



Peripheral Arterial Calcification: Clinical Implications and Management

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Abstract

Arterial calcification is common in peripheral arterial disease but its impact on subsequent health is poorly described. It is essentially observed among diabetic and uremic patients. It is independently associated with increased severity of limb ischemia. Furthermore, it is significantly correlated with severe forms of coronary artery disease and has been proposed as a marker for this disease. The presence of peripheral arterial calcification results in increased mortality and morbidity rate.

The author reviewed the most relevant published studies related to lower extremity arterial calcification. In this article, he describes pathophysiology and clinical presentation of this condition.

He analyses its implication on cardiovascular mortality and morbidity. The most recent trends in management and treatment of this disease will be exposed.

Keywords: Peripheral arterial disease; Calcification; Ischemia; Coronary artery disease

Introduction

Calcium deposition in arterial wall increases with age. Arterial calcification is reported among 30 % of Americans aged > 45 years [1]. Most individuals aged > 60 years have progressively enlarging deposits of calcium minerals in their major arteries.

Vascular calcification reduces aortic and arterial elastance, increases stiffness and rigidity which impair cardiovascular hemo dynamics resulting in substantial morbidity and mortality [2].

Materials and Methods

In this article, the author reviewed the worldwide published studies related to lower limb arterial calcification. He exposes anatomical characteristics and patho physiological mechanisms of this disease. He describes clinical forms and their effect on limb ischemia. He analyses the correlation between peripheral arterial calcification and coronary artery disease and its implication on mortality and morbidity. Different therapeutic modalities are reported focusing on the most recent emerging drugs proposed for the treatment of this condition.

Discussion

Diffuse tissue calcification arises from pathological conditions leading to systematically high calcium/phosphate products (hormonal calcium metabolism disorders, lithotripsy, genetic or auto-immune disorders ...) [3]. Monckberg's medial sclerosis is observed in infancy and is characterized by an increase of arterial stiffness and pulse pressure. Patients with this disease remain asymptomatic unless complicated by atherosclerosis or calciphylaxis. Arterial calcium deposition increases as we progress distally in the arterial tree. Vascular calcification occurs in both intima and media.

Intimal atherosclerosis is associated with patchy pattern calcification. This calcification is a feature of advanced plaques and may be quite extensive leading to the development of occlusive diseases. There is no consistent relationship between the plaque size or complexity and the degree of calcification. Calcific deposits are more prominent in plaques of older individuals, at the abdominal aorta and coronary arteries [4]. Atherosclerotic plaque calcification enhances plaque stability and decreases clinical events. Vascular calcification is an actively regulated process. Osteopontin and osteoprotegerin inhibit mineral deposition and osteo clastogenesis. They emerged as novel markers of acute cardiovascular events, coronary artery disease, carotid echogenecity and stability and poor long term cardiovascular outcome. Statins attenuate their serum levels.

Medial calcification causes stiffening and decrease in arterial wall elasticity and compliance

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which leads to atherosclerosis, reduced perfusion, peripheral arterial disease and increases cardiovascular mortality among patients with end stage renal disease [3]. Calciphylaxis is a severely morbid and life threatening form of patchy medial vascular calcification of arterioles (< 0.6 mm). It is an active vasculopathy causing cutaneous fibrosis and necrosis, skin ulcer, panniculitis and gangrene secondary to intimal proliferation and thrombotic occlusion [5]. It affects patients with advanced chronic kidney disease especially those receiving warfarin. Warfarin may affect calcification by blocking Matrix Y – carboxyglutamic acid (Gla) protein (MGP) and osteocalcin that regulates mineralization. To be fully functional, MGP requires posttranslational modification by Y carboxylation (vitamin K dependant process inhibited by warfarin). In some patients, even at low vascular risk, long term warfarin use is associated with lower extremity medial arterial calcification in men and women [6,7]. This may have implications for the choice of therapies for long term anticoagulation [8]. Thus a high dosage of vitamin K reverses warfarin induced vascular calcium deposition [5].

Vascular calcification is common among patients with diabetes Mellitus and chronic kidney disease and is associated with increased morbidity and mortality [8,9]. Ultrasound and CT scan using a lower limb arterial calcification scoring system has been used to assess the degree and severity of calcification [10-12]. Peripheral artery calcification is independently associated with decreased toe-brachial pressure index leading to an increased ischemia categories in patients with peripheral arterial disease [11]. Arterial calcification is significantly associated with disease severity and outcomes including clinical limb ischemia and amputation and all causes of mortality in patients with symptomatic peripheral arterial disease [1].

Claudication in diabetes mellitus is more often associated with calcification in the arterial wall. People with diabetes develop symptoms of peripheral arterial disease a decade earlier than average and have a 7 - fold higher rate of limb amputation than non diabetics. Predictive variables related to the presence of calcification of the pedal arteries among diabetic patients admitted for foot disease were duration of diabetes mellitus > 20 years, retinopathy, albuminuria and peripheral arterial disease. The severe outcome of these patients was related to the association of calcification of the pedal arteries [13,14]. At 5 years, 32% of patients with peripheral arterial disease will die from coronary artery disease and or stroke and at 10 years 50% will no longer be alive. Diabetic patients show two-fold prevalence of extensive coronary artery calcification compared with non diabetic subjects [15]. Lower extremity arterial calcification is significantly correlated with coronary artery disease extend [16]. Clinically, vascular calcification is now accepted as a marker for advanced systemic atherosclerosis and a valuable predictor of coronary artery disease [6,12,16]. It strongly and independently predicts cardiovascular morbidity and mortality [1,12]. Treatment for osteoporosis (calcitrol, estradiol, biophosphonate, calcium supplements and intermittent PTH) are likely to affect vessel calcification [3].

For calciphylaxis, hyperbaric O₂ has been used with modest success. Sodium thiosulfate infusion which restores cellular Glutathione and mobilizes amorphous calcium phosphate have shown promising results [17]. Subtotal parathyroidectomy for hyperparathyroidism and tissue - plasminogen factor have been also proposed for treatment of calciphylaxis [18]. Metformin use was independently associated with a lower below - knee arterial calcification score among patients with diabetes mellitus. This

association correlates with the well known vascular protective effect of mellitus [19]. The potential effect of metformin to inhibit vascular calcification in patients with or without type 2 diabetes needs to be confirmed by further prospective studies.

Vitamin K antagonists results in elevated uncarboxylated MGP and subsequently in extensive arterial calcification. The Rotterdam Study (2004) showed that high dietary intake of Vitamin K₂ (at least 32 mcg/day) results in 50% reduction of arterial calcification, 50% reduction of cardiovascular risk, and 25% reduction of all-cause mortality [20]. Menaquinone 7 MGP is now under investigation as a new biomarker for vitamin K₂ insufficiencies as well as a predictor of risk for cardiovascular disease. Menaquinone - 7 (vitamin K₂) has a significant effect on preventing osteoporosis and cardiovascular disease [21]. It improves arterial stiffness in healthy post-menopausal women [22]. Vossen LM et al. confirmed that Menaquinone - 7 slows down or arrest the progression of vascular calcification and coronary artery calcification [23]. Deficiency in vitamin K- dependent activation of MGP may lead to large artery stiffening and can be treated with vitamin K supplementation in diabetic patients [24].

Most hemodialysis patients have a functional vitamin K deficiency. Inactive MGP levels can be decreased markedly by daily vitamin K₂ supplementation [25]. In a recent study, Aoun M et al. demonstrated that daily 360 µg of menaquinone-7 given for 4 weeks reduces by 86% dephosphorylated - uncarboxylated MGP in the Eastern Mediterranean population [26].

Conclusions

The role of lower extremity arterial calcification deserves further comprehensive investigations. Arterial calcification should be considered as a novel parameter upon conventional risk factors in all patients with peripheral arterial disease. Concerning calciphylaxis, further research is needed to devise strategies to address this tragic disorder. The role of lower extremity arterial calcification in predicting severe coronary artery disease and in increasing morbidity and mortality needs to be assessed by further studies. These data reinforce the need for aggressive therapy and new strategies to improve cardiovascular outcomes in this high risk group. Prospective large studies to evaluate the value of Menaquinone 7 MGP as a new biomarker for vitamin K₂ insufficiencies and to confirm the efficacy of Menaquinone - 7 in stabilizing and decreasing arterial calcification are warranted.

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