

The Main Causes of the Heightened Risk of Cardiovascular Events in Individuals with Chronic Kidney Disease (CKD) are Vascular Calcification (VC) and Calcification of the Cardiac Valves (CVC)

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Abstract

In chronic kidney disease (CKD) patients, vascular calcification (VC) and cardiac valve calcification (CVC) are the major reasons of increased risk of cardiovascular events. Originally thought to be a passive kind of dead or dying cells, VC and CVC have since been identified as a disease caused by an active and highly controlled cellular process. Several of the processes implicated in VC have recently been identified, and many of them may be exacerbated in CKD patients. FGF-23/Klotho axis, Wnt pathways, PI3K/Akt signalling, P38MAPK signalling pathway, and microRNAs, in particular, have been demonstrated to be disturbed in CKD patients and may have a role in vascular calcification. Moreover, multiple researches confirmed the hazards of CVC in CKD patients as well as the molecular processes behind it. The purpose of this review is to describe the risk variables and pathophysiological processes that may be implicated in the relationship among CKD and VC and CVC development.

Keywords: Chronic kidney disease; Vascular calcification; Cells; Atherosclerosis

Introduction

Chronic kidney disease (CKD) progression is associated with a number of significant consequences, including cardiovascular events, which are the leading cause of mortality in CKD patients [1]. Cardiovascular events are frequently caused by vascular calcification (VC) and cardiac valve calcification (CVC) [2,3]. As compared to the non-CKD population, the incidence of vascular calcification or CVC in CKD is substantially greater, increasing the likelihood of sudden mortality [3,4]. In CKD patients, VC is caused by two separate but overlapping vascular pathologies: atherosclerosis and arteriosclerosis. Atherosclerosis is defined by lipid-laden plaques that are restricted to the tunica intima of the artery wall, causing vascular irritation, thickening, and calcification [5]. Arteriosclerosis, also known as medial arterial calcification, is associated with vascular fibrosis, thickness, and rigidity, all of which contribute to left ventricular hypertrophy [6]. The heart valve is made up of valve endothelial cells (VECs) and valvular interstitial cells (VICs) (VICs). The major cause of valve calcification is endothelial dysfunction, which leads to interstitial cell loss and differentiation [7]. We cover the modulation of vascular and cardiac valvular calcification in this paper. We emphasise fundamental insights into VC and CVC processes, as well as CVC risk factors, which may provide the groundwork for innovative treatment methods to address vascular and cardiac valve calcification in CKD. FGF-23, a bone-derived hormone, is localised at 12p13 in humans and contains 251 amino acids protein (molecular weight=30 kDa), and it is commonly thought to play a significant role in vascular alterations [8,9]. Klotho, a component of the klotho/FGF-receptor complex, was initially discovered by Kuro-o et al. and has since become an important factor in health and illness [10-12]. It encodes a single-pass transmembrane klotho protein associated in cardiovascular disease, including as atherosclerosis and VC, and is expressed at high levels in renal distal tubular epithelium, but not in the parathyroid gland or human vascular tissue [12,13]. The membrane klotho interacts with fibroblast growth factor receptors (particularly FGFR1) to produce a high-affinity for FGF-23 in order to maintain mineral homeostasis by promoting phosphate excretion into the urine and lowering blood $1,25(\text{OH})_2\text{D}_3$

levels [14,15]. While the klotho gene is expressed in the distal tubule of the kidney, renal phosphate reabsorption occurs mostly in the proximal tubule. Hence, how the FGF-23/klotho axis reduces phosphate resorption in the proximal has to be investigated further. It has been shown that a high level of FGF-23 in vascular smooth muscle cells (VSMCs) and CKD is associated with the advancement of arterial calcification score irrespective of blood phosphorus level [16,17]. FGF23 is also linked to artery endothelial damage, particularly in CKD [18,19]. Subsequent research revealed that the anti-VC effects of active vitamin D and its analogue can be mediated by reduced FGF-23 and enhanced klotho expression independent of serum parathyroid hormone (PTH) levels [20,21]. CKD is a disease characterised by vascular klotho deficit caused by chronic circulating stress factors such as pro-inflammatory, uremic, and disordered metabolic conditions, which can accelerate the development of human artery calcification and mediate resistance to FGF-23. Others argue that soluble klotho improves VC via increasing phosphaturia, maintaining glomerular filtration, and directly blocking phosphate absorption by vascular smooth muscle. Nevertheless, Cha et al. found that released klotho protein activates transient receptor potential vanilloid-5, which is involved for calcium reabsorption in the kidney and can cause vascular calcification. As a result, the link between klotho and vascular calcification remains unknown. The Wnt pathways are a collection of signal transduction pathways that include the canonical Wnt pathway as well as the non-canonical Wnt/calcium pathway. When Wnt ligands

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(e.g., Wnt1, Wnt3a) bind to their receptors, cell-surface Frizzled (FZD) and low density-lipoprotein-receptor-related protein 5/6 (LRP 5/6), the canonical Wnt signalling pathway is activated. When the FZD/LRP 5/6 receptor complex is activated, GSK-3 β is inactivated, and catenin accumulates in the cytoplasm and translocates to the nucleus, where it can heterodimerize with members of the lymphoid enhancer factor/T-cell factor transcription factor family to induce the expression of specific genes. Wnt signalling pathways have been implicated in vascular diseases, including endothelial dysfunction and migration, VSMC trans differentiation, and VC. Wnt signalling is important in VSMC calcification produced by high-phosphate and bone morphogenetic protein 2 (BMP-2). We found higher expressions of β -catenin, GSK-3, and Wnt-5a in the calcific region of VC in patients with end-stage renal disease (ESRD), and logistic regression analysis revealed that Wnt-5a was an independent risk factor for vascular calcification in ESRD patients. Moreover, PI3K/Akt can activate the β -catenin signalling pathway by cross-linking the MAPK signalling pathway to cause VC and CKD. The MAPK signalling pathway is an important mechanism that facilitates eukaryotic signal transmission and is important in osteoblast development and mineralization of VSMCs. A recent research found that P38MAPK can modulate the canonical Wnt-catenin signalling pathway in the brain, thymus gland, and spleen by inactivating GSK-3. Nevertheless, whether this route is implicated in calcification has to be investigated further. MicroRNAs (miRs) are short noncoding RNAs that control cellular processes such as proliferation, differentiation, and death by regulating target gene expression via mRNA degradation, translational repression, or mRNA modification. Many investigations have found that miRs are linked to VSMC calcification. MiR-125b was shown to be down regulated in calcified aortas of apoE mutant rats, and its analogues have been shown to suppress calcification of rat aortic SMCs cultivated in high-phosphate media. BMP-2 inhibited the expression of miR-30b and miR-30c in vitro, and miR-30b expression was likewise inhibited in calcified human coronary arteries. MiR-29 a/b expression was shown to be low in calcific aortas from mice as well as CKD patients. The Wnt pathways are a collection of signal transduction pathways that include the canonical Wnt pathway as well as the non-canonical Wnt/calcium pathway. When Wnt ligands (e.g., Wnt1, Wnt3a) bind to their receptors, cell-surface Frizzled (FZD) and low density-lipoprotein-receptor-related protein 5/6 (LRP 5/6), the canonical Wnt signalling pathway is activated. When the FZD/LRP 5/6 receptor complex is activated, GSK-3 β is inactivated, and β -catenin accumulates in the cytoplasm and translocates to the nucleus, where it can heterodimerize with members of the lymphoid enhancer factor/T-cell factor transcription factor family to induce the expression of specific genes. Clinical investigations have revealed that diabetics have a high risk of vascular calcification, and valve failure is a more severe disease. High blood glucose and carbohydrate metabolic products such as AGEs can harm human cells, including endothelial cells, by activating numerous signalling pathways (e.g., PI3K and JAK/STAT) and downstream factors (e.g., RANK). Hypertension was seen in almost 70% of the CKD patients studied in China, and blood pressure regulation was inadequate. Hypertension-induced vasospasm contraction and endothelial dysfunction might impair the synthesis and release of vascular dilators, worsening the endothelium-dependent vasodilator response system. Pathological investigations of aortic valve disorders revealed that the most prominent pathological features are lipidosis and inflammatory infiltration. As a result, hyperlipemia, hypertension, and diabetes can all cause endothelial dysfunction, which can then lead to valvular and vascular calcification. Inflammation and reactive oxygen species (ROS) are two prevalent diseases related with CVC in

CKD patients. Inflammatory cytokines such as the interleukin-6 (IL-6) and TNF superfamily, as well as the inflammation-related transcription factor NF- κ B, have been shown to increase calcification in cultured VICs, VSMCs, and experimental animal models. Leskinen et al. discovered that IL-6 levels in CKD patients are risk factors for valvular calcification. Moreover, TNF production may stimulate the Wnt signalling pathway, leading to CVC. Miller et al. found that individuals with aortic valve calcification had a higher hydrogen peroxide level than the control group, indicating that hydrogen peroxide-mediated oxidative stress may play a major role in CVC.

Discussion

Many CKD patients have arterial or valvular calcification, which has a significant impact on their survival chances. There are currently relatively few alternatives for either preventing or treating arterial or valvular calcification in CKD.

Conclusion

Despite recent advances in understanding of the processes of ectopic calcification, further research and understanding of this complex process is required, particularly the interplay between VECs and VICs and their regulatory mechanisms in the development of valve calcification. Only by better understanding the mechanism of vascular and valvular calcification will we be able to develop more effective treatments for CKD patients.

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Conflict of Interest

Author declares no conflict of interest.

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