randomized trials available in the literature with therapeutic interventions aimed at controlling cardiovascular disease and improving survival in patients with advanced CKD. Their general message is rather pessimistic since most of the trials failed to prove that therapeutic interventions really change outcome (exceptions include one small study with carvedilol in patients with ESRD and heart failure, and another large trial demonstrating benefits of combined treatment with simvastatin and ezetimibe *vs* placebo in advanced CKD)[104,105]. Since there is an association between CKD-MBD, vascular calcification and mortality, mineral balance abnormalities became an obvious target for therapeutic interventions. Unfortunately, none of the interventions available in the field (including older and new phosphate binders, vitamin D and other VDRA, calcimimetics, low phosphate diet) was demonstrated to change patient prognosis and improve survival. This rather pessimistic notion was also upheld and emphasized by the most complex and comprehensive document in the field, namely, KDIGO clinical practice guidelines on CKD-MBD[106]. Unfortunately, since publication of the KDIGO guidelines, no additional data have been published to change this perspective. Probably the most disappointing news was the results of the EVOLVE trial; 3883 HD patients in this study were randomized to cinacalcet or placebo to test the hypothesis that treatment with cinacalcet would reduce the risks of death and nonfatal CVEs in this population. Unfortunately, no benefit was demonstrated from using the calcimimetic drug[107]. Several other studies were performed to demonstrate the usefulness of certain drugs to reduce the advancement of vascular (and coronary) calcification or at least to slow down the progression over time.

### *Phosphate binders*

The most obvious therapeutic intervention in CKD-MBD is using phosphate-binding agents to reduce absorption of calcium and phosphate from GI (and thus limit the availability of substrates and stimulating agents for vascular calcification). Since the drugs traditionally used for this purpose, namely calcium containing phosphate binders (usually calcium carbonate, calcium acetate and citrate), may be the source of additional and unwanted calcium supply (which may promote vascular calcification, limit possibilities of using vitamin D and lead to parathyroid gland oversuppression)[108], most of the studies focused on the comparison between calcium-containing and calcium-free phosphate binders. The most important preparations in the field include lanthanum carbonate and synthetic compounds, sevelamer hydrochloride and sevelamer carbonate.

First, it is important to mention that in agreement with the KDIGO statement, other meta-analyses did not show survival benefit or attenuation in vascular calcification in patients using non-calcium containing phosphate binders *vs* those treated with calcium-based drugs[109]. Thus, early enthusiastic reports on the positive impact of sevelamer on CAC progression or even mortality could not be confirmed; they were also criticized as being underpowered to detect any outcome differences and influenced by the pharmaceutical industry[110-112]. In addition, other trials demonstrated similar efficacy of calcium acetate combined with a statin and sevelamer in control of CAC progression in patients on hemodialysis[113]. The newer studies in the field point on the higher efficacy of sevelamer in limiting the progression of CAC compared to calcium-containing phosphate binders, although these publications are also statistically underpowered due to small study samples and relatively short observation periods. Shantouf *et al*[114] found in a cross-sectional study that long-term sevelamer users on hemodialysis display lower values of CACS compared to those treated exclusively with calcium-containing phosphate binders. Barreto *et al*[115] assigned treatment with sevelamer or calcium acetate to 101 HD patients and followed them for one year, with baseline and follow-up bone biopsy and CAC assessment. They failed to demonstrate any difference both in terms of changes in bone turnover and CACS progression over 12 mo between the two treatment groups. A randomized study completed recently in Japan

included 183 HD patients with a relatively long (118 ± 89 mo) history of dialysis. They were randomly assigned in a 1:1 ratio to sevelamer or calcium carbonate. CACS increased significantly in both treatment arms after one year (in both groups with *P* value of < 0.001 *vs* baseline), although the increase of CACS was significantly lower in patients using sevelamer after adjustment for baseline differences between groups[116]. Similar results were also demonstrated for earlier stages of CKD. Russo *et al*[117] randomized 100 patients with CKD 3-5 (in stage 5 patients not yet on dialysis) to low-phosphate diet only, sevelamer or calcium carbonate. A significant increase of CACS was noted after an average observation period of two years in patients randomized to diet only and calcium carbonate (in both groups with $P < 0.001$ *vs* baseline), whereas it remained stable in those using sevelamer hydrochloride. An annualized progression in CACS equaled 205 ± 82 Agatston units in controls, 178 ± 40 units in the calcium carbonate group and 36 ± 32 units in the sevelamer group[117].

Sevelamer interacts with bile acid recirculation in the gut and may also influence lipid profile (with LDL-cholesterol lowering effect); some benefits of this polymer referred to this mode of action.

Lanthanum carbonate is a phosphate binder introduced to replace aluminum hydroxide in the treatment of hyperphosphatemia. In contrast to aluminum, GI absorption of lanthanum, a rare earth element, is considered negligible and thus it has been accepted as an effective phosphate binder without noticeable toxicity. In a recent study, it has been demonstrated that treatment with lanthanum carbonate is more effective compared to calcium carbonate in preventing the progression of CAC in patients on hemodialysis; in fact, regression by 6.4% was noticed in lanthanum-treated group *vs* 41.2% progression in those receiving calcium carbonate[118].

### Statins

The above mentioned study of Qunibi[119] combined a statin with calcium acetate and demonstrated a similar efficacy in controlling CKD-MBD and CACS progression, as in the case of sevelamer. Lipid disorders are well-recognized triggers of atherosclerosis and they also contribute to arterial calcification[119,120]. There were attempts to control CACS progression with statins, although the results are equivocal and today there is no scientific background to conclude that these drugs really stop CAC progression[121-125]. Recently, Lemos *et al*[126] randomized 117 patients with CKD stage 3 and 4 (eGFR 36 ± 16.5 mL/min) to treatment with rosuvastatin, sevelamer or control group and found no difference between the three groups in terms of CACS progression *vs* baseline after two years. Statins are widely used in the general population in both primary and secondary prevention. Data on the beneficial influence of statins on cardiovascular health in non-renal patients are extrapolated to CKD patients and most of them are treated with these drugs; there are also some preliminary data on the usefulness of the benefits of statins in CKD[105,127]. Hence, preventing CAC would probably not be the primary indication to commence these drugs in CKD patients since they are already widely used.

### VDRA, vitamin K, cinacalcet

Although there is some pathological background to believe that low vitamin D status is associated with CAC progression, there are no clinical trials on the therapeutic role of vitamin D (native, calcidiol, calcitriol) in the prevention of CAC progression. The same holds true for paricalcitol, the leading vitamin D analogue which controls hyperparathyroidism with a less pronounced action on calcium and phosphate absorption from the gastrointestinal tract. The results of the most important recent trial testing the impact of cinacalcet on CAC progression are somewhat inconclusive. A total of 360 patients in this study (known as ADVANCE) were randomized to cinacalcet with vitamin D or to vitamin D alone. After 5 wk, CACS increased by 24% as measured in Agatston units and by 22% as measured using the volume method in cinacalcet users, whereas in the vitamin D group the respective increases equaled 31% and 30%. The difference between treatment arms was non-significant when values in Agatston units were compared but became significant ($P = 0.009$) when the volume scoring was applied. Cinacalcet significantly attenuated the progression of aortic valve calcification but had no influence on mitral valve and thoracic aorta[21]. The results of this trial are difficult to interpret since VDRA were used in both treatment arms. ADVANCE was followed by publication of the EVOLVE trial, which demonstrated no impact of cinacalcet compared to placebo on mortality and major CVEs in the group of 3883 patients on maintenance dialysis[107]. As mentioned above, although there are multiple publications on the role of vitamin K-dependent proteins in the development of vascular calcification, to date no interventional study has been performed to show the benefit of vitamin K treatment in slowing down the progression of CAC.

### Bisphosphonates

The role of bisphosphonates in the treatment of CKD-MBD is unknown since classical osteoporosis is not included in the classification of this disease[128]. In addition, a low value of GFR is a generally accepted contraindication for using these drugs. Small sample size trials performed in Japan some years ago suggested benefits associated with bisphosphonate use on CAC progression but it seems that this idea was abandoned since no further papers have emerged recently[129,130]. As mentioned in this review, there is a link between bone metabolism and soft-tissue calcification. Osteoporosis as a main indication for bisphosphonates may per se promote vascular calcification since calcium and phosphate mobilized from bone may serve as a source of substrates. Bisphosphonates interact with vitamin K metabolism and thus may decrease γ-carboxylation of MGP, a well-recognized inhibitor of

pathological calcification. Specifically in patients with CKD (including moderate CKD after kidney transplantation), low-turnover bone disease develops which may be additionally worsened with bisphosphonates. These mechanisms may explain why the increased risk of calcification in the aortic valve, aortic valve ring, mitral annulus, thoracic aorta and coronary arteries was found in a substantial percentage of post-menopausal women using bisphosphonates to treat or prevent osteoporosis[100]. On the other hand, bisphosphonates decrease expression of TNFα, down-regulate the inflammatory process and decrease the uptake of LDL-cholesterol by macrophages within atherosclerotic plaque; all these effects may potentially protect from calcification[131].

## CONCLUSION

Soft tissue and especially arterial calcification is a dangerous process which may affect patients from the general population but poses a special threat to subjects with chronic (advanced) kidney disease. Although many risk factors of the development and progression of arterial calcification were identified, they are not universally confirmed across studies; only age seems to determine CAC in all studies and baseline CAC usually determines its progression over time. The extremely complex nature of uremic toxicity, additionally complicated by treatment (dialysis or transplantation), makes the identification of a single or main modifiable risk factor extremely difficult. In an attempt to prevent the development and progression of CAC, several pathological pathways (mostly related to mineral and bone disorders) are targeted but due to multi-factorial etiology many others remain unaddressed. This results in a very high prevalence and fast progression of CAC in patients with CKD, with potential consequences in terms of increased cardiovascular morbidity and mortality.

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