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Vascular Calcification in End-stage Renal Disease

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Introduction

CKD patients have an higher incidence of cardiovascular morbidity & mortality. Vascular calcification is a major cause of cardiovascular disease in the dialysis population. Increased mortality risk associated with arterial calcification. Intimal calcification occurs only within atherosclerotic plaque. It is a disease of ischemia-related occlusion in which inflammatory plaques are present in the intima. Risk factors for atherosclerosis are well known in the normal population (hypertension, dyslipidemia, DM, smoking). Medial calcification, muscular arteries undergo non-inflammatory medial calcification. Calcifications of the media increase vascular stiffness and decrease arterial capacity, which results in hypertrophy of the left ventricle, disturbed blood flow through the coronary vessels in the diastole, as well as in increased mortality in patients undergoing dialysis. Common sites are ankle, abdominal aorta, feet, pelvis, hands and wrists.

Diagnosis

Physicians can use a variety of noninvasive imaging tools to identify cardiovascular calcification, some with merely qualitative and others with both qualitative and quantitative capabilities. Plain x-rays and ultrasonography can be used to identify macroscopic calcification of aorta and peripheral arteries, echocardiography is helpful for assessment of valvular calcification, and computed tomography technologies constitute the gold standard for quantification of cardiovascular calcification. The latter is also useful to monitor calcification progression and to assess the effect of different therapeutic strategies directed at modifying calcification progression.

Clinical Consequences of Vascular Calcification

Hemodynamic and cardiac consequences of vascular calcification have been widely studied in ESRD patients. Arterial calcification induces arterial wall stiffness, and increased arterial stiffness is associated with an increased pulse pressure (a small increase in systolic BP & small decrease in diastolic BP). The stiff calcified arteries cause both ventricular afterload & left ventricular mass increases, it leads left ventricular hypertrophy and results in increased cardiovascular mortality risk in ESRD patients.

Risk factors

Classic risk factors of vascular calcification are age, sex, family history, smoking, obesity, hypertension, diabetes and dyslipidemia. Uremia-associate risk factors of vascular calcification are time on dialysis, uremic toxins (Inflammation, AGE, oxidative stress, NO & homocysteine), increased serum levels of phosphate, increased serum levels of calcium-phosphate product and increased serum levels of PTH.

Mechanism and Pathophysiology

The exact mechanisms of uremic calcifications are not yet completely understood. For many years the predominant view has been that vascular and soft tissue calcification occurred by a passive, unregulated physico-chemical

mechanism due to elevated serum calcium levels, and high calcium-phosphorus product resulting in supersaturated plasma. Recent observations have provided some evidence that it is not simply a precipitation of divalent ions, but also a highly regulated process of mineral deposition.

The role of phosphate

Phosphate plays a major role in the calcification process. An increase in intracellular phosphate concentration causes the formation of matrix vesicles via, as yet unknown, pathways. Matrix vesicles are important in osteogenesis. High intracellular phosphate concentration down-regulates typical smooth muscle cell genes and stimulates the production of the core-binding factor-1 (Cbfa-1), which is a central transcription factor in osteogenic differentiation. Increased intracellular phosphate levels also contribute to various other osteoblast-like phenotypic changes of vascular smooth muscle cells, including the expression of alkaline phosphatase on their surface, production of Ca-binding proteins such as osteocalcin and osteopontin, and the laying down of a collagen-rich extracellular matrix. Moe et al. proved in vivo that Cbfa-1, alkaline phosphatase and osteopontin were present in calcified, but not in non-calcified arteries.

Other modulators of calcification

Blood lipids have been suggested as possible modulators of calcification. In vitro, blood lipids, LDL accelerate vascular calcification, while HDL inhibits calcification. In vivo, the reduction of total cholesterol slowed the progression of coronary artery calcification in non-ESRD patients, but in uremia, the role of lipid less clear. In contrast to lipids, the concept of inflammation as a protagonist of calcification in ESRD has been well proved. The impact of inflammation on osteoporosis and vascular calcification can explain the correlation between increase vascular calcification and decreased bone density in dialysis patients. The indexes of inflammation are positively correlated with cardiovascular calcification scores in ESRD. And pro-inflammatory cytokine TNF- also enhances both alkaline phosphatase activity and matrix mineralization in bovine aortic smooth muscle cells. Other potential modulators of calcification in ESRD are poor glycemic control, calcitriol, leptin and iron overload.

Inhibitors of calcification

Fetuin, matrix Gla protein (MGP)osteoprotegerin and osteopontin have been mentioned as important natural inhibitors of vascular calcifications in health. Fetuin-A also called α-2 Heremans-Schmid glycoprotein (AHSG) is a major circulating protein that is mostly synthesized in the liver and inhibits calcification by binding hydroxyapatite structures. Matrix Gla protein, another inhibitor of both arterial and cartilage calcification is expressed in chondrocytes and VSMC. MGP can also decrease osteogenic differentiation by inhibiting bone morphogenic protein-2 activity a pro-mineralization factor. In human studies the CAC score has been found to correlate with serum levels of MGP in nonuremic patients but in uremic patients the clinical evidence of this interaction remains uncertain. Osteoprotegerin, an osteoblast-derived inhibitor protein of the TNF superfamily has a physiologic role in the regulation of bone mass by inhibiting osteoclast differentiation and activation. It binds to osteoprotegerin ligand (OPGL) and thereby inhibits the interaction between receptor activator of nuclear factor (NF)-κB (RANK) and OPGL on osteoclasts. Osteopontin is an acidic phosphoprotein normally found in bones and teeth. This protein is a potent inhibitor of vascular calcification via direct inhibition of apatite growth by binding to crystal surfaces and induction osteoclast function. Parathyroid hormone-related peptide (PTHrP) resembles parathyroid hormone (PTH), activates PTH receptor and causes hypercalcemia. PTHrP expression was associated with down-regulation of bone morphogenic protein-2 (BMP-2) and alkaline phosphatase in calcifying cell cultures, thus reducing calcifications. Calcitriol ($1,25(OH)_2D_3$) directly inhibits the expression of PTHrP and facilitates vascular calcification in bovine VSMC.

Management

There are four therapeutic goals for the prevention and management of cardiovascular calcifications : Optimization of serum phosphorus levels & calcium-phosphorus product. Avoidance of calcium-containing phosphate binders. Treatment of dyslipidemia. Use of efficient & biocompatible dialysis membranes. The K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease recommend more strict control of serum phosphorus (3.5-5.5 mg/dL) and calcium levels (8.4-9.5 mg/dL), and maintaining calcium phosphorus product at less than 55 mg_2/dL_2. Existing treatment and prevention options for calcification include modifying Ca load and the use of phosphate binders. The application of phosphate binding polymers (sevelamer HCl) is better than that of Ca-containing phosphate binders. Calcimimetics, analogs of vitamin D, bisphosphonates may also affect the development of calcifications by way of decreasing Ca and phosphate concentrations. Some therapeutic options such as treatment with BMP-7, osteoprotegerin, or fetuin A have been tested for direct inhibition of vascular calcification.

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