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# Vascular calcification, cardiovascular risk and arterial stiffness in hemodialysis patients

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## INTRODUCTION

Intimal and medial calcification, the two main types of arterial calcification, are associated, respectively, with arteriosclerosis and mediosclerosis. In non-dialysis patients, both intimal[1] and medial calcification[2] may be the result of an active regulated process with different aetiologies, where local cells, such as macrophages in the intima or vascular smooth cells in the media, differentiate into osteoblasts[3]. In haemodialysis patients it has also been demonstrated that medial calcification is an active cellular process, similar to bone formation[4,5]. Vascular smooth muscle cells can differentiate into osteoblasts due to different stimuli, some of which may be hyperphosphatemia or hypercalcemia[6]. A passive calcification mechanism is, however, not excluded. High calcium phosphorus product may also contribute to the matrix mineralization[6]. Reduction of calcification inhibitors in dialysis patients, such as fetuin-A or matrix-Gla protein, may be other factors associated with the development of calcification[7]. It has already been demonstrated that calcium carbonate and calcium acetate are associated with the progression of vascular calcification, a phenomenon that can be attenuated or arrested by sevelamer, a phosphorus binder that does not increase calcium levels and also reduces LDL-cholesterol[8,9]. In a rat model of hyperparathyroidism treatment with calcitriol or cinacalcet reduced PTH but, unlike calcitriol, cinacalcet did not produce hypercalcemia, increase in calcium phosphorus product or aortic calcification[10].

## VASCULAR CALCIFICATION AND CARDIOVASCULAR RISK

Blacher et al.[11] showed for the first time that a vascular calcification score evaluated by B-mode ultrasonography in large arteries was associated with an increased risk of mortality in dialysis patients. Brawn et al.[12] had previously demonstrated that dialysis patients, when compared with non-dialysis patients, presented a higher coronary calcification score evaluated by electron beam computed tomography (EBCT). In general population this score, the Agatston score, is mainly caused by intimal calcification and is related with arteriosclerosis and coronary stenosis[13,14]. The higher values of this score in dialysis patients may be explained by the presence of both intimal and medial calcification. Medial calcification is not occlusive but modifies the properties of the arterial wall and may also contribute to coronary ischemia. The quantitative significance of Agatston score may be different from that described for the general population where a score greater than 400 is associated with a very high cardiovascular risk. In a study evaluating 43 dialysis patients a mean score of 559±255 was found in patients with normal coronary angiographies while abnormal coronary angiographies were associated with a mean score of 2869±417[15]. In dialysis patients, high values of Agatston score may occur in the absence of occlusive coronary atherosclerosis[16] but, like other calcification scores, Agatston score was an independent predictor of death in haemodialysis patients[16]. The discriminative significance of Agatston score in dialysis patients remains, however, to be identified.

Multislice computed tomography (MSCT)[17] has already been employed for the diagnosis of vascular calcifications in dialysis patients, but, as well as EBCT, it is very expensive to be used in a routine way. Evaluation of vascular calcifications in plain radiographs has been proposed by KDOQI guidelines[18]. We have already verified that a simple vascular calcification score based on plain radiographs of pelvis and hands was a predictor of cardiovascular mortality, cardiovascular hospitalizations and fatal and non-fatal cardiovascular events[19]. Radial, iliac and femoral arteries were the arteries evaluated for the estimation of this score. This score may be used as a simple and inexpensive tool for the assessment of cardiovascular risk in haemodialysis patients.

Development of a numeric cardiovascular calcification index for cardiovascular risk evaluation in dialysis patients has been recently suggested[20]. The methodology recommended for the assessment of this calcification index should be non-invasive and low-cost, in order to be widely accessible, such as conventional blood pressure measurements for pulse pressure evaluation, standard radiographs for vascular calcifications assessment and echocardiography for valvular calcifications diagnosis.

Vascular[11] and valvular[21] calcification are demonstrated risk factors for cardiovascular death in dialysis patients. Pulse pressure increase is associated with vascular stiffness and has been related with cardiovascular risk in general population[22] and in haemodialysis patients as well[23].

We have developed, in a cohort of haemodialysis patients, a combined cardiovascular score based on pulse pressure and on vascular and valvular calcifications and compared it with the previously described simple vascular calcification score. This combined cardiovascular score was a stronger predictor of cardiovascular risk than the simple vascular calcification score[24]. We verified that the addition of a valvular and of a pulse pressure score to the simple vascular calcification score allowed a more accurate prediction of cardiovascular risk in this group of patients.

## CLINICAL SIGNIFICANCE OF INTIMAL AND MEDIAL CALCIFICATION IN HAEMODIALYSIS PATIENTS

Intimal and medial calcifications are highly prevalent in dialysis patients. Intimal calcification corresponds to the type Vb of atherosclerotic plaques (American Heart Association classification) and medial calcification is associated with mediosclerosis. Standard radiographs can be employed to differentiate these two different types of arterial calcification[25] since other more sophisticated diagnostic techniques such as ultrasonography, EBCT or MSCT can not discriminate these calcification types. Using this methodology, London et al. demonstrated that intimal and medial calcification are independent predictors of cardiovascular and all-cause death in dialysis patients[26]. Intimal calcification was associated with older age and lower survival when compared with medial calcification. Medial calcification was associated with haemodialysis duration, diabetes, hyperphosphatemia and with calcium carbonate dose treatment.

## VASCULAR CALCIFICATION CONTRIBUTES TO ARTERIAL STIFFNESS IN HAEMODIALYSIS PATIENTS

Arterial stiffness is an alteration of the arterial wall properties with multiple causes, some of which are old age, diabetes, hypertension and medial calcification. All these features are highly prevalent in dialysis patients and arterial stiffness is a common finding in this population. Some of the manifestations of arterial stiffness are isolated systolic hypertension, pulse pressure increase and high pulse wave velocity. Pulse pressure is the difference between systolic and diastolic pressure. The arterial wall stiffness creates an early aortic pulse wave reflection that finds the aortic valve still opened and causes a systolic blood pressure increase and a diastolic blood pressure decrease. Increase in systolic pressure provides an increase in after load that can contribute to the development left ventricular hypertrophy. Decrease in diastolic pressure decreases coronary perfusion which occurs during diastole and may aggravate coronary ischemia.

Pulse pressure increase has already been connected to cardiovascular risk in the general population[22] and in haemodialysis patients[23].

Pulse wave velocity is also a marker of arterial stiffness. The loss of elasticity of the arterial wall increases the velocity of the blood flow through the arterial system. Guérin et al demonstrated that, in haemodialysis patients, vascular calcifications were associated with increased stiffness of elastic type arteries like the aorta and common carotid artery[27]. In this study vascular calcifications were evaluated by ultrasonography. We have also verified in a cohort of haemodialysis patients that the simple vascular calcification score, assessed in plain radiographs of hands and pelvis and evaluating not elastic arteries but muscle arteries such as radial, iliac and femoral arteries, was independently and directly associated with pulse wave velocity[28]. This study was another evidence of the usefulness of this simple vascular calcification score in this population.

## PERIPHERAL ARTERY DISEASE IN DIALYSIS PATIENTS

There is a remarkably high prevalence of peripheral artery disease among patients with renal insufficiency. Its prevalence may reach 24% of patients with creatinine clearance < 60ml/min versus 3.7% of persons with creatinine clearance $\geq$ 60 ml/min[29]. Both moderate and

severe renal insufficiency are associated with an increased risk of death in patients with peripheral artery disease[30]. In this study, the percentages of patients who presented with gangrene or ischemic ulceration rather than rest pain increased with declining renal function. Lower limb amputations are a major problem in dialysis patients. Histological patterns found in 11 dialysis patients submitted to distal amputations (figures 1 to 3) reflect the diversity of lesions present in this population that may contribute to the chronic distal artery disease[31]. Occlusive lesions consisted of luminal thrombi and cholesterol emboli. Arteriosclerosis plaques and medial calcification may be present in the same patient and even in the same artery. In other evaluation of 56 patients submitted to lower limb amputations (non-published data) medial calcification was present in 48% of the samples and was associated with atherosclerotic plaques type II or III (American Heart Association classification) in 50% of cases. In this group of patients submitted to lower limb amputations there was no histological evidence of intimal calcification in any sample. This data confirm the association of medial calcification with distal artery disease. Dialysis vintage, diabetes, calcium carbonate dose and hyperphosphatemia have already been associated with medial calcification[26]. In a registry study, hyperphosphatemia was independently associated with future amputations[32]. These observations raise the hope of modifying the evolution of peripheral artery disease in dialysis patients by the correction of some of these factors.

In summary, vascular calcifications are highly prevalent in dialysis patients, and contribute to cardiovascular mortality and morbidity. Plain




**Fig. 2** – Exuberant medial calcification. (Hemotoxilin Eosin x 100)

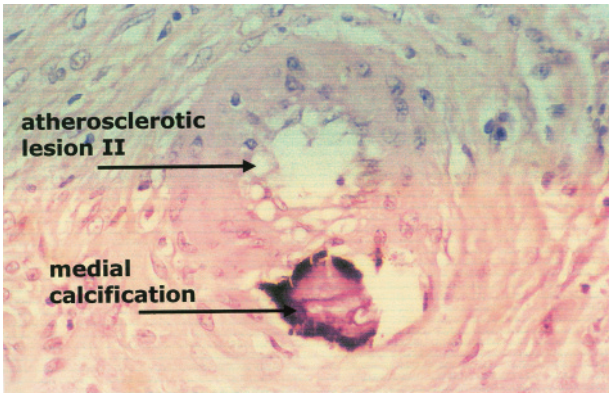



**Fig. 3** – Type II atherosclerosis lesion and medial calcification. (Hemotoxilin Eosin x 100)

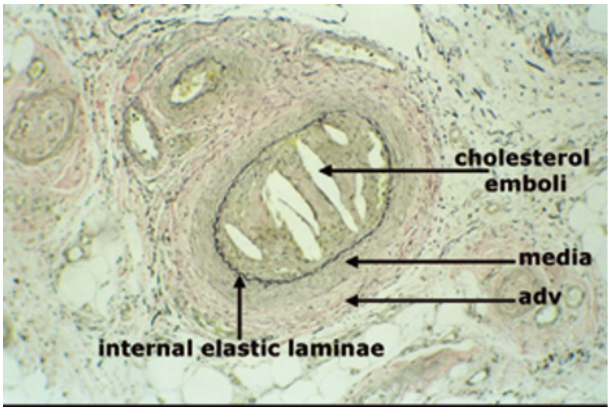



Fig. 1 – Muscular artery: cholesterol emboli. (Elastic van Giesen x 100)

radiographs are a simple and inexpensive tool for the assessment of cardiovascular risk. Arteriosclerosis and mediosclerosis are the histological setting for the development of vascular calcifications. Intimal calcification is associated with arteriosclerosis and medial calcification with mediosclerosis. In dialysis patients, medial calcification has been associated with diabetes, dialysis vintage, hyperphosphatemia and treatment with calcium carbonate. Decrease of calcification inhibitors facilitates this process. Sevelamer can arrest vascular calcification progression. In a rat model of hyperparathyroidism Cinacalcet, unlike calcitriol, was not associated with vascular calcification development. It is necessary to demonstrate that the correction of those factors contributing to vascular calcification is associated with a better cardiovascular outcome in dialysis patients.

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