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An Overview on Vascular Calcification in Chronic Kidney Disease

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ABSTRACT

Vascular calcification (VC) is a prevalent and severe complication in chronic kidney disease (CKD), contributing significantly to cardiovascular morbidity and mortality. Its pathogenesis involves disordered mineral metabolism, chronic inflammation, and vascular smooth muscle cell trans differentiation.

Keywords: *Vascular calcification, chronic kidney disease, mineral bone disorder, cardiovascular disease, inflammation*

1. INTRODUCTION

Vascular calcification (VC) is defined as mineral deposition in the vasculature in the form of calcium-phosphate complexes. Although VC is regarded as part of the normal aging process, certain pathological processes, such as diabetes, hypertension, chronic kidney disease (CKD), and rare hereditary disorders may precipitate the condition. VC causes a loss of arterial elasticity, increased pulse pressure and systolic blood pressure, and left ventricular hypertrophy, and the severity of VC is closely associated with an increased risk of cardiovascular morbidity and mortality **(1)**.

VC has been observed more frequently in adults with CKD than in age-matched general population, and a similar trend is observed in younger CKD patients. Considering that cardiovascular disease is the most common cause of death in CKD patients, it is important to understand the pathophysiology of VC in CKD patients to detect early signs of VC and prepare for appropriate management **(2)**.

Types of Vascular Calcification

Vascular calcification can be classified into two forms depending on its location within the intimal or the medial layer of the vessel wall. Coronary arteries are mostly associated with intimal calcification, whereas medial calcification mostly affects the peripheral arteries of the lower extremities **(3)**.

Intimal vascular calcification

Intimal VC is closely associated with atherosclerotic plaque formation **(4)**. Traditional cardiovascular risk factors, including older age, smoking, hypertension, diabetes, obesity and hyperlipidemia provokes the formation of atherosclerotic plaques, and intimal calcification occurs in the plaque as a late event in atherosclerosis (Figure 1A). CKD patients already have a number of traditional risk factors for cardiovascular disease, and atherosclerotic arterial lesions are more prevalent in CKD patients **(5)**.

Medial vascular calcification

Medial calcification theoretically appears to be more specific to CKD patients than intimal calcification, considering the pathogenic similarity between bone ossification and medial calcification. Hypercalcemia, hyperphosphatemia, secondary hyperparathyroidism and other CKD-MBD-related factors trigger mineral deposition on the medial layer of the vascular wall; also, the formation of micro-calcific foci accelerates the accumulation of additional calcification **(1)** .

Therefore, medial VC can frequently occur in CKD, despite the absence of traditional risk factors (Figure 1B). Arterial medial calcifications are not directly related to cholesterol deposits and do not induce occlusive lesions in the lumen. However, medial calcification is associated with an increased pulse pressure, arterial stiffness, poor vascular compliance and left ventricular hypertrophy. These changes lead to an increased rate of future cardiovascular events and mortality risk in the CKD population **(6)**

The intimal and medial VCs represent different clinical entities with distinct pathogenic signatures and it would also appear that the basic pathogenic principles remain relevant in the CKD population (intimal calcification - atherosclerosis and medial calcification - loss of the cushioning function). However, the CKD patients retain common risk profiles and signaling pathways, which overlap in intimal and medial calcifications **(7)**.

In particular, oxidative and inflammatory signaling are the common pathways for both types of VC, and uremic conditions considerably activate these two pathways **(8)**. Therefore, intimal and medial VC in CKD patients can frequently occur at the same time and several studies have reported the co-existence of the two types of VC (Figure 1C) **(9)**.

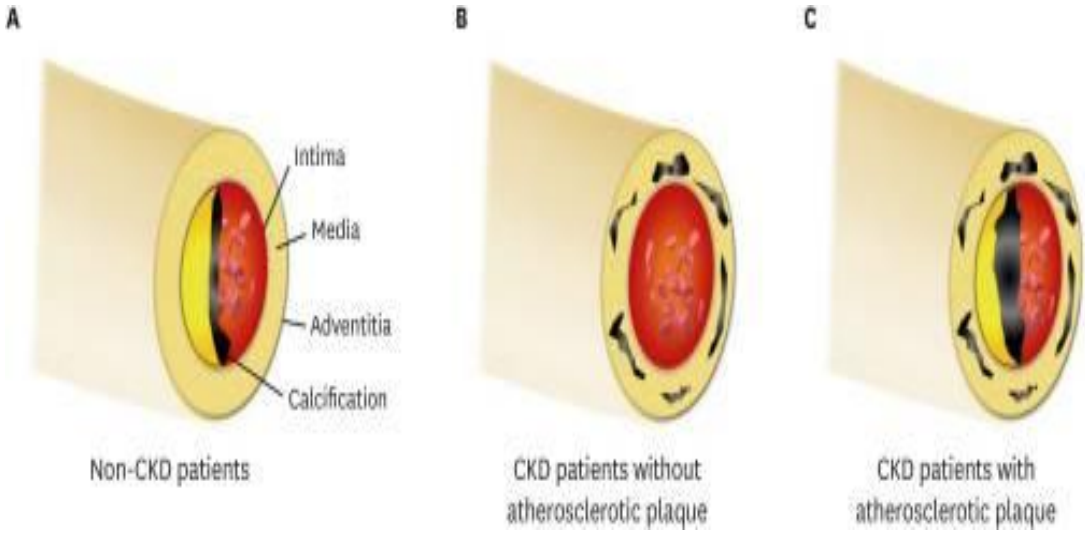

Figure 1: A) In patients without renal dysfunction, calcification is deposited in the intimal layer; (B) CKD patients obtain the medial calcification in the absence of the atherosclerotic factor, because mineral bone disorder accelerates the calcific process; (C) In clinical practice, intimal and medial calcification frequently co-exists in CKD patients, because they already had several traditional risk factors. Notably, the intimal or medial calcific burden is greater in CKD patients than in non-CKD patients (1)

Mechanisms of Vascular Calcification

Vascular calcification has been noted as a consequence of aging for many decades. Growing evidence now suggests that vascular calcification, similar to bone remodeling, is an actively regulated process, including both inductive and inhibitory processes. Bone-related proteins, such as alkaline phosphatase, osteocalcin, osteopontin, Runx2, and matrix vesicles, which nucleate hydroxyapatite mineral crystals, have all been observed in calcified valvular lesions. In addition, outright cartilage and bone formation have been identified **(10)**.

The identification of genes that cause ectopic calcification disorders in human and/or mice has contributed to our knowledge about the regulation of vascular calcification. Remarkably, single-gene mutations in type II TGFβ receptor and Notch 1 are associated with bicuspid aortic valve and valve disease **(11)**

Additionally, in vivo and in vitro models have been developed to mimic important aspects of vascular and valvular calcification and have identified new pathways important for this process. The current major mechanisms of vascular calcification based on these studies are summarized in Figure 2, including

Failed Anticalcific processes

Induction of Osteochondrogenesis

Cell Death

Abnormal Ca/Pi Homeostasis

Bone remodeling

Matrix Degradation/Modification.

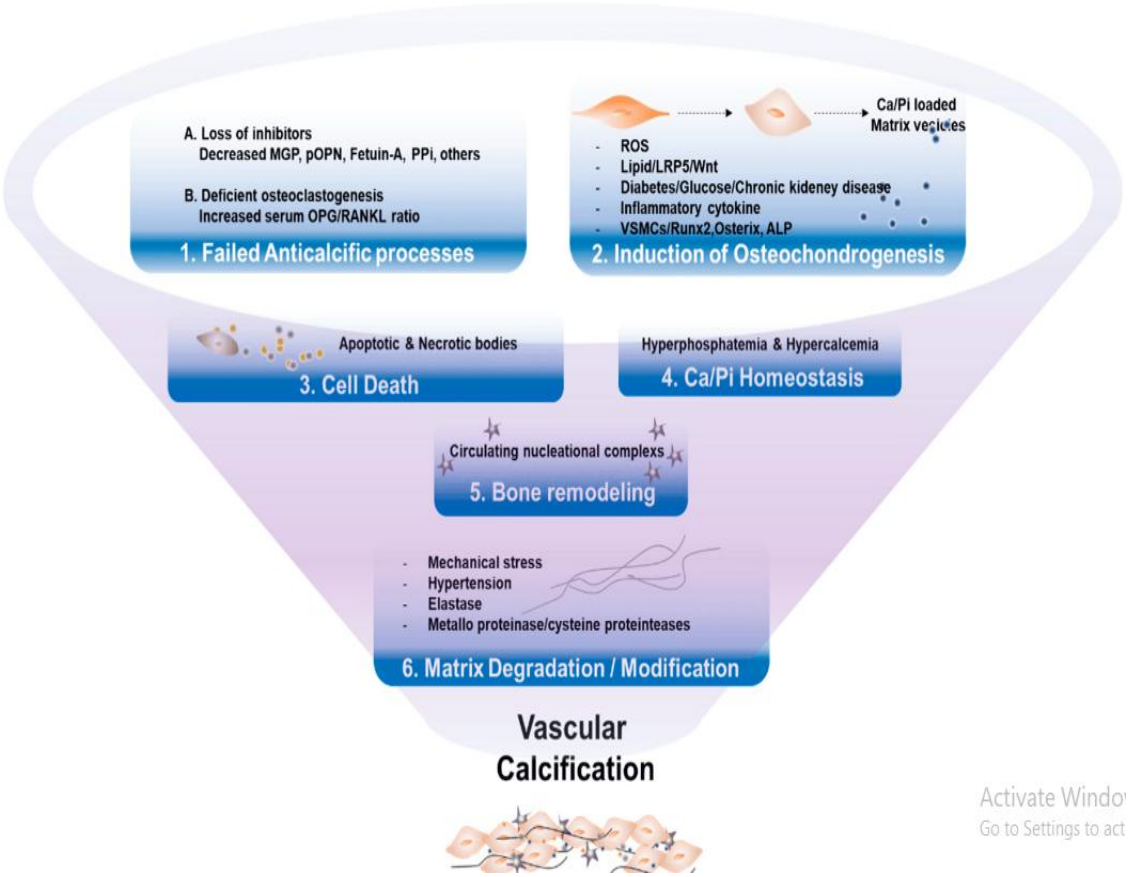

Figure 2: Key mechanisms of vascular calcification. (1) Failure of anti-calcification processes, due to loss of inhibitors and deficiency of constitutively expressed mineralization inhibitors, leads to vascular calcification. (2) Various stressors induce osteogenic transdifferentiation of VSMCs, products of matrix vesicles, which act as a nidus of calcium phosphate deposition. (3) Cell death by apoptosis or necrosis leads to release of apoptotic bodies, or necrotic debris, which may act as nucleation of apatite. (4) Abnormal mineral homeostasis causes deposits calcium phosphate hydroxyapatite. (5) Nucleational complexes formed during bone remodeling, promote ectopic mineralization. (6) Matrix degradation/modifications, caused by environmental stressors, are involved in vascular calcification (10).

Role of Magnesium in Modulating Vascular Calcification

Vascular calcification is a prognostic marker for cardiovascular mortality in chronic kidney disease (CKD) patients. In these patients, magnesium balance is disturbed, mainly due to limited ultrafiltration of this mineral, changes in dietary intake and the use of diuretics. Observational studies in dialysis patients report that a higher blood magnesium concentration is associated with reduced risk to develop vascular calcification **(12)**.

Magnesium prevents osteogenic vascular smooth muscle cell transdifferentiation in in vitro and in vivo models. In addition, recent studies show that magnesium prevents calciprotein particle maturation, which may be the mechanism underlying the anti-calcification properties of magnesium. Magnesium is an essential protective factor in the calcification milieu, which helps to restore the mineral-buffering system that is overwhelmed by phosphate in CKD patients **(13)**.

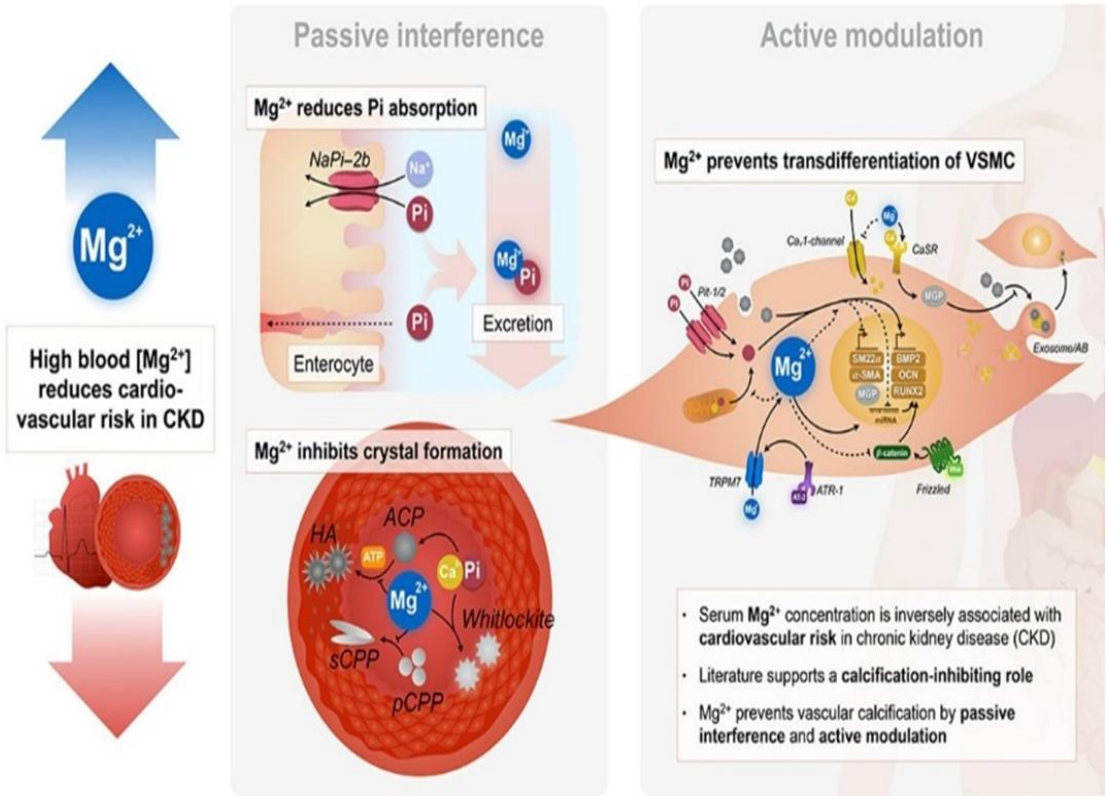

Figure 3: Role of magnesium in modulating Vascular Calcification (13)

Imaging and Detection of Vascular Calcification

VC can be detected by several imaging techniques. Plain radiographs are simple and readily available and the presence of VC can be examined in a single X-ray film. Plain radiographs also allow differentiation between intimal and medial calcification, which comes in useful in CKD population. Mammography is especially advantageous among women because the severity of medial calcification can be assessed in images acquired during the routine screening mammogram **(14)**.

Ultrasonography offers a mean to evaluate arterial wall thickness and lumen size as well as calcification with the benefit of no radiation exposure. CT scan, the gold standard, is the most sensitive technique that offers an accurate and an objective analysis of the severity of VC. Plain radiographs are appropriate in situations where risk evaluation is the main focus, whereas CT scan is indispensable for accurate analysis of progression or changes after intervention **(14)**..

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