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Review

Vascular Calcifications, Major Risk Factor for Cardiovascular Events in Chronic Kidney Disease: An Update on the Pathophysiological Process

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REZUMAT

Calcificările vasculare, factor de risc major pentru evenimente cardiovasculare în boala renală cronică: update privind procesul fiziopatologic

Tulburările metabolismului mineral și osos sunt frecvent întâlnite la pacienții cu boală renală cronică, ducând în final la calcificări vasculare. Ele contribuie la boala cardiovasculară asociată bolii renale cronice și la rata înaltă de mortalitate. Mecanisme complexe implică retenția de fosfați, scăderea concentrației calciului ionizat și a 1,25-dihidroxivitaminei D, creșterea concentrației de FGF-23, hiperparatiroidismul secundar. Un număr mare de substanțe proinflamatoare și antiinflamatoare (osteopontina, osteoprotegerina, fetuina, pirofosfatul) au fost studiate în încercarea de clarificare a mecanismelor etiopatogenice ale calcificărilor vasculare. Aspectele fiziopatologice, clinice și terapeutice complexe ale afectării cardiovasculare în boala renala cronica necesită o abordare complexă, multidisciplinară.

Cuvinte cheie: calcificări vasculare, boală renală cronică, fiziopatologie

ABSTRACT

Mineral and bone metabolism disorders are common in patients with chronic kidney disease, leading finally to vascular calcification. They contribute to the associated cardiovascular disease in patients with chronic kidney disease and also to high mortality rate. Complex mechanisms involve retention of phosphates, decreased ionized calcium and 1,25 dihydroxyvitamin D, increased FGF-23, secondary hyperparathyroidism. A large number of proinflammatory and anti-inflammatory factors (osteopontin, osteoprotegerin, fetuin, and pyrophosphate) were

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studied in an attempt to clarify the etiopathogenic mechanisms of vascular calcifications. Complex pathophysiological mechanism of the cardiovascular damage in chronic kidney disease, clinical and therapeutic implications require a comprehensive, multidisciplinary approach.

Key words: vascular calcifications, chronic kidney disease, pathophysiology

INTRODUCTION

Hypertension, diabetes mellitus, dyslipidaemia are frequently encountered in patients with chronic kidney disease (CKD) (1). They are the major risk factors for the development and progression of the endothelial dysfunction and atherosclerosis and contribute to the progression of renal failure (1). Microalbuminuria increases to two- to four-fold the cardiovascular risk (1). It is also a quantitative association between glomerular filtration rate (GFR) and cardiovascular risk (1). The risk increase to two- to four-fold in stage 3 of CKD (GFR 30-59 mL/min/1.73 m^2), four- to 10-fold in stage 4 (GFR 15-29 mL/min/1.73 m^2) and 10- to 50-fold in stage 5 renal failure (GFR <15 mL/min/1.73 m^2 OR dialysis) in comparison with persons free of CKD (1). Atherosclerosis with intimal involvement and Moenckeberg's media sclerosis are the main cardiovascular determinations in CKD. Coronary artery calcifications attain the highest levels in young adults patients with renal failure and dialysis, as has been shown in angiographic studies (2). These patients have many coronary risk factors leading to intimal calcifications and these are coexisting with medial calcification founded only in CKD (2). The degree of coronary artery calcifications seems to be related to the estimated GFR in a multivariate analysis (2).

KDIGO guidelines recommend that patients with CKD stages 3–5D with known vascular/valvular calcification be considered at highest cardiovascular risk (class 2A recommendations) (3).

Calcium and phosphate deficiencies

Calcium deposition in the media vessels is common in dialyzed patients. It is associated with stiffening of vessels mainly due to the increased phosphate levels and affected elastin. Calcium deposition in the intima is associated with advanced atherosclerosis, and the inflammatory process is related to deposition of cholesterol (3). In patients with CKD both types of calcification are co-located in the coronary, aortic and ilio-femoral arteries (3).

Different patterns of vascular calcification have different implications. Intimal calcification appears in patients with hypertension, dyslipidemia, with advancing age, and smoking (5). Intimal layer calcium is associated with intimal occlusive disease (5). It leads to vascular stiffening and reduced endothelial reactivity (4). Intimal calcification involves inflammatory macrophages and vascular smooth muscle cells (VSMCs) in lipid-rich regions of the atherosclerotic plaque (5). This process is patchy and discontinuous (5). In contrast with intimal calcifications, medial calcification (Mönckeberg's sclerosis) typically seen in diabetes and CKD, involves sheet-like calcification in the tunica media, with a concentric thickening of the vessel wall (5). The calcium in vascular media increases the vascular stiffness by effects on vascular distensibility (4).

Vascular calcifications in CKD patients are a complex process, with Calcium (Ca) and phosphate (P) playing key roles (6).

The normal range of serum Ca is between 9 and 10.5 mg/dL. It is maintained by the active vitamin D metabolites, parathyroid hormone (PTH), calcitonin and klotho (6). In CKD there are a diminished activity of 1-α hydroxylase in the kidney and an increased serum FGF-23 (a direct inhibitor of 1-α hydroxylase activity) resulting in a 1, 25-dihydroxy-vitamin D deficiency and secondary hypocalcemia (6). Hypocalcemia and hyperphosphatemia cause the secondary hyperparathyroidism. Both vitamin D deficiency and secondary hyperparathyroidism are treated with activated vitamin D receptor agonists. Hyperphosphatemia is treated with calcium-containing phosphate binders. The resulting hypercalemic episodes and the affected bone remodeling contribute to dysregulation of calcium homeostasis in CKD (6). Extracellular Ca is increased up to 30 mmol/L by releasing calcium in the vessel wall at the sites of apoptotic or necrotic cell death (6). This promotes VSMCs calcifications via mineral

nucleation sites and participates in the earliest events in the calcification cascade (6).

Elevated serum phosphate (P) is another major risk factor for cardiovascular events in CKD (6). High normal values of serum P have been correlated with increased risk of cardiovascular and all-cause mortality in CKD patients (6). Serum P levels >5.5 mg/dL raise the mortality in the end-stage CKD (6). Parathyroid hormone (PTH), fibroblast growth factor 23 (FGF-23), klotho, and 1, 25-dihydroxyvitamin D maintain serum P levels in a normal range of 2.8 to 4.5 mg/dL (6). In early CKD, normal serum P levels are maintained by upregulation of FGF-23 and PTH renal, despite the impaired P excretion and a decline in klotho levels (6). In advanced CKD appears hyperphosphatemia caused by continued ingestion of P, inefficient urinary P excretion, affected bone remodeling and overwhelmed defense mechanisms (6). VSMCs matrix calcification is P-mediated via multiple mechanisms: osteogenic/chondrogenic conversion, apoptosis, and matrix remodeling (6).

Dysregulated Ca and P homeostasis plays a major role in VSMCs calcification in CKD patients and the effects are synergistic (6). The pathways are directly as well as overlapping (6). Hypercalcemia initiates distinct pathways by ER stress, type III NaPi cotransporters PiT-1, matrix Gla protein MGP, alkaline phosphatase, lysosomal loading, Calcium sensing receptor (6). Hyperphosphatemia initiates distinct pathways by matrix metalloproteinase MMP-9, cathepsin-S, osteoblastic transcription factor Msx2, osterix, alkaline phosphatase, reactive oxygen species, smooth muscle (SM) lineage gene expression SM22α (6). Overlapping pathways include Erk1/2, transcription factor P-Runx2, vesicle loading, caspase-3, matrix metalloproteinase MMP-2 factors (6). Finally the uraemic milieu in dialyzed patients has important effects on VSMCs as apoptotic cell death, deranged vessel architecture, abnormal fetuin-A and MGP expression, osteo/condrocytic transformation and vesicle release, with accelerated calcifications (5).

Genetic risk factors

The process of vascular calcifications in CKD is so complex that many other factors play also key role, like genetics (7). There are multiple inherited risk factors who affects endothelial function, leukocyte adhesion and activation (angiotensin-converting enzyme, E-Selectin, CC chemokine receptor 2), redox stress modulation, vitamin K metabolism and arterial matrix remodeling (matrix metalloproteinase 3, antisense noncoding RNA in the INK4 locus ANRIL), and bone metabolism, osteocondral differentiation, calcification (MGP, BMP-7, osteoprotegerin OPG, fetuin A, klotho) (7). As a defense mechanisms, multiple physiologic artery calcifications inhibitors play a role in this complex process, like a piece in a puzzle: klotho, fibrillin 1, osteopontin, osteoprotegerin, MGP, fetuin A, adiponectin, pyrophosphate, magnesium (7,8,9). Host and environmental factors (atherosclerosis, diabetes, hypertension, serum phosphate, serum calcium, PTH, bone metabolism, aging) seems to finish the puzzle leaving many unknowns to be completed in time (7).

Vascular calcifications involves a phenotypic change of vascular smooth muscle cells into bone forming cells, since both smooth muscle cells and osteoblasts are derived from mesenchymal stem cells (10). The next step in this physiopathological cascade is matrix mineralization with hydroxyapatite crystals (10). The mechanism involves production of extracellular matrix proteins and release of matrix vesicles and apoptotic bodies (10). After that mineral crystals are deposited by biomineralization (10). Matrix vesicles and apoptotic bodies derived from dying VSMCs concentrate calcium in the same way (10).

Elastin

Elastin secreted by VSMCs suffer a degradation process mediated by MMP, elastase and other proteases (9,10). The resulted elastin has a high affinity for calcium, facilitating growth of hydroxyapatite along the elastic lamellae, the major component of the aortic medial layer (9). Also play a role in osteochondrogenic differentiation of VSMCs, by binding elastin derived peptides to surface elastin laminin receptors on these cells (9).

Serum magnesium deficiency

Low serum magnesium is also a contributing factor to vascular calcification in dialyzed patients by many ways: promotes inflammation, increases oxidative stress, impairs endothelial function, increases vasospasm and accelerates atherogenesis (10).

There is also an important link between bone and arterial abnormalities in CKD (11,12). Vascular and valvular calcifications are more frequently observed in the presence of low bone turnover disease with a decreased osteoblast number or osteoblastic activity (11). Multiple mechanisms could be involved in this complex relationship: common factors who act on bone remodeling and atherosclerosis/calcification, direct action of osteoblasts/osteocytes on vascular biology and structure, compromised bone blood supply of bone vessels (11). Bone and osteoblast physiology control the fat-tissue metabolism and adipokine release, energy expenditure, and insulin secretion and sensitivity, via osteocalcin, adiponectin and leptin (12). In CKD patients, elevated serum leptin promotes vascular calcifications and lower bone activity while adiponectin has a inverse-relationship with vascular calcifications (12).

CONCLUSIONS

Vascular calcifications are major risk factor for cardiovascular disease in CKD patients. The complex mechanisms involve minerals deficiencies, genetic factors, VSMCs elastin abnormality, phenotypic change of VSMCs into bone forming cells with biomineralization.

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