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Review Article

Vascular calcification in CKD-MBD: Roles for phosphate, FGF23, and Klotho

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ABSTRACT

Vascular calcification (VC) is highly prevalent in aging, diabetes mellitus, and chronic kidney disease (CKD). VC is a strong predictor of cardiovascular morbidity and mortality in the CKD population. Complex pathological mechanisms are involved in the development of VC, including osteochondrogenic differentiation and apoptosis of vascular smooth muscle cells, instability and release of extracellular vesicles loaded calcium and phosphate, and elastin degradation. Elevated serum phosphate is a late manifestation of CKD, and has been shown to accelerate mineral deposition in both the vessel wall and heart valves. α-Klotho and fibroblast growth factor 23 (FGF23) are emerging factors in CKD-mineral and bone disorder (CKD-MBD) and are thought to be involved in the pathogenesis of uremic VC. There are discordant reports regarding the biomedical effects of FGF23 on VC. In contrast, mounting evidence supports a well-supported protective role for α-Klotho on VC. Further studies are warranted to elucidate potential roles of FGF23 and α-Klotho in VC and to determine where and how they are synthesized in normal and disease conditions. A thorough systemic evaluation of the biomedical interplay of phosphate, FGF23, and α-Klotho may potentially lead to new therapeutic options for patients with CKD-MBD.

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1. Cardiovascular mortality and vascular calcification (VC)

Patients with chronic kidney disease (CKD) and end stage kidney disease (ESKD) have an increased risk for cardiovascular mortality and morbidity [1,2]. Cardiovascular diseases account for 30–50% of all-cause mortality in patients with CKD and ESKD worldwide. Although traditional risk factors contribute to the development of cardiovascular disorders in CKD, they cannot fully explain the unacceptably high

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Abbreviations: CAVD, calcific aortic valve disease; CKD, chronic kidney disease; CKD-MBD, CKD-mineral and bone disorder; ESKD, endstage kidney disease; FGF23, fibroblast growth factor 23; FGFR, fibroblast growth factor receptor; Pi, phosphate; PTH, parathyroid hormone; SMCs, smooth muscle cells; VC, vascular calcification.

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incidence of cardiovascular mortality in these patients. Hence, non-traditional risk factors, including abnormal mineral metabolism, are considered to be involved in the enhanced risk of cardiovascular events [3,4].

VC, abnormal deposition of calcium-phosphate (Pi) salts in vascular tissues including blood vessels, valves, and heart, is frequently observed in aging, diabetes mellitus, CKD, calcific aortic valve disease (CAVD), and several genetic diseases [5–8]. Mounting clinical evidence has shown that VC is indeed an independent predictor of cardiovascular morbidity and mortality in CKD and ESKD [9–11]. Dialysis patients show a 5-fold to 30-fold increase in cardiovascular mortality risk compared to the general population [1]. Hence, VC is now considered to be a major contributor to increased cardiovascular mortality rates. Importantly, nontraditional risk factors including abnormal mineral metabolism appear to underlie this increased risk [3,12]. There are currently no treatments available that can halt or reverse the progression of VC. Hence, understanding how abnormal mineral metabolism leads to VC is greatly needed in order to develop earlier diagnostic tools and new therapies that prevent or regress VC in the CKD population.

2. VC in CKD-mineral and bone disorder (CKD-MBD)

CKD-MBD is a newly termed systemic disorder that is characterized by abnormal serum biochemistries including hyperphosphatemia and hypercalcemia, bone disorders, and VC [13]. Among these defining characteristics, VC is the hallmark of CKD-MBD.

VC can be classified by the vascular site of abnormal mineral deposition. Deposition of calcium salts in the intimal layer and medial layer are termed as intimal calcification and medial calcification, respectively [14]. Valvular calcification, often observed in CAVD, is characterized by the deposition of calcium salts in the heart valves. These three types of VC are highly prevalent and accentuated in the CKD population [7,14].

The impact of VC on cardiovascular outcome relates to the location of mineral deposition. Intimal calcification reflects atherosclerotic plaque burden and may influence plaque rupture, and is a strong predictor of cardiovascular events and mortality [15]. On the other hand, medial calcification induces stiffening of the vessel, increased pulse wave velocity, and left ventricular hypertrophy, and can result in heart failure [16]. Valvular calcification causes valve stenosis, and can lead to cardiac hypertrophy, valve and heart failure, and sudden cardiac death [17]. All forms of calcification contribute to increased cardiovascular mortality in CKD-MBD [13,18]. Deeper understanding of the pathological calcification process is required to reduce the risk of VC, create novel therapeutic options, improve quality of life, and extend the life expectancy in CKD population.

3. Mechanisms of VC

VC was once considered to be a passive deposition of calcium-Pi salts from supersaturated fluids related to aging and degenerative process in the vasculature. It is now clear that VC is an actively cell-regulated pathology [19]. Advances in this field have unveiled the complex molecular mechanisms regulating VC [20]. Under normal conditions, vessels and valves are protected from supersaturated concentrations of serum calcium and Pi by a number of active inhibitors that protect against abnormal mineral deposition in soft tissues [21–24]. Several calcification inhibitors have been identified, including: pyrophosphate, adenosine, matrix Gla protein, osteopontin, fetuin-A, osteoprotegerin, and bone morphogenetic protein-7. However, once the balance between the total capacity of active inhibitors and active inducers is tipped, VC can occur in the vessel walls and valves (Fig. 1). In the CKD population, active inducers of calcification include hypercalcemia, increased levels of parathyroid hormone (PTH), inflammatory cytokines, oxidative stress, uremic toxins, advanced glycation end products, and perhaps most importantly, Pi [20]. A number of these calcification inducers are increased and, simultaneously, active inhibitors are decreased, likely explaining the extremely high prevalence of vascular intimal, medial, and valvular calcification [25–27].

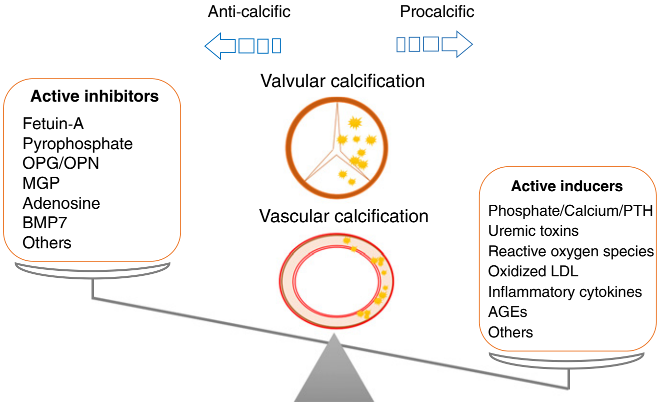

Fig. 1. Imbalance between active inducers and inhibitors of vascular calcification. Vessels and valves mineralize when active inducers exceed the capacity of active inhibitors. Active inducers are increased and active inhibitors are decreased in aging, diabetes mellitus, and CKD. AGEs, advanced glycation end products; BMP, bone morphogenetic protein; CKD, chronic kidney disease; LDL, low density lipoprotein; MGP, matrix Gla protein; OPG, osteoprotegerin; OPN, osteopontin; PTH, parathyroid hormone.

4. Elevated Pi as a major inducer of VC

Among various inducers of calcification in CKD, hyperphosphatemia is most strongly associated with VC and a typical manifestation of CKD-MBD [3,28]. Serum Pi level is maintained in the normal range by the balance among intestinal Pi absorption, renal tubular Pi reabsorption, and equilibrium of extracellular Pi with Pi in intracellular fluid or bone [29]. Among them, renal Pi filtration and reabsorption are believed to be the main determinants of serum Pi level at steady state.

As kidney function declines and nephron mass decreases, phosphaturic hormones such as PTH and fibroblast growth factor 23 (FGF23) are synthesized and secreted in response to relative Pi overload as early as CKD stages 2 and 3 [30]. These hormones act on the renal proximal tubules and down-regulate sodium-Pi co-transporter type IIa and IIc, important transporters that regulate Pi resorption in the renal tubules, thereby increasing renal Pi excretion and maintaining serum Pi level within normal range [31]. However, as CKD reaches advanced stages, kidneys can no longer filter as much Pi as dietary Pi intake, finally leading to overt hyperphosphatemia at CKD stages 4 and 5.

Clinical studies have shown that elevated serum Pi is a risk factor for VC and cardiovascular mortality and morbidity in the CKD population and particularly, patients with ESKD on dialysis [3,32,33]. More recently, even Pi levels at the high end of the normal range have been correlated with increased risk of cardiovascular mortality in the general population, indicating the potential toxicity of Pi [34,35]. Clinical studies have shown that hyperphosphatemia is closely associated with advanced VC in CKD and multiple in vivo studies have now shown that Pi loading promotes VC in uremic rodents [36–42].

A growing amount of evidence has begun to reveal the mechanisms by which Pi promotes VC (Fig. 2). Vascular smooth muscle cells (SMCs) express type III sodium-dependent Pi co-transporters; PiT-1 and PiT-2, encoded by SLC20A1 and SLC20A2, respectively [43]. In vascular SMCs, PiT-1 promotes and PiT-2 inhibits matrix mineralization induced by elevated Pi [44,45]. PiT-1 utilizes both Pi uptake-dependent and -independent mechanisms to promote osteochondrogenic phenotype change, synthesis of bone-related proteins, and calcification of the extracellular matrices [46–48]. In contrast, PiT-2 protects against Pi-induced vascular SMCs calcification, though the precise mechanism for this effect is still under investigation [44]. In addition, elevated Pi regulates vascular SMCs extracellular matrix stability, apoptosis, and extracellular vesicle release, though the receptors mediating these effects

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