

# Research Progress on the Relationship between Coronary Artery Calcification and Chronic Renal Failure

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## Abstract

**Objective:** Coronary artery calcification (CAC) is thought to be a controlled metabolic process that is very similar to the formation of new bone. In patients with chronic renal failure (CRF), CAC is very common, and CAC severity correlates with the deterioration of renal function. We summarized the current understanding and emerging findings of the relationship between CAC and CRF.

**Data Sources:** All studies were identified by systematically searching PubMed, Embase, and CNKI databases for the terms “coronary calcification”, “chronic renal failure”, “vascular smooth muscle cell”, and their synonyms until September 2017.

**Study Selection:** We examined the titles and abstracts of all studies that met our search strategy thoroughly. The full text of relevant studies was evaluated. Reference lists of retrieved articles were also scrutinized for the additional relevant studies.

**Results:** CRF can accelerate CAC progression. CRF increases the expression of pro-inflammatory factors, electrolyte imbalance (e.g., of calcium, phosphorus), parathyroid hormone, and uremic toxins and their ability to promote calcification. These factors, through the relevant signaling pathways, trigger vascular smooth muscle cells to transform into osteoblast-like cells while inhibiting the reduction of vascular calcification factors, thus inducing further CAC.

**Conclusions:** Coronary heart disease in patients with CRF is due to multiple factors. Understanding the mechanism of CAC can help interventionists to protect the myocardium and reduce the prevalence of coronary heart disease and mortality.

**Key words:** Chronic Renal Failure; Coronary Calcification; Vascular Smooth Muscle Cell

## INTRODUCTION

Epidemiologic data have shown that coronary artery calcification (CAC) increases with age. A CAC prevalence of 50% among people aged 40–49 years and 80% in those aged 60–69 years has been documented.<sup>[1]</sup> Vascular calcification, especially CAC, is associated with cardiovascular events. CAC is often located at the site of atherosclerotic lesions and can also occur at the early stage of atherosclerosis. CAC is closely related to coronary atherosclerosis, so it contributes to the diagnosis of coronary heart disease. The more severe the CAC, the greater is the probability of severe coronary stenosis, which increases the difficulty and management of coronary artery stenosis. The high mortality in patients with chronic renal disease (CRD) is associated with cardiovascular disease (CVD), which is the cause of death of >50% of patients with end-stage renal disease (ESRD), whereas coronary artery disease accounts for half of all CVD-associated deaths.<sup>[2]</sup> CAC is very common in patients with chronic renal failure (CRF),

and CAC severity correlates with the deterioration of renal function.<sup>[3]</sup> Understanding the relationship between CRF and CAC may help the management of coronary heart disease in patients with CRF. Furthermore, targeted treatment that can slow down CAC progression has been a research focus in recent years.

## PATHOGENESIS OF CORONARY ARTERY CALCIFICATION

For many years, vascular calcification was considered to be a passive, degenerative, and end-stage process of atherosclerosis and inflammation. However, recent studies have shown that CAC is an organized, regulated, proactive

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process.<sup>[4]</sup> CAC involves expression of an altered phenotype of vascular smooth muscle cells (VSMCs) and expression of bone-related proteins such as osteopontin, osteoprotegerin (OPG), osteocalcin, and bone morphogenetic proteins (BMPs). Hence, CAC is thought to be a controlled metabolic process that is very similar to the formation of new bone, with hydroxyapatite as the main component of its calcium salts instead of calcium phosphate.<sup>[5,6]</sup>

Recent studies on calcification formation have, in general, involved three aspects. The first aspect is osteoblast differentiation (i.e., transformation of the VSMC phenotype). The Msh homeobox 2 gene and Wnt signaling pathway can be activated if a change occurs in the surrounding environment (pro-inflammatory cytokines, high levels of calcium/phosphate). This activates the expression of runt-related transcription factor 2 (Runx2) and osterix, which are the key transcription factors that induce osteoblast differentiation.<sup>[7]</sup>

The second aspect is expression of bone-associated proteins. Runx2 regulates the expression of bone-related proteins such as osteocalcin, osteopontin, as well as receptor activator of nuclear factor kappa-B ligand (RANKL), and alkaline phosphatase (ALP).<sup>[8]</sup> Osterix is located downstream of Runx2, and its main role is to increase the expression of osteopontin and ALP.<sup>[9]</sup> Thus, VSMCs undergo phenotypic transformation and downregulation of expression of the contractile proteins smooth muscle (SM) 22 and alpha-smooth muscle actin ( $\alpha$ -SMA). Hence, they change from a contracted phenotype to a synthetic phenotype of the dedifferentiation state and differentiate into osteoblasts, thereby causing vascular calcification.<sup>[10]</sup> ALP is a key enzyme in vascular calcification, and oxidative stress can stimulate an increase in ALP activity in VSMCs. ALP can hydrolyze phosphate bonds, resulting in an increase in the local concentration of phosphate, which provides a good microenvironment for calcification. Osteocalcin is a marker of the late differentiation of osteoblasts. Osteocalcin and hydroxyapatite have a high degree of affinity and can cause hydroxyapatite deposition, which leads to vascular calcification.<sup>[11]</sup> In addition, other related proteins, cytokines, and other interactions are involved in the regulation of vascular calcification.

The third aspect is mineralization. The synthesis of bone-related proteins by VSMCs is accompanied by the release of matrix vesicles and apoptotic bodies, and some studies have shown that apoptosis and vesicle formation are the initial events of vascular calcification.<sup>[12]</sup> Vesicles have active ALP and contain large amounts of calcium and phosphorus; deposition of the latter two chemicals can result in the formation of apatite crystals and the release of calcium and phosphorus into the extracellular environment. Calcified nodules can be formed under the action of extracellular matrix proteins and cytokines, which eventually leads to vascular calcification.

## EFFECT OF CHRONIC RENAL FAILURE ON CORONARY ARTERY CALCIFICATION

CRF refers to a decline in the estimated glomerular filtration rate (eGFR) caused by CRD and its related metabolic disorders and symptoms. In CRF, metabolic acidosis and electrolyte imbalance (e.g., hyperphosphatemia and hypocalcemia) are common. The latter can cause hyperthyroidism and a decline in autocrine secretion (e.g., a decrease in serum levels of erythropoietin and active Vitamin D) followed by an increase in levels of uremic toxins.

CAC is also affected by sex, age, smoking, hypertension, diabetes mellitus, and high levels of cholesterol. CAC prevalence tends to increase exponentially with an increase in risk factors. CVD is a major cause of death in patients with CRF. An eGFR reduction equivalent to Stage-2 CRD can stimulate early vascular calcification.<sup>[13]</sup> Kestenbaum *et al.*<sup>[14]</sup> found that CAC is common in people with Stage-3 CRD, progresses rapidly, and may contribute to cardiovascular risk. Wajeh *et al.*<sup>[15]</sup> compared the prevalence of CAC between a group with early (Stages 1 and 2) CRD (29 patients) and a group with advanced (Stages 4 and 5) CRD (26 patients). They found that CAC was present in 38% and 73% of patients in early CRD and advanced CRD groups, respectively. Some investigators have reported an eGFR <60 ml/min (Stage 3–5 CRD) to be associated with an eightfold increased odds ratio for a CAC score >400 versus a CAC score  $\leq$ 10 compared with no CRD after adjustment for all covariates.<sup>[16]</sup> Górriz *et al.*<sup>[17]</sup> followed up 742 patients with non-maintenance hemodialysis (MHD) CRD Stages 3–5 for 3 years and showed a correlation between reduction in basal eGFR and increase in CAC.

CAC starts early in the course of CRD and progresses further with the deterioration of renal function. However, some studies on MHD patients have investigated CAC. Chen *et al.*<sup>[18]</sup> reported that 60.83% of patients on MHD had significant abdominal aortic calcification. Studies conducted in Germany showed calcification of the carotid artery to be present in 61.4% of MHD patients.<sup>[19]</sup> Peritoneal dialysis can help patients to remove most of the metabolites retained in their body, slows down the decline of residual renal function, maintains hemodynamic stability, and prolongs survival, but  $\leq$ 80% of patients have the complications of vascular calcification [Figure 1].

## INFLAMMATION-RELATED FACTORS

Recent studies have shown that arterial calcification and atherosclerosis are chronic inflammatory diseases.<sup>[20]</sup> Among the risk factors that can stimulate vascular endothelial dysfunction, denaturation of macrophages and endothelial surfaces, followed by the deposition of low-density lipoprotein, initiates the inflammatory response. This leads to increased expression of interleukin (IL)-6, tumor necrosis factor (TNF)- $\alpha$ , C-reactive protein (CRP), transforming growth factor- $\beta$  (TGF- $\beta$ ), IL-1, and other pro-inflammatory cytokines. This stimulates endothelial

cells to release BMPs, thus activating the BMP/Smad pathway and promoting the differentiation of VSMCs and stromal cells into osteoblasts. IL-1 and IL-6 are the important pro-inflammatory cytokines. *In vitro* studies have shown that IL-1 and TNF- $\alpha$  enhance the expression of Wnt signaling and BMP2 in osteoblasts.<sup>[21]</sup> IL-1 can also stimulate ALP activity and mineralization by inducing a mechanism that is independent of Runx2 in VSMCs.<sup>[22]</sup> IL-6 can promote TNF- $\alpha$  expression and increase Runx2 expression associated with sodium-dependent phosphate transporter 1 (PiT1) and aid calcium deposition in mice.<sup>[23]</sup> Persistent activation of the inflammatory response leads to activation of inflammation-related signaling pathways, macrophages, and T-lymphocytes, thereby leading to the osteoblast-like differentiation of VSMCs.<sup>[24]</sup> Studies have shown that levels of pro-inflammatory factors in the peripheral blood such as CRP and TNF- $\alpha$  are increased significantly in CAC patients. Related studies have confirmed a correlation between levels of IL-22, IL-37, and CAC.<sup>[25,26]</sup>

## METABOLIC FACTORS

In CRF, the eGFR is decreased which leads to gradual emergence of disorders of the metabolism of calcium and phosphorus. Hyperphosphatemia can cause vascular injury directly, thereby inducing endothelial cells to release cytokines. Phosphorus is mediated mainly in SMCs by PiT1, which causes VSMCs to lose expression of the SM contractile proteins  $\alpha$ -SMA and SM22 and instead express the bone markers Runx2, osteocalcin, and ALP, thereby causing vascular calcification.<sup>[27]</sup> High levels of phosphorus can also induce VSMCs to secrete BMP2, which further stimulates the activation of related transcription factors. This action can also induce the apoptosis of VSMCs, and apoptotic bodies result in calcification. In ESRD, increased levels of pro-inflammatory cytokines, calcium, and uremic environments can increase PiT1 expression in VSMCs, thereby increasing phosphorus deposition and promoting vascular calcification.<sup>[28]</sup>

Calcium and phosphate promote vascular calcification in synergy, but it is believed that the behavior of calcium is mediated mainly by the induction of apoptosis. The latter promotes the release of membrane-bound vesicles and further deposition of calcium and phosphate with apoptotic VSMC lesion.<sup>[5]</sup> High levels of phosphorus can stimulate the differentiation of VSMCs into osteoblasts, but they may also promote mineralization.<sup>[29]</sup> In patients with CRF and ESRD, an increase in serum levels of phosphorus is often linked to the appearance of secondary metabolic disorders such as Vitamin D disorders and hyperparathyroidism. Studies have shown that even low levels of calcium or normal levels of phosphorus and even with normal renal function, high levels of parathyroid hormone (PTH) can lead to vascular calcification. PTH can affect the expression of pro-inflammatory factors and has a negative role in the regulation of vascular remodeling.<sup>[30]</sup> Talmor-Barkan *et al.*<sup>[31]</sup> found that PTH can activate protein kinase C/K pathways and induce expression of nitric oxide, advanced glycation

end products, and IL-6. High secretion of PTH disrupts the balance between osteoclasts and osteoblasts, allowing large amounts of phosphorus to be released into the blood. This results in a reduction in the amount of 1,25-dihydroxyvitamin D3 (1,25(OH)<sub>2</sub>D) produced, thereby reducing the level of Vitamin D in plasma.

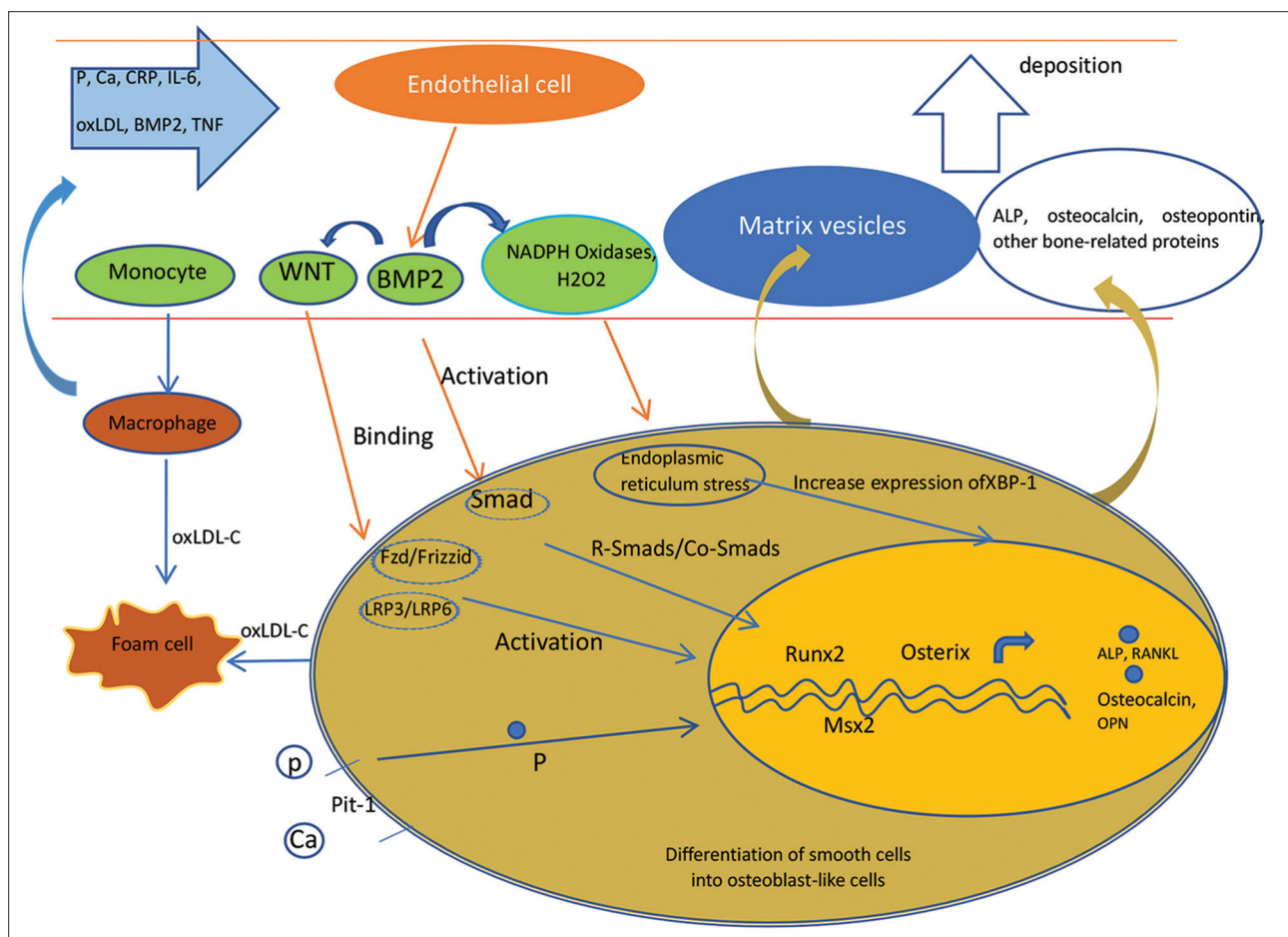
Several studies have shown that Vitamin D can regulate serum levels of calcium and phosphorus and improve the cardiovascular function and survival of patients with CRD. Active Vitamin D inhibits the phagocytosis of cholesterol by macrophages and reduces foam cell formation, leading to a decrease in macrophage activity, which reduces the risk of arterial calcification and atherosclerosis. Vitamin D can regulate renin-angiotensin system (RAS) activity and control the flow of calcium ions in VSMCs simultaneously.<sup>[32]</sup> Vitamin D also inhibits BMP expression and the production of pro-inflammatory cytokines, thereby reducing calcium deposition in the blood vessels.<sup>[33]</sup> If levels of active Vitamin D are low, the regulatory functions mentioned above decrease. This leads to increased macrophage activity, resulting in strong phagocytosis, increased formation of foam cells, and RAS activity. Hence, calcium ions are deposited within SMCs to promote arteriosclerosis and calcification.

## OTHER FACTORS

### Fibroblast growth factor 23

Fibroblast growth factor 23 (FGF23) is a hormone-like FGF secreted by bones. If serum levels of FGF23 increase in patients with CRD, FGF23 can inhibit phosphorus reabsorption in PiT1 (which is expressed in proximal tubules) to induce phosphorylation and inhibition of 1,25(OH)<sub>2</sub>D synthesis, thereby increasing PTH secretion.<sup>[34]</sup> In the meantime, high serum levels of FGF23 can lead to vascular endothelial dysfunction.<sup>[35]</sup> However, to maintain a normal phosphorus level in the body, FGF23 must combine with the membrane protein klotho. The FGF23–klotho system is indispensable as an endocrine axis that maintains phosphate balance.<sup>[36]</sup> The klotho gene encodes a single-channel transmembrane protein that is expressed predominantly in the kidneys, whereas vascular VSMCs also provide functional expression of klotho.<sup>[37]</sup> In fact, klotho can be found in the blood, urine and cerebrospinal fluid. Thus, klotho is present in two forms: membrane and secreted. The former is an exclusive co-receptor of FGF23, whereas secreted klotho is independent of the FGF23 humoral factor. An absence of klotho affects different tissues in different ways.<sup>[38]</sup> In the mechanism of CAC, first, secreted klotho inhibits the activity of PiT1 and PiT-1 mRNA, thereby inhibiting calcification and maintaining VSMC differentiation.<sup>[39]</sup> Second, klotho can inhibit the Wnt signaling pathway to reduce osteoblast differentiation and VSMC calcification; klotho can also reduce phosphorus absorption by inhibiting PiTs in renal proximal tubules.<sup>[40]</sup> With the decline of renal function, the eGFR and klotho expression decreases, leading to a big loss of a very important factor that inhibits vascular calcification. Along with increased expression of FGF23, the PTH level





**Figure 1:** Under the action of BMP2 and inflammatory mediators such as tumor necrosis factor, the expression of transcription factors Runx2 and osterix can be activated via the BMP/Smad pathway. Moreover, BMP can induce Wnt signaling pathway to activate the relevant transcription factors. It can increase the activity of NADPH oxidase during the oxidative stress and upregulate  $H_2O_2$ , leading to the endoplasmic reticulum stress response, increased XBP-1 expression; the latter induces Runx2 activation. NADPH oxidase,  $H_2O_2$  can directly promote Runx2 activation.

increases, causing decreased activity of Vitamin D. Taken together, these factors promote VSMC differentiation and coronary calcification.

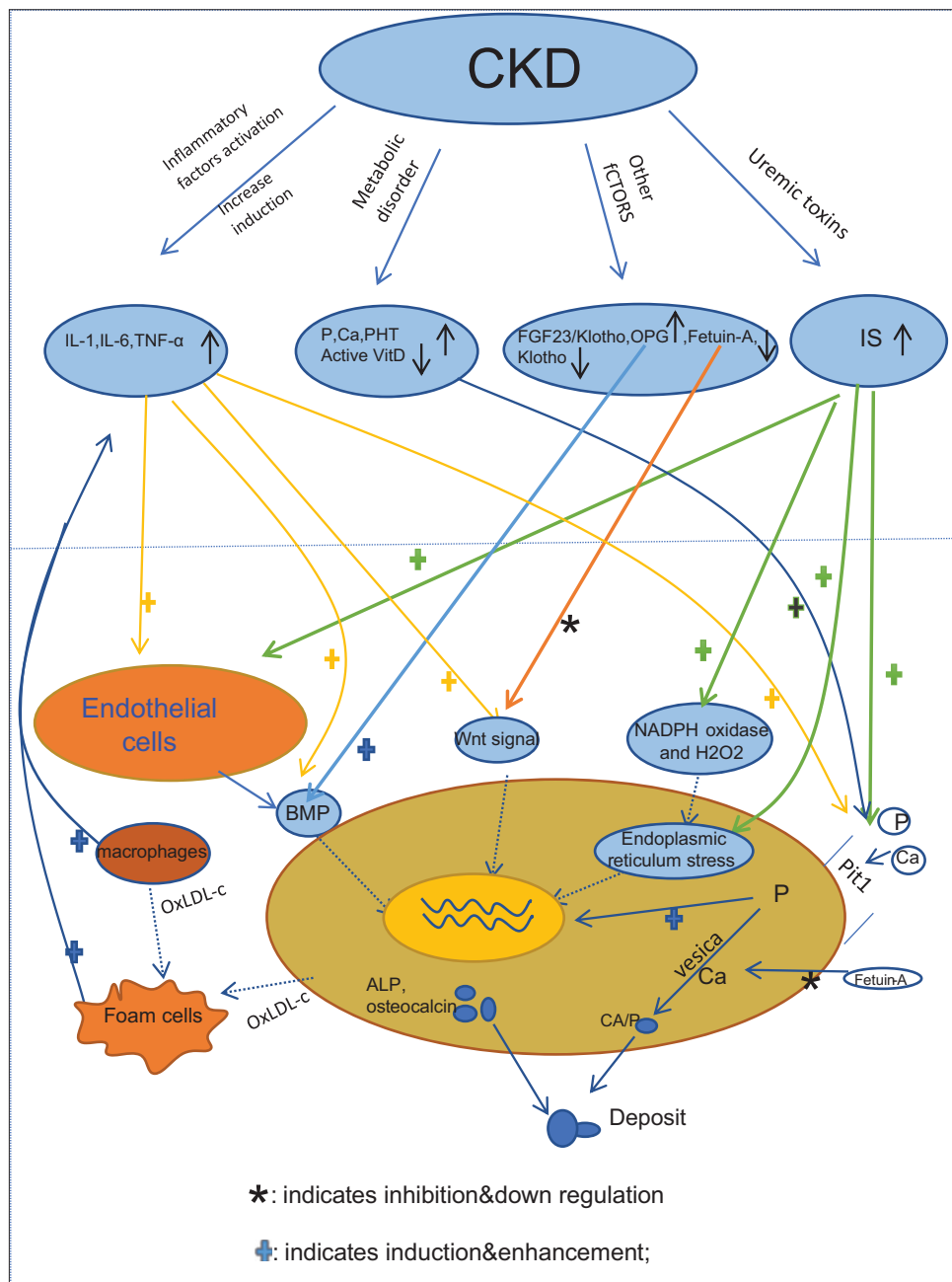
### Fetuin-A

Fetuin-A is a glycoprotein of fetal globulin released into the blood after being secreted from the liver. It is present in the extracellular fluid and accounts for 50% inhibition of the deposition of calcium and phosphorus.<sup>[41]</sup> Fetuin-A in serum is absorbed by VSMCs and is concentrated in intracellular vesicles. Fetuin-A forms a soluble mineral complex with calcium and phosphorus, thereby inhibiting the formation and precipitation of apatite precursors, and therefore, inhibiting calcification. Subsequently, fetuin-A is secreted by apoptotic and surviving VSMC vesicles.<sup>[42]</sup> Extracellular fetuin-A can inhibit apoptosis.<sup>[43]</sup> In addition, fetuin-A enhances the phagocytosis of vesicles through VSMCs. Furthermore, it can inhibit the activation of inflammatory cells, reduce the release of inflammatory factors, and reduce the effects of inflammation on vascular endothelial injury.<sup>[44,45]</sup> However, Xinling *et al.*<sup>[46]</sup> found that the fetuin-A level in patients with ESRD undergoing MHD

was significantly lower than that in patients with Stage-2/3 CRD and that the fetuin-A level was negatively correlated with the calcification score in patients undergoing MHD. In addition, CRD patients are often in a state of malnutrition, micro-inflammation, or inflammation, and in such cases, downregulation of expression of proteins such as fetuin-A is possible.<sup>[47]</sup> Price *et al.* treated rats with high doses of Vitamin D for several hours to ensure that their serum level of calcium reached 10 mmol/L and returned it to normal concentrations within 1 day. They observed that the serum level of fetuin-A fell to half of its initial concentration. When the calcification burden increases to a certain extent in long-term CRD, a compensatory system, such as fetuin-A release, may eventually be depleted.<sup>[47,48]</sup> If this hypothesis of an initial overproduction of fetuin-A and late CRF is correct, then future studies should try to identify factors that affect the expression and secretion of fetuin-A [Figure 2].

### Bone-related proteins

OPG is a soluble secretory glycoprotein, a member of the TNF receptor family, and is distributed widely in the liver, heart, lungs, kidneys, and bones. It is also present in the



**Figure 2:** Coronary calcification mechanism in CKD patients. \*Indicates inhibition and down regulation. †Indicates induction and enhancement. CKD: Chronic kidney disease.

endothelial cells and SMCs and operates through autocrine and paracrine ways.<sup>[49]</sup> During CAC formation, several inflammatory factors and cytokines can upregulate the expression and release of OPG in VSMCs and endothelial cells. OPG can prevent the vascular damage caused by pro-inflammatory cytokines by improving the viability of endothelial cells.<sup>[50]</sup>

RANKL is a cytokine synthesized by osteoblasts and bone-marrow stromal cells that promote bone differentiation. It binds to RANK in the membranes of endothelial cells and mediates BMP2 release by vascular endothelial cells, leading to vascular calcification.<sup>[51]</sup> OPG and RANKL combine with RANK competitively, inhibit the RANKL/RANK

system, and inhibit vascular calcification. Simultaneously, OPG also inhibits osteoclast differentiation, reduces the bone resorption activity of mature osteoclasts, and induces apoptosis.<sup>[52]</sup> Experimental and clinical data suggest that renal expression of OPG mRNA is associated with a degree of renal impairment and that the increase in OPG level observed *in vivo* may be compensatory and protective but does not prevent injury completely; OPG may slow the progress of tissue damage.<sup>[53]</sup> Numerous studies have shown that serum concentrations of OPG and the CAC score are positively correlated. Studies have shown that OPG is associated with the number of coronary artery lesions and to be correlated with the number of coronary plaques.

## Uremic toxin-related factors

Studies have shown that, compared with age- and sex-matched healthy populations, the risk of death in MHD patients is increased by 10–20-fold.<sup>[40,54]</sup> MHD is the preferred treatment for patients with ESRD, but the degree of CAC in MHD patients is 2–5-fold higher than that of patients with angiographic evidence of coronary artery disease.<sup>[41,55]</sup> In one study, 79% of CRD patients had vascular calcification before they received MHD and, afterward, the proportion was close to 100%,<sup>[56]</sup> suggesting that, besides the factors mentioned above, other factors that affect calcification might be involved.

Uremic toxins are considered to be a new type of cardiovascular risk factor in CRD patients. Uremic toxins are divided into three categories of compounds: water-soluble small molecules, molecular, and macromolecular. MHD eliminates most uremic toxins, but it cannot remove toxins bound to macromolecular proteins.

Indoxyl sulfate is a class of albumin-bound uremic toxin that cannot be cleared by MHD. Tryptophan contained in food undergoes transformation within intestinal flora and oxidation in the liver to form indole sulfuric acid and is then cleared by the kidneys. Indoxyl sulfate can induce leukocyte adhesion in vascular endothelial cells and enhance TNF- $\alpha$  activity and vascular inflammation, leading to vascular calcification.<sup>[57]</sup> Indoxyl sulfate can upregulate NADHP oxidase and stimulate the production of reactive oxygen species. Indoxyl sulfate induces the expression of osteocyte-specific proteins in SMCs, thereby accelerating CAC.<sup>[58]</sup> Indoxyl sulfate enhances phosphorus absorption by SMCs by stimulating the expression of PiT1 and its mRNA.<sup>[59]</sup> At the cellular level, animal experiments have demonstrated that indoxyl sulfate can promote methylation of the klotho gene by upregulating expression of DNA methyltransferase and then downregulation of klotho expression.<sup>[60]</sup> In CRD, other toxins may also be involved in CVD pathogenesis, but their biologic effects have not been shown.

## CONCLUSIONS

Vascular calcification in patients with CRF is an active cell-mediated process involving VSMC apoptosis and vesicle release, inhibitors of calcification, and control of this balance by promoters. Vascular calcification is the most serious complication in CRD patients. The only treatment for vascular calcification is prevention. More in-depth understanding of the various factors leading to CRD is needed.

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## Conflicts of interest

There are no conflicts of interest.

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# 冠状动脉钙化与慢性肾功能衰竭关系的研究进展

## 摘要

**目的：**目前认为冠脉钙化是一种与新骨形成极为相似的受调控的主动性代谢过程。而在慢性肾功能衰竭患者，冠状动脉钙化非常普遍，并且随着肾功能的恶化钙化病变越重。此综述总结了关于冠状动脉钙化和慢性肾功能衰竭之间关系的理解及新发现。

**方法：**所有文献都是以“冠状动脉钙化”、“慢性肾衰”、“血管平滑肌细胞”及他们的同义词，通过PubMed, Embase, 和CNKI数据库系统检索的，且这些文献发表年限为2017年9月以前。对符合检索条件文献的标题、摘要及全文，我们都进行了仔细的审阅。为了进一步了解学习，对文章的参考文献也进行了详细解读。

**结果：**慢性肾衰会加速冠脉钙化的进程。慢性肾衰使得炎症因子增加，钙磷、PTH等代谢紊乱，尿毒素分子及其促进钙化的因素增加，这些因素通过相关信号通路让血管平滑肌细胞向成骨样细胞转变，同时抑制血管钙化的因素减少这样就更加诱导冠脉钙化的形成。在各因素影响血管病变的同时，实际上各自又在相互作用。

**结论：**由此可见慢性患者发生冠脉钙化是有多因素共同影响。尽管目前冠脉钙化的机制并非十分明确，但了解清楚冠脉钙化机制有助于我们保护心肌并降低冠心病的发病率及死亡率。因此，需要进一步的学习及研究慢性肾衰患者发生冠脉钙化的精确机制。

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