Vascular and Valvular Calcification in Chronic Kidney Disease: Pathogenesis and Clinical Outcomes

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Introduction

Patients with chronic kidney disease (CKD) are two to four times as likely to have cardiovascular disease (CVD) compared to the general population, when adjusted for traditional CVD risk factors [1]. CVD is the leading cause of death in these patients, with vascular and valvular calcification being an integral part of its pathophysiology. Calcium phosphate crystals are deposited through a multifactorial dynamic process that leads to the development of atherosclerosis, arteriosclerosis, and valvular calcification. This chapter will discuss the pathogenesis of vascular and valvular calcification, focusing on the unique risk factors associated with the milieu of chronic kidney disease. Utilizing this knowledge, this chapter will delve into the clinical manifestations, complications, treatments, and outcomes associated with vascular and valvular calcification in CKD and end-stage kidney disease (ESKD).

Vascular Calcification

Vascular calcification can be classified into intimal calcification and medial calcification according to the location of calcium deposition within the arterial wall. Intimal calcification is commonly associated with atherosclerotic plaques

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that partially occlude the arterial lumen, reducing blood flow and resulting in peripheral ischemia, myocardial infarction, stroke, and sudden death [2, 3]. Alternatively, medial calcification is deposited circumferentially along the elastic lamellae, which damages the elastic collagen resulting in an increase in wall stiffness and a decrease in vascular compliance [4, 5]. Clinically, medial calcification is more commonly seen in patients who are older, diabetic, and those with CKD [6].

Valvular Calcification

Valvular calcification is an independent predictor of CVD, heart failure, and death [7, 8], and is often responsible for leaflet and annular thickening with resulting valve dysfunction (i.e., stenosis). Calcification is more common in the aortic and mitral valves due to the higher pressures, turbulence, and mechanical stress seen on the left side of the heart compared to the right side. In the aortic valve, the increased calcium deposition often causes aortic stenosis (AS). Though symptoms of AS (angina, syncope, and dyspnea) are identical in patients regardless of baseline kidney function, the natural course of the disease is accelerated in patients with CKD and as a result these rapid progressors have severe, symptomatic AS at a younger age than the non-CKD population [9, 10].

In the mitral valve, mitral annular calcification (MAC) arises early in the course of renal insufficiency and often has clinical consequences prior to the onset of ESKD [11]. In most patients, MAC is initially isolated to the ventricular base under the posterior mitral leaflet, and can spread to involve the entire posterior annulus [12, 13]. Advanced posterior MAC can cause mitral regurgitation (MR) due to restriction of the posterior leaflet movement, while the anterior leaflet remains mobile (Fig. 2.1). In patients with ESKD, MAC can progress further to involve the anterior annular ring. This circumferential calcific ring restricts the

movement of both the anterior and posterior leaflets resulting in mitral stenosis [12, 13] (Fig. 2.1).

Pathogenesis of Vascular Calcification

Extraskeletal calcification was previously believed to be an inert process that resulted from an increase in serum levels of calcium and phosphate. It is now understood that both intimal and medial calcification share a common downstream pathway involving the de-differentiation of vascular smooth muscle cells (VSMCs) into cells with osteogenic capability [14, 15]. Despite similar risk factors, medial and intimal calcification are likely initiated through different primary mechanisms.

Intimal calcification, seen in atherosclerosis, has a patchy morphology composed of calcium crystal aggregates within atherosclerotic plaques [16]. The primary event in atherosclerosis is endothelial dysfunction due to physical or chemical stressors. The breakdown of the endothelial barrier allows lipids to become trapped and oxidized within the sub-endothelial space, inducing an inflammatory response that results in the production of a fatty streak. A fatty streak is composed of foam cells or fat-laden macrophages, lipids, and necrotic tissue surrounded by leukocytes. Necrotic tissue and the formation of matrix vesicles likely serve as nucleation sites for intimal calcification [16].

In contrast, medial calcification consists of a focal, circumferential sheet of calcium crystals surrounded by VSMCs in the absence of lipid aggregation or inflammatory mediators [16]. Evidence suggests that elastin degradation by matrix metalloproteinases (MMP) may be the initial step facilitating medial calcification [17]. Elevated MMP is correlated with increased arterial stiffness and severity of medial calcification [18].

Once the aforementioned initial stimulus has occurred, the mechanism of calcium deposition downstream is the same regardless of the location (intimal vs. medial). In normal human development, mesenchymal stem cells differentiate into osteoblasts, chondrocytes, adipocytes, and VSMCs. Chemical stressors such as diabetes, dyslipidemia, inflammation, and other cytotoxins promote de-differentiation of VSMCs into cells with an osteochondrogenic phenotype. Bone associated-proteins such as osteocalcin, osteopontin, matrix γ-carboxyglutamic acid protein, bone morphogenic protein, and osteoprotegerin have been found in atherosclerotic plaques and mineralized heart valves [15, 19–21]. Transcription factors essential to osteoblastic differentiation such as runt related transcription factor (Cbfa1/RUNX2) and muscle segment homeobox (MSX-2) are upregulated in cells

surrounding calcified arterial walls and are indicative of phenotypic de-differentiation [14, 19, 21]. VSMCs expressing these osteogenic indicators deposit collagen and non-collagenous proteins in a mechanism similar to osteoblastic bone formation. VSMCs then form matrix vesicles similar to exosomes that contain calcium, phosphate, alkaline phosphatase, and annexin to initiate calcification [2, 5, 19]. Calcium and phosphorus are further mineralized into hydroxyapatite in the vesicles.

Pathogenesis of Valvular Calcification

Valvular calcification results from the deposition of calcium-phosphate crystals on the annulus and the leaflets of the valves, at sites of inflammation or mechanical stress [22]. Similar to vascular calcification, valvular calcification is also an active process that involves de-differentiation of matrix cells into cells with osteoblastic potential. Although the pathogenesis of valvular calcification is not fully understood, it is believed to be similar to that of atherosclerosis, explaining the shared risk factors between these two conditions [23]. Cardiac valves, particularly on the left side of the heart, are subject to cyclic mechanical stress from high pressure gradients and turbulent flow related to high peak velocities and rapid acceleration [10]. The mechanical stress on the valve with each cardiac cycle leads to endothelial microfractures that cause rearrangement of elastin and breakdown of the collagen structure [10, 22]. Over time, the repetitive damage to the valve will result in fibrosis and calcification via mechanisms similar to those described in vascular calcification.

Pathogenesis of Vascular and Valvular Calcification in CKD and ESKD

In CKD, the contributions of traditional risk factors such as hypertension, dyslipidemia, smoking, diabetes, gender, and older age do not fully account for the high incidence of calcification associated CVD, suggesting that there is a unique set of calcification promoting risk factors in the CKD milieu [6, 24]. In the early stages of renal impairment, the complex balance between promoters and inhibitors of osteogenesis begins to breakdown, resulting in the deposition of calcium in extraskeletal organs. In CKD, calcium deposition is partially attributed to a disturbance in mineral metabolism, an alteration in inhibitory regulation, an increase in MMP concentration, the presence of chronic inflammation, and the effect of mechanical stress (Fig. 2.2).
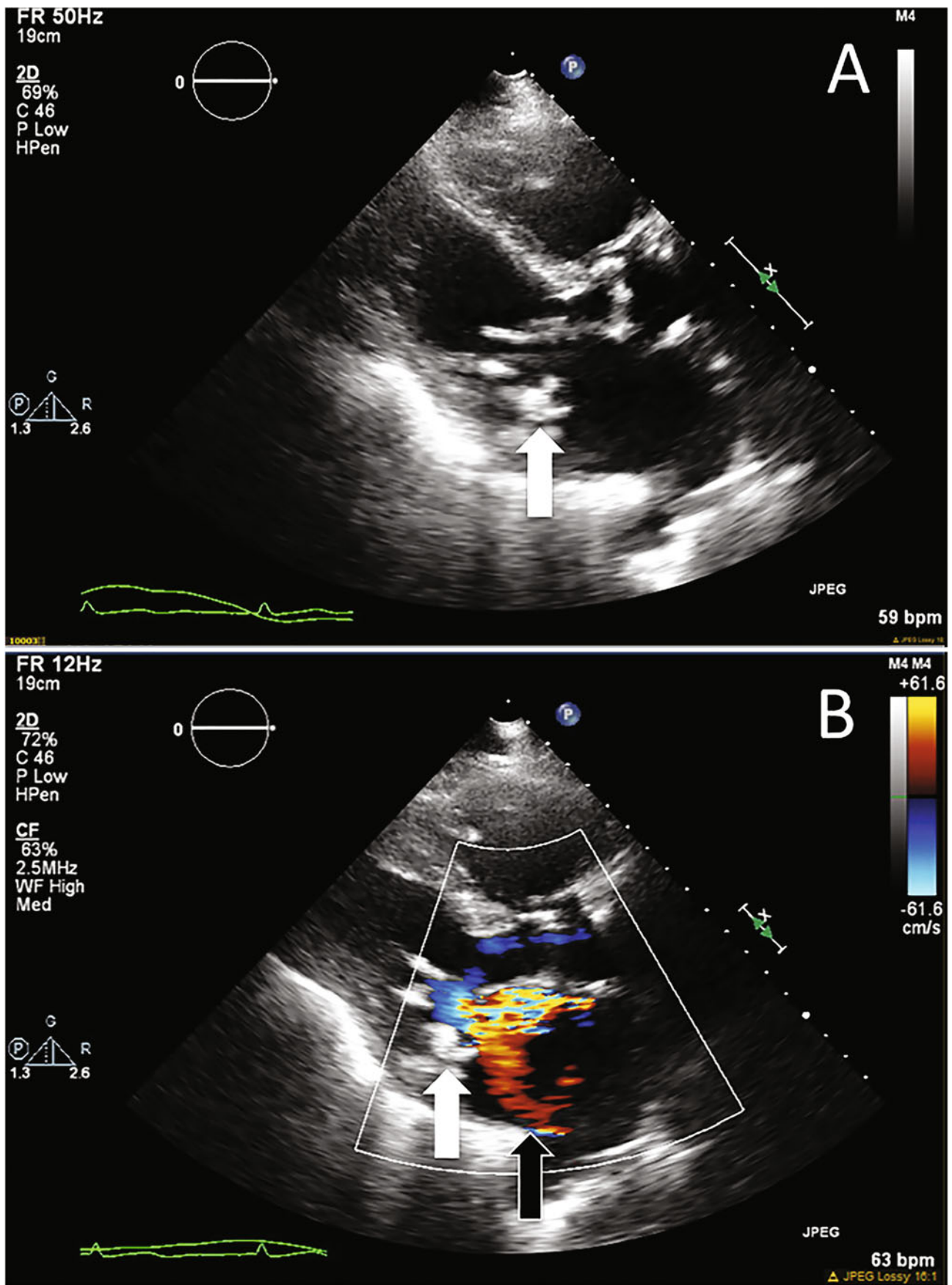
Fig. 2.1 Transthoracic echocardiogram (TTE) revealing posterior mitral annular calcification (MAC, *white arrows* **a**, **b**) causing restriction of the posterior mitral leaflet with the resulting severe mitral regurgitation on Doppler (b, *black arrow*)
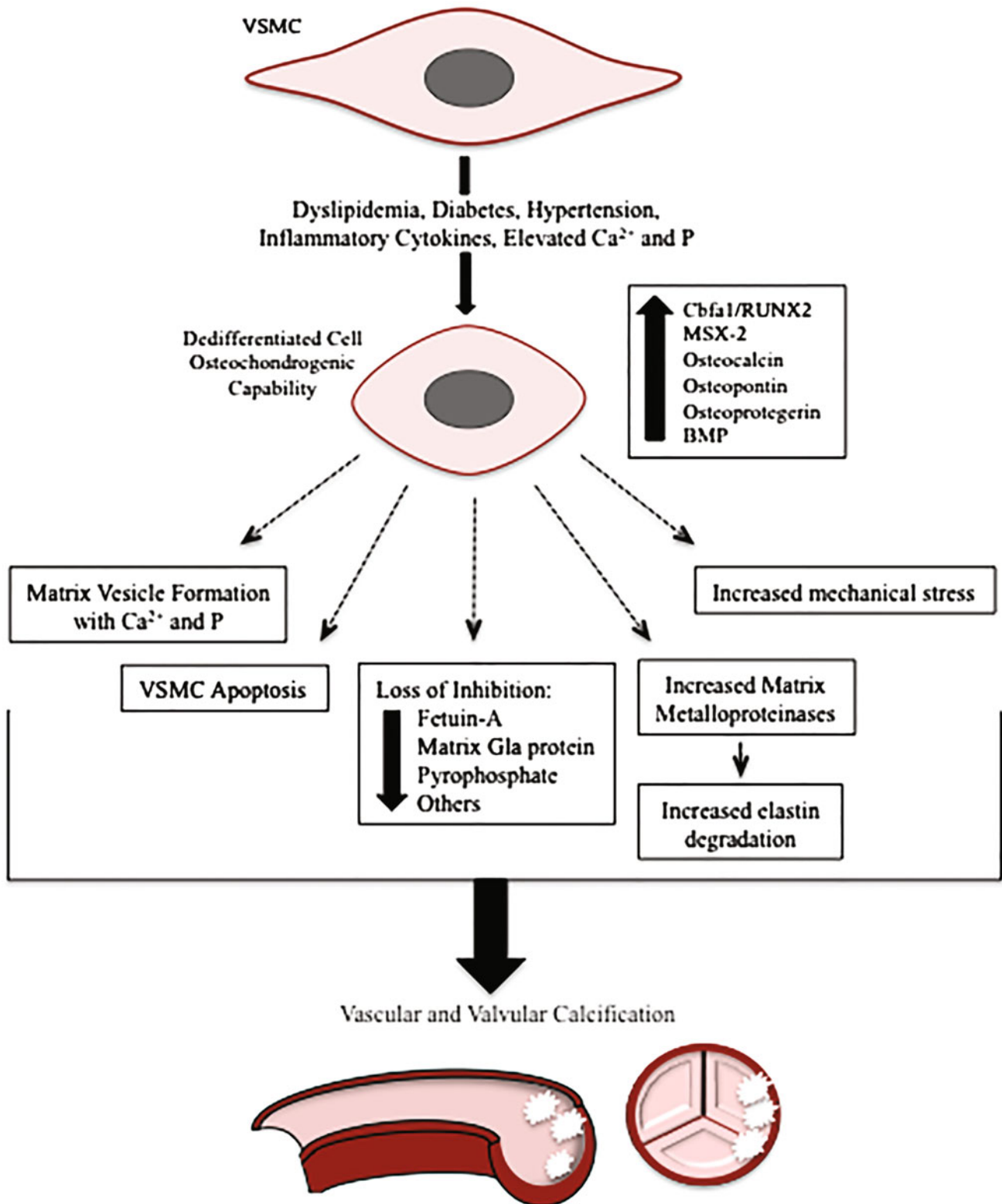
Fig. 2.2 Pathophysiology of vascular/valvular calcification in patients with chronic kidney disease

Disturbance in Mineral Metabolism

Early in CKD, disturbances in mineral metabolism result in a positive calcium and phosphate balance. Increases in fibroblast growth factor-23 (FGF-23) cause inhibition of 1-α hydroxylase, decreasing 1,25-dihydroxyvitamin D_3 (calcitriol) synthesis. Calcitriol, which is produced by the proximal tubular cells of the nephron, normally inhibits the renin–angiotensin system (RAS) and has anti-inflammatory effects. The decrease in calcitrol also decreases calcium absorption in the stomach resulting in a decrease in total body calcium. This triggers secondary hyperparathyroidism caused by hyperplasia of the parathyroid gland, which promotes osteoclast resorption of bone to release calcium and phosphate. PTH directly stimulates the renin–angiotensin system causing a hypertensive state that may further promote endothelial damage and calcification [25]. Increases in PTH and FGF-23 also promote increased phosphate excretion from the kidney; therefore, hyperphosphotemia is only a clinical finding in late CKD when GFR is significantly reduced. Elevated levels of calcium, phosphate, FGF-23, and PTH are all associated with increased vascular and valvular calcification in patients with CKD and are almost ubiquitous in advanced CKD [3, 26]. Some patients with CKD may develop a relative resistance to PTH and resultant adynamic bone disease. Despite elevated levels of PTH compared to the normal population, these patients have decreased osteoblast and osteoclast activity, which can cause skeletal abnormalities and increased CVD [27, 28].

The presence of hyperphosphotemia in ESKD is associated with increased mortality rates, particularly when the serum phosphorous levels are higher than 6.5 mg/dl [26, 29]. Elevated phosphate promotes VSMC de-differentiation to osteogenic cells and induces mineralization of VSMC.

The increase in total body calcium and phosphate in patients with CKD have independent and additive effects promoting extraskeletal calcification. Serum calcium concentrations however, can be misleading because patients on dialysis can have an increase in total calcium balance despite a normal serum calcium [3]. Calcium is deposited within and on the surface of matrix vesicles, which enables calcium-phosphate nucleation via matrix proteins. The increase in cytoplasmic calcium induces VSMC apoptosis, releasing the hydroxyapatite matrix vesicles and forming a nidus for vascular calcification [30].

Alteration in Inhibitory Regulation

Proteins that are responsible for inhibiting calcification such as *Fetuin-A*, *matrix Gla protein* (MGP), and *inorganic pyrophosphate* are often reduced in patients with CKD. Fetuin-A is a circulatory defense mechanism, working to prevent systemic inflammation and vascular calcification without affecting bone mineralization. Fetuin-A binds to both calcium and phosphorus in the serum to promote removal through the reticuloendothelial system. This prevents matrix vesicle formation and increases phagocytosis of matrix vesicles by VSMCs [31]. In ESKD patients, serum Fetuin-A levels are inversely associated with carotid artery plaques, coronary artery calcification, valvular calcification, and death [19].

MGP is a vitamin K dependent regulator of vascular calcification that is normally expressed in arteries and bone. The role of MGP is not well understood, but it is generally accepted that MGP inhibits arterial calcification [15]. High calcium levels are associated with CKD overwhelm endogenous MGP activity, thereby reducing inhibition of calcification in matrix vesicles. Warfarin, a vitamin K antagonist, is believed to promote calcification in the aorta and in the arterial elastic lamina due to its effect on MGP [15, 32]. This hypothesis has been further corroborated by studies showing that supplementation with vitamin K in patients on hemodialysis can increase carboxylated MGP levels and to reduce vascular calcification [33].

Pyrophosphate is another calcification inhibitor, which prevents VSMC formation of hydroxyapatite. Increased levels of alkaline phosphatase, which hydrolyzes pyrophosphate, may be responsible for the decrease in pyrophosphate in patients with renal insufficiency and are negatively associated with arterial calcification in these patients [34].

Increase in Matrix Metalloproteinases (MMP)

Elevated MMP may cause an increase in medial elastic fiber fragmentation, which promotes medial calcification by preventing excess elastin degradation. In patients on hemodialysis, there is an increase in MMP-2 and an associated increase in elastin fragmentation [35]. MMP-2 is also elevated in patients with advanced CKD and is correlated with increased arterial stiffness and increased calcification [18, 35]. The role of MMP in elastin degradation may explain why medial calcification is more prevalent in patients with renal insufficiency and may be a target for future therapy [6, 24].

Chronic Inflammation

In ESKD, protein–energy malnutrition (PEM) and inflammation often occur concomitantly as malnutrition–inflammation complex syndrome (MICS) or malnutrition atherosclerosis. Chronic inflammation is thought to contribute to the decrease in total body protein and reduced

functional capacity seen in PEM [36]. The chronic inflammatory state is also responsible for osteochondrogenic differentiation of matrix elements and increased VSMC apoptosis, which results in vascular and valvular calcification [9, 23].

Mechanical Stress

In patients with impaired renal function, valvular endothelial microfractures from mechanical stress initiate valvular calcification. Valvular microfractures are more prevalent in patients with renal insufficiency and are particularly apparent in patients on hemodialysis because of the high output state associated with anemia, AV fistulas, hypertension, and volume overload [9, 10]. This increases the mechanical stress on the valves and promotes valvular calcification.

Clinical Impact of Vascular Calcification

Vascular calcification begins in the early stages of CKD and rapidly progresses as renal function decreases. Patients with CKD stage 3 or above are considered to be the highest risk population for subsequent cardiovascular events associated with worsening vascul1ar/valvular calcification [37]. The most prevalent clinical complications of vascular calcification include coronary artery disease (CAD) and peripheral artery disease (PAD).

In patients with CKD, diagnosis of CAD can be challenging due to atypical clinical presentations. Many commonly used diagnostic tests for CAD, such as single-photon emission computed tomography (SPECT), have a decreased sensitivity and specificity in ESRD patients [38, 39]. In these patients, the determination of coronary artery calcification using electron-beam CT (EBCT) can be a useful, noninvasive tool for the evaluation and diagnosis of CAD. Ultimately, invasive coronary angiography continues to be the gold standard for diagnosis of anatomic CAD burden [40]. However, contrast-induced nephropathy (CIN) during coronary angiography and percutaneous intervention remains a concern in patients with CKD. New research suggests that fluid administration based on LVEDP can reduce the risk of CIN in patients with CKD [41]. Additionally, increased operator experience and improved imaging technology have enabled physicians to reduce the use of contrast in patients with CKD.

The most feared complication of CAD is myocardial infarction (MI). CKD patients presenting with an MI have 3 times higher mortality rates than the general population and ESKD patients with MI have an astounding 15 times higher mortality than the general population [42]. The observed worse outcomes in CKD patients, can in part be explained by a greater frequency of triple vessel or left main disease, increased calcific severity of culprit coronary lesions [43], and uncertainty regarding the optimal treatment strategies for this patient population. Coronary reperfusion with either CABG or PCI is associated with higher rates of operative and long-term mortality in patients with CKD compared to non-CKD patients [44, 45]. In CKD patients undergoing PCI, the widespread vascular calcification can complicate stent implantation due to the presence of complex coronary lesions. In general, the increased calcification of the myocardium and microvasculature of the heart contributes to depressed cardiac function and reserve capacity. This manifests clinically as an increased risk of both surgical and percutaneous procedural complications [45]. The complexity of cardiovascular management in patients with CAD and CKD supports the utilization of a team approach with input from cardiac surgeons, interventional cardiologists, and nephrologists.

Peripheral artery disease is also a common cause for percutaneous intervention or surgical treatment in the CKD population. There is an incremental increase in mortality and morbidity associated with peripheral vascular intervention (PVI) as CKD progresses from mild to severe. CKD is an independent predictor for perioperative re-intervention with no change in perioperative mortality when adjusted for age, CAD, critical limb ischemia (CLI), and diabetes [46]. Severe CKD (stage 4 or 5) has been associated with a decrease in short and long-term survival and an increase in amputation rates. This is possibly due to the presence of small vessel disease and increased multilevel PVI in CKD patients [46].

Medical Strategies to Prevent Calcification

There is currently no medical treatment that can reverse calcification in patients with CKD. Therefore, controlling traditional risk factors such as hypertension, dyslipidemia, smoking, and diabetes is crucial to prevent vascular calcification and associated CVD [47]. Treatment modalities that focus on reducing the calcium phosphorus product (CaXP) to recommended targets (<55, K DIGO) help reduce extra skeletal calcification burden [48].

Treatment options for secondary hyperparathyroidism such as activated vitamin D supplementation and calcimimetics reduce the need for surgical parathyroidectomy and reduce the progression of calcification in patients on dialysis [49]. The application of bisphosphonates, vitamin K supplementation, and sodium thiosulfate in reducing in vascular calcification and mortality are still undetermined and warrant further study [15].

Clinical Impact of Valvular Calcification

In CKD (with or without dialysis), the prevalence of aortic and mitral calcification is significantly higher than in the general population. In CKD, there is a graded relationship between the progressive decrease in GFR and the prevalence of calcification, hospitalizations, cardiovascular events, and death [50]. Complications often associated with valvular calcification include thromboembolism, cardiac arrhythmias, and valvular stenosis.

Thrombotic lesions and ulcers are found on calcified valves and can potentially dispense bursts of calcium-phosphate crystals into the lumen of the heart [11]. Additionally, vegetations that may be present in MAC and aortic valvular calcification (AVC) can embolize and travel through the blood stream to cause ischemia in other organs, most commonly stroke. In patients with MAC, emboli are typically larger and are more likely to cause cerebral ischemia, whereas in patients with AVC, emboli are often smaller and more prone to land in the retinal artery causing monocular blindness [9–11]. In MAC and AVC, calcium can also invade the conduction system of the heart, causing conduction abnormalities such as atrial fibrillation, atrioventricular block, and intraventricular block [10]. Once the calcification begins to impinge on the valvular lumen or restrict the valve leaflets it can cause valvular stenosis.

Aortic Valve

Valvular stenosis is more common in the aortic valve and can lead to severe hemodynamic complications. The progression from asymptomatic aortic disease with calcification to severe symptomatic AS is rapid in patients with renal insufficiency. In patients with CKD, annual reduction in aortic valve area was 0.23 cm^2 as compared to 0.05–0.10 cm^2 in patients without kidney disease [51]. This is a dramatic and rapid decrease in valvular area, given that the aortic valve area is on average 3–4 cm^2. After the onset of symptomatic AS, mean survival in CKD patients is approximately 23 ± 9 months [52].

Valve replacement is the only therapy with survival benefit for severe AS, regardless of whether the patient has CKD. The two main treatment options for AVR are surgical (SAVR) and transcatheter aortic valve replacement (TAVR). In SAVR, CKD is a risk factor for increased 30-day and long-term mortality, with a more than 50% increase in median postsurgical mortality over a span of 15 years [53]. Patients with renal insufficiency have increased complications from SAVR, in part because the technical challenges associated with severe vascular and valvular calcification lead to increased in-hospital mortality, increased hospital length of stay, and increased ICU duration [54].

The less invasive TAVR may be an alternative for valve replacement in patients with advanced CKD, due to the inherent higher surgical risk and the potential to avoid some of the complications observed with SAVR [54]. In patients undergoing TAVR with CKD, femoral access may be limited due to excess vascular calcification (Fig. 2.3), requiring the use of alternative accesses with potentially higher risk of complication such as transapical, transaortic, transcarotid, or transcaval access [55]. The enhancement of technology, technique, and experience has decreased the use of IV contrast and the incidence of complications, suggesting that in the future, TAVR can become the preferred therapeutic choice in patients with advanced CKD (Fig. 2.3)

Despite advances in surgical and percutaneous techniques, valvular calcification is still associated with complications after SAVR and TAVR. Preexisting damage to the heart's conduction system increases the risk of pacemaker requirement after surgical or transcatheter intervention [56]. Porcelain aorta is another risk factor associated with worse outcomes after SAVR and is often considered a nontraditional risk factor for surgical death. This is probably due to the requirement for extensive aortic replacement. Additionally, the degree of annular and left ventricular outflow track calcification is linked to a higher degree of paravalvular regurgitation post-TAVR. Calcification can prevent adequate sealing between the native and bioprosthetic valve after deployment. Evaluation with a preprocedural multidetector computed tomography (MDCT) characterizes the location and severity of calcification and provides critical information necessary to decide the best treatment strategy (TAVR vs. SAVR, Fig. 2.4) [57].

Mitral Valve

Mitral stenosis and/or regurgitation can occur secondary to MAC and may require either surgical or transcatheter intervention. The extensive mitral calcification associated with CKD increases surgical complications such as hemorrhage, atrioventricular disruption, left ventricular rupture, and peri-prosthetic leakage [58]. Ironically, the presence of severe mitral valve disease (MS or MR) associated with severe MAC makes these high-risk patients potential candidates for percutaneous interventions, specifically transcatheter mitral valve replacement. A circumferentially calcified annulus can provide the necessary support and anchoring for a stented transcatheter heart valve deployment and can reduce the risk of embolization [59]. As discussed with TAVR, preprocedural planning for percutaneous intervention with MDCT can help evaluate the MAC distribution in detail (Fig. 2.5). Evidence of transcatheter mitral valve replacement in these situations is limited to case reports and case series [60], with multicenter registries currently being created to better study this treatment strategy.
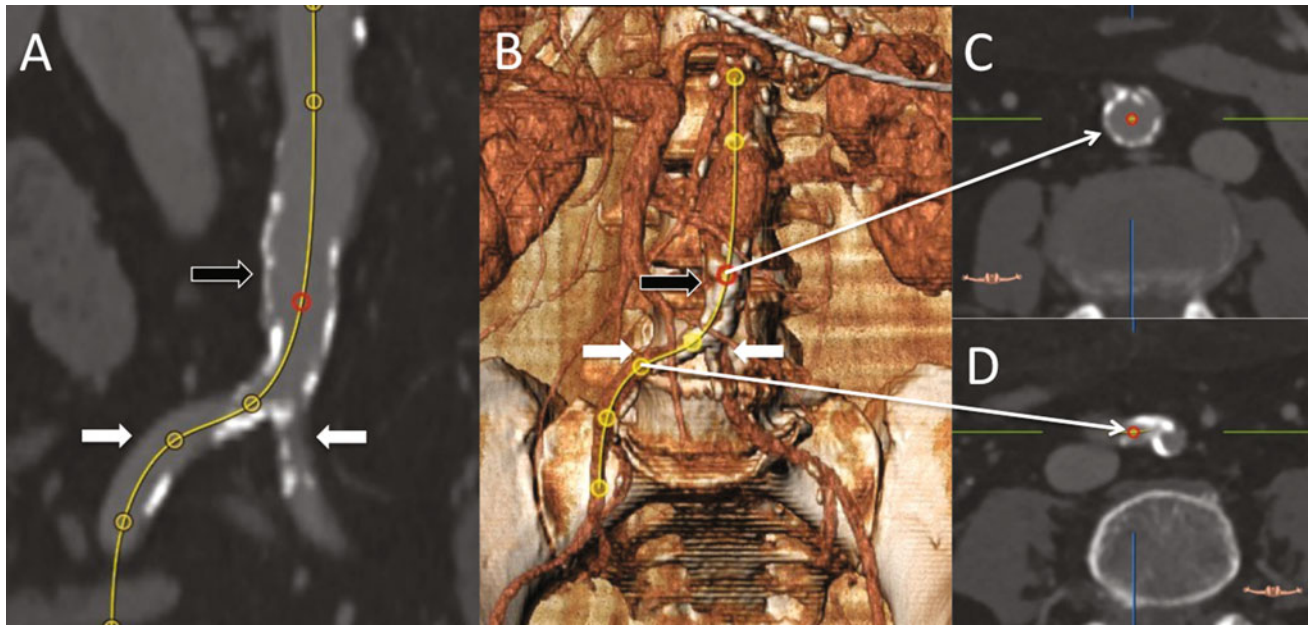
Fig. 2.3 Evaluation of vascular calcification during preprocedural planning for transcatheter aortic valve replacement. Coronal view (**a**) and 3D-reconstruction (**b**) of the abdominal aorta (*black arrows*) and iliac arteries (*white arrows*) allows for visual determination of calcification. The size of the vessels can then be determined from the transverse plane (**c**, **d** transverse plane of locations with severe vessel calcification)

Fig. 2.5 Multidetector cardiac computed tomography for the planning of percutaneous mitral valve intervention, reveals posterior mitral annular calcification (MAC, *white arrows* **a**, **b**) and descending aorta calcification (*gray arrow*, **b**)
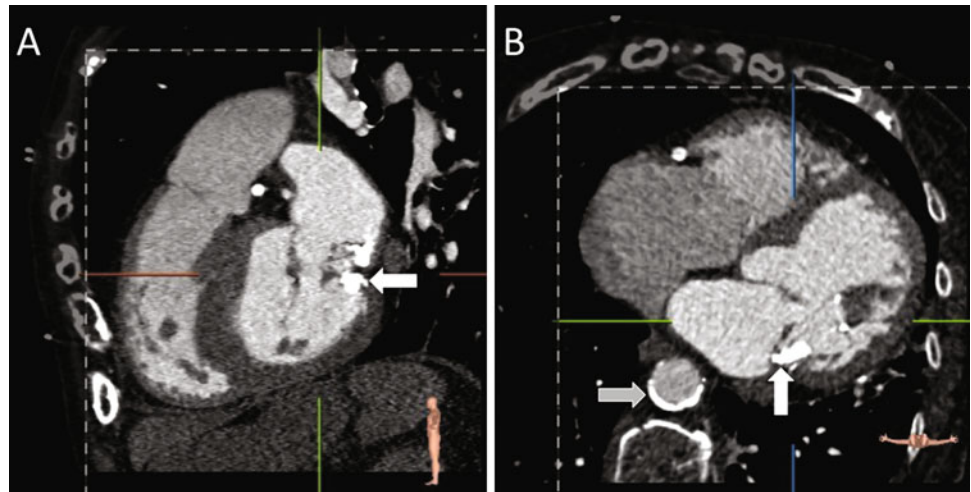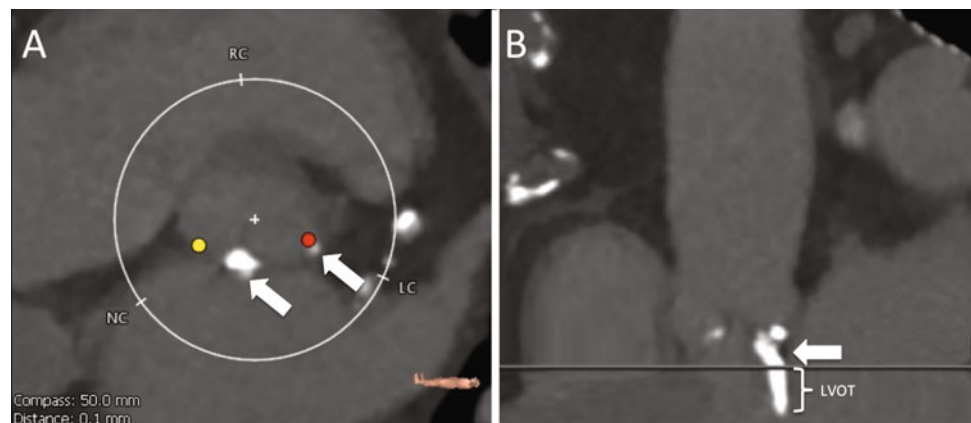

Fig. 2.4 Multidetector cardiac computed tomography revealing severe focal calcification (*arrows*) of the aortic annulus (**a**) and left ventricular outflow track (LVOT, **b**). These calcifications can be related to worse outcomes after surgical or transcatheter aortic valve replacement

Conclusion

Vascular and valvular calcification in CKD is associated with increase CVD burden, and worse outcomes after coronary reperfusion or valve replacement, respectively. Though calcification in these patients is multifactorial, aggressive control of traditional and nontraditional risk factors can help prevent and slow the progression of disease. However, in those patients requiring intervention for CAD or valvopathy, a multidisciplinary team evaluation is critical to improve outcomes.

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