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**Review**


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# Evaluation of vascular calcifications in CKD patients

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*ABSTRACT: In observational studies on dialysis patients, there has been a consistent association between vascular calcifications and mortality. Hyperphosphatemia and calcium treatment are some of the factors associated with development of vascular calcifications, especially in the presence of low bone turnover disease. Several non-invasive imaging techniques have been used to screen for the presence of vascular calcifications: plain X-Ray, echocardiography, ultrasonography, and computed tomography. Presence of vascular calcifications is a warning sign for increased cardiovascular risk and this information may be relevant for choosing the most suitable treatment for dialysis patients. (Int J Artif Organs 2009; 32: 81-6)*

*KEY WORDS: Vascular calcifications, Imagiology, Chronic kidney disease*

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## INTRODUCTION

High cardiovascular risk in chronic kidney disease patients is not fully explained by traditional risk factors. The Framingham risk score, based on age, gender, diabetes, hypertension, lipid profile and smoking habits, fails to predict cardiovascular events in dialysis (1) and pre-dialysis (2) patients and several non-traditional risk factors are commonly considered to contribute to the high cardiovascular risk in this population.

In the last few years a new explanation has been added to the list of the already numerous cardiovascular risk factors of chronic kidney disease patients. The association of cardiovascular calcifications with mortality, verified in multiple observational studies, is considered to be a consistent finding and has been classified as grade B evidence in recent KDIGO recommendations. In experimental studies, it is demonstrated that an altered mineral metabolism has a direct causal effect on vascular calcifications. In a model using vascular smooth muscle cells from the human aorta, Giachelli (3) demonstrated that hyperphosphatemia and hypercalcemia were inducers of vascular calcification by activation of intracellular Cbfa1, which led to the transformation of the vascular smooth muscle cell into an osteoblast.

Hypercalcemia and hyperphosphatemia are commonly seen in dialysis patients under two opposing conditions. In secondary hyperparathyroidism, a situation with high

bone turnover, the bone itself contributes to the high levels of phosphorus and calcium. In adynamic bone disease, a condition with low bone turnover, the bone behaves as if it were “frozen” and is unable to capture extraosseous calcium and phosphorus derived mainly from food and, in the case of calcium, from treatment as well.

These observations have led to the hypothesis that a link exists between bone disease and vascular disease in dialysis patients. In the KDIGO position paper published in 2006, the presence of soft tissue and of vascular calcifications have been included in the definition of chronic kidney disease mineral and bone disorder (CKD-MBD) (4).

## Types of vascular calcification

Vascular calcifications present two different histological types: intimal and medial calcification. Thus far, intimal and medial calcifications have been considered to be two distinct entities, with different clinical presentations and prognoses. The possibility that these two entities may constitute a continuum of vascular pathology in CKD patients has been hypothesized (5). However, the fact that media calcification is detected earlier in the course of CKD, and in the absence of lipid and cholesterol deposition, challenges this hypothesis (6). Intimal calcification is related to dyslipidemia and accompanies the progression

of atherosclerotic plaque. Medial calcification is associated with arteriosclerosis, and develops mainly in diabetic, chronic kidney disease, and elderly patients. Clinical manifestations of intimal calcification are related to the presence of atherosclerotic plaques that obstruct the arteries by rupture and /or thrombosis. Medial calcification does not cause arterial obstruction and was once considered a radiological finding with no clinical consequences. Today we know that medial calcification modifies the properties of the arterial wall and is one of the factors that contributes to arterial stiffness. Arterial stiffness is manifested by an increase in pulse wave velocity and in pulse pressure. Due to the loss of distensibility in the aorta, there is an earlier reflection of the aortic wave that finds the aortic valve still opened. The consequence is an increase in the systolic and a decrease in the diastolic pressure. Systolic pressure increase contributes to the development of left ventricular hypertrophy. Decrease in diastolic pressure may compromise the coronary perfusion that is mainly performed during diastole. Medial calcification may then be associated with symptomatic coronary disease in the absence of obstructive coronary artery disease.

### Methods to diagnose vascular calcifications: quantitative evaluation of coronary calcifications

#### *Electron Beam Computed Tomography (EBCT) and Multislice Computed Tomography (MSCT)*

Braun et al (7) in 1996 used Electron Beam Computed Tomography (EBCT) to evaluate coronary calcifications in dialysis patients. Quantification of calcification is performed by calculating the Agatston score. This method is based on the maximum X-ray attenuation coefficient, measured in Hounsfield units, and the area of calcification is multiplied by the density scores. Analysis of 49 hemodialysis patients demonstrated that the mean cardiac calcification score was more than 10-fold higher in hemodialysis patients than in 102 non-dialysis control patients with documented or suspected cardiovascular disease. The meaning of the Agatston score may be different in renal and non-renal patients. In non-renal patients the amount of coronary calcium is related to the overall atherosclerotic plaque burden and is an effective predic-

tor of coronary artery disease. It is well established that individuals with Agatston scores above 400 have an increased occurrence of coronary procedures (bypass, stent placement and angioplasty) and of cardiac events (myocardial infarction and cardiac death) within the 2 to 5 years after the test. The extent and site of calcification may not correspond to the site of stenosis but the greater the amount of calcification, the greater the likelihood of obstructive disease somewhere in the coronary arteries. In general population, several studies have shown a good correlation between calcium scores and coronary stenosis (8).

Dialysis patients, however, can have very high coronary Agatston scores without coronary stenosis. Haydar et al (9) compared coronary angiographies with coronary Agatston scores obtained by EBCT in a group of 46 hemodialysis patients. A higher coronary Agatston score was associated with a higher number of diseased vessels, however, eleven patients with no occlusive coronary disease in the angiography had a median coronary Agatston score of 619, which, in the general population, is associated with coronary stenosis. Three- or four-vessel disease in twenty dialysis patients was associated with a median coronary Agatston score of 3748, a score rarely seen in the general population. Since this method does not discriminate intimal from medial calcification, these very high calcification scores in dialysis patients may be explained by the probable occurrence of both types of vascular calcification in coronary arteries.

The existence of a different morphology of coronary lesions in CKD and non-CKD patients has been demonstrated in an autopsy study (10). CKD patients show heavy calcification of the media, with higher calcium content in the media and in the intima and with more frequent presence and greater intensity of inflammation markers. In dialysis patients, there is, however, a good correlation between coronary calcifications and cardiovascular risk. Coronary calcifications have been related with cardiovascular events (11) and with mortality (12, 13). Nevertheless, the clinical significance of Agatston score cut-off values in the general population for the diagnosis of occlusive coronary disease cannot be applied to dialysis patients. Likewise, coronary calcification has also been a predictor of mortality in dialysis patients but in association with lower coronary Agatston score values than those described in association with coronary occlusive disease (9). In prevalent patients a coronary Agatston score greater than 200 was associated with all-

**Fig. 1** - Simple vascular calcification score evaluation. Calcification score is the sum of the presence (1) or absence (0) of vascular calcifications in each section. Pelvis score (1+1+1+1) = 4 and hands score (1+1+1+1) = 4. Total score is 8.



cause death (12), and in incident patients, a coronary Agatston score greater than 400 was associated with lower survival (13). Therefore, the association of coronary calcifications with mortality is consistent with all the other observational studies showing that the presence of vascular calcifications, independently of their location, is predictive of mortality.

Currently, evaluation of coronary calcifications with EBCT has been substituted by multislice computed tomography (MSCT). Application of EBCT is limited to the assessment of coronary calcification, while MSCT has multiple uses and with software adjustments may also evaluate coronary calcification. This technique is widely available and is now an alternative for quantitative evaluation of coronary calcification. It has been demonstrated that MSCT is a viable technique for the evaluation of coronary arteries and aortic vascular calcification in CKD patients (14).

#### *Ultrasonography and echocardiography*

Ultrasonography was the method used by Blacher (15) to evaluate vascular calcifications in four arterial territories in dialysis patients: the carotid, aorta, iliac and femoral arteries. This study, performed in 2001, was the first to demonstrate that vascular calcifications were associated with increased mortality in dialysis patients and it showed that the higher the number of territories affected, the lower the survival.

Calcification of heart valves can be evaluated by echocardiography; this type of calcification was associated with lower survival in peritoneal dialysis patients (16). In a group of 127 hemodialysis patients we have also ver-

ified that valvular calcification is a predictor of all-cause and cardiovascular death. The simple vascular calcification score evaluated in plain X-ray of pelvis and hands (17), described in the next section, was associated with valvular calcification, raising the hypothesis of a common pathogenesis for valvular and vascular calcification in this population (18).

#### *Plain X-ray*

In 2003 London et al (19) were the first to demonstrate that vascular calcifications evaluated by plain X-ray were associated with all-cause and cardiovascular mortality. These authors differentiated medial from intimal calcification in plain X-ray films. Medial calcification is linear and regular, presenting a railroad track type, while intimal calcification is patchy and irregular. This study demonstrated that medial calcification is not a radiological finding but has an important clinical significance. These two types of calcification were sometimes found in the same patient and in the same vessel and were independent predictors of mortality. Intimal calcification was associated with older age and higher LDL-cholesterol levels. Medial calcification was associated with hemodialysis vintage and diabetes. Calcium carbonate dose and phosphorus levels were associated with both types of calcification.

Other studies (17, 20) have confirmed the association between vascular calcifications, evaluated with plain X-ray, and mortality in the CKD stage-5 hemodialysis population. We developed a simple vascular calcification score, evaluated in a plain X-ray of the pelvis and hands (17) (Fig. 1). This simple score was an independent pre-

dictor of cardiovascular death, cardiovascular hospitalizations and vascular disease in dialysis patients and was an independent predictor of arterial stiffness evaluated by pulse wave velocity and pulse pressure (21).

The Kauppila score evaluates the presence of vascular calcifications in the anterior and posterior wall of the abdominal aorta using a lateral plain X-ray of the lumbar vertebral segments from L1 to L4. This score has been associated with cardiovascular death in a subgroup of participants of the Framingham Heart Study (22). This score has also been tested in dialysis patients. It presents a good correlation with the coronary Agatston score and demonstrates high sensitivity and specificity in predicting a high coronary Agatston score (23). The preliminary results of the CORD study, evaluating outcomes in relation with the Kauppila score, have shown that abdominal aortic calcification is associated with age, dialysis duration and previous cardiovascular disease (24). The plain X-ray score and Kauppila scores are semi-quantitative evaluations of vascular calcifications. Simpler evaluations of vascular calcifications, assessing only the presence or absence of vascular calcifications have also been associated with mortality, such as the identification by plain X-ray of vascular calcifications in the abdominal aorta (20) or in the hemodialysis vascular access (25).

## CONCLUSIONS

### *What is the best non-invasive method to diagnose vascular calcifications?*

Several non-invasive imaging techniques have been used to screen for the presence of vascular calcifications: plain X-ray to evaluate different arterial territories, echocardiography for assessment of valvular calcification; two-dimensional ultrasound for calcification of carotid arteries, femoral arteries and aorta; and computed tomography technologies.

Existing studies demonstrate that vascular calcifications, independently of their location, are predictors of mortality in CKD patients. EBCT and MSCT are considered to be the gold standard for evaluating coronary calcifications. They allow a quantitative assessment of vascular calcifications and have been used in several randomized clinical trials for evaluating progression of calcification. These methods do not differentiate intimal from medial calcification, and high coronary scores in dialysis

patients, though related with higher cardiovascular risk, may not be related with coronary obstructive disease. The clinical implications of this score in dialysis patients are not identical to those for the general population.

Plain X-Ray, ultrasonography and echocardiography are less expensive and, for that reason, more convenient for screening vascular calcifications. Plain X-ray methods have the advantage of greater simplicity and the possibility of being easily interpreted by the attending physician. The simple vascular calcification score and Kauppila score perform a semi-quantitative evaluation of vascular calcification with cut-off values that allow the identification of patients with a higher cardiovascular risk. A cardiovascular calcification index using the Kauppila score and valvular calcification evaluated by echocardiography have been demonstrated to be associated with coronary calcification in hemodialysis patients evaluated by EBCT (26). Simpler methods to evaluate vascular calcifications seem to be an attractive option but the final choice of the method to employ would depend on the available tests and on the preference of the nephrologist.

### *Is it useful to screen vascular calcifications in dialysis patients?*

Cardiovascular death is the main cause of mortality in CKD patients and, at present, very few therapeutic interventions have shown success in the reduction of all-cause or cardiovascular mortality in this population. Candesartan (27), which has been associated with reduction of cardiovascular events in dialysis patients, carvedilol (28) in patients with dilated cardiomyopathy, and sevelamer (29), used to control phosphorus levels in incident patients, are some of the few treatments that have been associated with increased survival in dialysis patients. In CKD patients, the presence of vascular calcifications is a marker of increased cardiovascular risk and this association, based on observational studies, is classified as grade B evidence by the recent KDIGO recommendations. Vascular calcifications are multifactorial and result from a complex balance between inducers and inhibitors. At the present stage of knowledge we can only intervene in a very small number of these factors, mainly, in the correction of the mineral metabolism. Several studies have already demonstrated that vascular calcifications in dialysis patients may progress or remain stable depending on the control of the mineral metabolism and on the type of phosphate binder (30-32). London et al demon-

strated an association between vascular calcifications and low bone turnover (33) and found a significant interaction between calcium-containing phosphate binders and aortic calcification and stiffness in the presence of adynamic bone disease (34).

Identification of vascular calcifications in CKD patients is included in the classification of CKD-MBD. This information may be used for selecting the most suitable control of the mineral metabolism, such as intensive control of hyperphosphatemia, suitable choice of phosphate binder and prevention of low bone turnover status, for instance, by avoidance of calcium-containing binders or of PTH oversuppression. In predialysis (35) and dialysis patients it has been demonstrated that, vascular calcifications are progressive and for this reason it seems logical to begin evaluation of vascular calcifications at an early stage, possibly in predialysis patients.

In conclusion, different methods can be used for screening vascular calcifications. Plain-X-ray is a simple

and inexpensive method to perform this evaluation. Considering the poor results of therapeutic interventions on cardiovascular mortality in CKD patients, the available evidence justifies the more frequent use of this simple evaluation in these patients. This information may be used to detect cardiovascular risk and to guide therapeutic intervention in chronic kidney disease patients.

#### Conflict of interest statement

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