Uso do ultrassom intracoronariano para a caracterização da doença arterial coronariana em pacientes com doença renal crônica

Use of intravascular ultrasonography for the characterization of coronary artery disease in patients with chronic kidney disease

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Submitted on: 05/22/2011
Approved on: 07/04/2011

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Financial Support: CNPq.

This study was undertaken at the Ambulatório de Cardiologia of Pontifícia Universidade Católica do Paraná.

The authors report no conflicts of interest.

Resumo

Introdução: Neste estudo, objetivou-se identificar os pacientes em alto risco de desenvolvimento de DAC entre todos os indivíduos com DRC tratados em um grande centro universitário para estimar a prevalência de DAC e determinar a morfologia das placas ateroscleróticas através do IVUS em comparação com seus pares com função renal preservada. Métodos: Pacientes foram investigados à procura de doença arterial coronariana, e a angiografia coronariana foi realizada quando indicada. Após avaliação sistemática para DAC os pacientes que apresentaram indicação foram encaminhados para cineangiocoronariografia e IVUS. As imagens de IVUS foram comparadas as de um grupo de pacientes com DAC, mas com função renal preservada, pareados cuidadosamente para todos os fatores analisados. Resultados: Cento e trinta e nove pacientes de um centro de hemodiálise foram analisados para o estudo. Aqueles que tiveram a confirmação das lesões coronarianas na angiografia mostraram níveis séricos mais baixos de hemoglobina (10,8 ± 1,5 *versus* 12,0 ± 19; p < 0,046) e níveis elevados de LDL (110,6 ± 25,8 *versus* 75,5 ± 43,1; p < 0,004) quando comparados àqueles sem DAC. O IVUS revelou um maior diâmetro de referencia proximal e uma maior área de secção transversal nos pacientes com DRC em comparação ao grupo com função renal normal (4,1 ± 0,6 *versus* 3.7 ± 0,5; p < 0,007 e 4,2 ± 1,6 *versus* 5,2 ± 1,8; p < 0,02, respectivamente). Calcificação coronariana foi identificada pelo IVUS em 81% das lesões no grupo com DRC, 31% delas em mais de 180º da circunferência arterial. Os depósitos de cálcio estavam localizados em uma camada mais profunda da parede arterial

Abstract

Introduction: Chronic kidney disease patients present a very high cardiovascular mortality. Nevertheless, a comparative description of lesion characteristics, using intravascular ultrasound in dialysis patients, has not yet been reported. The objective of the present study was to analyze the plaque morphology through intravascular ultrasound in comparison to their counterparts with normal renal function. **Methods:** Patients were screened for coronary artery disease, and the coronary angiography was performed when indicated. Plaque morphology was evaluated by ultrasound, and findings were compared to a group of patients with coronary artery disease, who presented normal renal function, it carefully matched for all Framingham risk factors and lesion location at the coronary artery tree. **Results:** One hundred and thirty-nine patients from a single center of hemodialysis were screened for the study. Patients with coronary lesions confirmed at the angiography presented lower hemoglobin (10.8 ± 1.5 *versus* 12.0 ± 19; p < 0.046) levels and higher levels of low-density lipoprotein (110.6 ± 25.8 *versus* 75.5 ± 43.1; p < 0.004), when compared to the ones without coronary artery disease. The ultrasound revealed greater proximal reference diameter (4.1 ± 0.6 *versus* 3.7 ± 0.5; p < 0.007), smaller crossed sectional area (4.2±1.6 *versus* 5.2 ± 1.8; p < 0.02), and the calcification was located in a deeper arterial layer (69 *versus* 9%; p < 0.004) in patients with chronic kidney disease when compared to the Control Group. **Conclusion:** Lesions of the patients with chronic kidney disease presented a larger proximal diameter and intense calcification in the deeper layer of the vessel,

nos pacientes com DRC (69 *versus* 30%; p < 0,004). Conclusões: As lesões coronarianas apresentaram um maior diâmetro proximal e uma calcificação mais intensa em camada profunda da parede arterial sugerindo um efeito de remodelamento positivo exacerbado em resposta a um processo aterosclerótico mais agressivo na porção medial da parede arterial.
Palavras-chave: Falência renal crônica. Doença da artéria coronariana. Angiografia.

which suggest a greater positive remodeling effect in response to a more aggressive atherosclerotic process in the medial section of the artery.
Keywords: Kidney failure, chronic. Coronary artery disease. Angiography.

Introduction

Cardiovascular disease (CVD) is the main cause of death and morbidity in patients with chronic kidney disease (CKD) on renal replacement therapy (dialysis and transplantation).[1,2] This group presents a 20-30-fold increase in cardiovascular mortality, when compared to the population with normal renal function. The prevalence of classic CVD risk factors is extremely common,[3,4] since most CKD patients present arterial hypertension,[5] type II diabetes *mellitus*[6] and lipid disorders.[7] Nevertheless, traditional risk factors for CVD do not fully explain this increased risk, which appears to be influenced by nontraditional (fluid overload, activation of the renin-angiotensin system, inflammation, and oxidative stress) and CKD-related (anemia, disorders of mineral metabolism) risk factors.[8-10] The combination of these factors accelerates the progression of vascular disease, which represents the most important cause of death in this group of patients.

Since CKD patients are exposed to a peculiar combination of risk factors, mechanisms involved in the pathogenesis of Coronary Artery Disease (CAD) are potentially distinct. Studies combining an atherosclerotic-prone animal model with renal dysfunction[11] showed that even moderate renal dysfunction could cause a dramatic increase in the plaque size and intense inflammatory changes in its phenotype.[12] In addition, we observed that the exposure of endothelial cells to a uremic environment resulted in a time and CKD stage, which is dependent of increased expression of chemokines and adhesion molecules. These facts suggest a link between vascular activation, systemic inflammation, and uremic toxicity.[13] The presence of calcifications, both in the intimal and at the medial arterial layer, has been identified as one of the main characteristics of CAD in this population.[14-16]

Although it is has a good description in the candidate for renal transplant population,[17] routine screening and investigation of dialysis patients for CAD, as well as comparative description of lesion characteristics in CKD patients using intravascular ultrasonography (IVUS), have not yet been reported. Based on this scenario, we aimed to identify CAD in a group of patients under hemodialysis and to analyze the coronary morphology through IVUS in comparison to their counterparts exposed to similar traditional risk factors, with normal renal function.

Methods

Study population

This study complied with the Declaration of Helsinki. The Institutional Review Board of the Pontifícia Universidade Católica do Paraná (PUCPR), in Brazil, granted an ethical approval for this research. Patients gave informed consent at the time of enrollment. From June 2006 until December 2007, patients on kidney replacement therapy in the hemodialysis clinic of the University Hospital at PUCPR, in Curitiba/Brazil, were screened for evaluation of the CAD.[18,19] A standard questionnaire and a careful medical chart review were applied by an investigator.

The exclusion criteria were: failure or unwillingness to provide the informed consent form, age less than 18 years-old, inability to be transferred to the cardiology department for further investigation, and absence of cardiovascular symptoms or traditional risk factors for CAD. Patients who did not fit these exclusion criteria and that report any complain that could be translated into CAD or traditional risk factors associated with CAD were then referred to the cardiology department of the same University for noninvasive CAD evaluation. Blood samples were taken based on the clinical routine of the center. The standardized noninvasive routine evaluation of CAD, including a 12-lead electrocardiogram (ECG, Dixtal EP-3®), transthoracic echocardiogram (Siemens Cypress®, 1.8-3.6 MHz transducer) and an exercise test on the treadmill, following Bruce's protocol (TEB Apex 1,000®), were performed. All

noninvasive examinations were performed by experts complying with the appropriate Guidelines of the American College of Cardiology and American Heart Association Task Force (ACC/AHA).[20-22]

Characterization of CAD

Patients presenting positive evidence of myocardial ischemia or those with typical chest pain and an inconclusive noninvasive test were referred to coronary angiography plus IVUS of native coronary arteries. The exclusion criteria for the angiographic study were: the presence of clinically manifested vasculitis, active infection, homeostasis disturbance, lack of a proper arterial access, hypocalemia, uncontrolled arterial hypertension or digital intoxication, uncompensated heart failure, and the severe allergic reactions known to contrast media.

Standard coronary angiography was performed at the day preceding the hemodialysis session. All lesions greater than 50% by visual assessment were considered representative of CAD diagnosis, therefore, an IVUS evaluation followed. Plaque with ostial location of the main coronary vessels (n = 2), with percentage of stenosis greater than 95% (n = 5) or with unstable characteristics, such as thrombus, ulcers, and dissections (n = 1) was excluded from the IVUS study due to the increased risk of complications. IVUS imaging was obtained with Boston Scientific iLab® and a 40 mHz Isight™ Imaging Catheter. The images were analyzed offline by a blind expert following the American College of Cardiology Clinical Expert Consensus Document on Standards for Acquisition, Measurement and Reporting of Intravascular Ultrasound Studies.[23] The atherosclerotic plaque content was identified as calcified and noncalcified. The presence of calcium was classified as larger than 180° or smaller than 180° of the vessel circumference.

In order to evaluate the peculiarity of CAD in CKD patients, IVUS images were compared to images from a group of patients with CAD (extracted from the clinic's database), who presented normal renal function carefully matched for all Framingham risk factors and lesion location in the coronary artery tree.

Statistical analysis

Baseline characteristics were assessed with the Student's *t*-test (parametric) and Mann-Whitney test (nonparametric) for continuous variables. The dichotomic variables were compared with the Fisher Exact Test, and the normality condition of the variables was evaluated by the Shapiro-Wilk Test. P-values < 0.05 were considered to be significant.

Results

During the study period, 139 patients were screened (65 ± 49 months on hemodialysis, 53 ± 13 years of age and 62% male). Patients were dialyzed three times a week using Althin dialysis machines and synthetic dialyzers, with standard dialysis schedules of 3.5 to 4 hours to achieve adequate solute clearance and dry weight. Chest pain was reported by 48% of the interviewed subjects, and traditional CAD risk factors were identified as follows: hypertension in 86% of the patients, type II diabetes *mellitus* in 27%, 16% were current smokers, family history of CAD was detected in 46%, dyslipidemia in 15%, and 48% of them were sedentary. Sixty-nine patients were excluded from the study during the early screening phase. Therefore, 70 patients were evaluated at the Cardiology Department. The main characteristics of the study population are displayed on Table 1.

The 12-lead ECG was normal in 31% of the patients and presence of myocardial ischemia was identified in only 6%, primarily on the left ventricle anterior wall. The exercise test was ineffective in 82% due to the incapacity of the majority of the patients to achieve desired heart rate often, due to poor physical capacity and/or motion impairment. Echocardiogram analysis revealed a mean ventricular septum thickness of 12.58 ± 1.27 mm and a left ventricle posterior wall thickness of 12.06 ± 1.14 mm. The left ventricle mass was 149 ± 36 g/m^2 and the ejection fraction ranged from 33 to 75%, with a median of 64%.

After the noninvasive evaluation, 19 (27%) patients were selected to undergo coronary angiography, none of them presented the mentioned exclusion criteria. One patient died before the scheduled date of his exam during a hemodialysis session. The indications were based on positive results, which indicate presence of ischemia or of multiple traditional risk factors in association with borderline ECG abnormalities or myocardial contraction abnormalities at echocardiography. From the 18 remaining patients submitted to the coronary angiography, 12 (67%) showed CAD with a total of 24 lesions ≥ 50%.

There were no statistical differences among patients with CKD, who presented CAD at coronary angiography and those who did not when comparing gender, history of previous myocardial infarction, and traditional risk factors (hypertension, smoking habit, diabetes, family history of CAD, dyslipidemia,

and sedentary lifestyle). In addition, serum levels of glucose, total cholesterol, high density lipoprotein (HDL), calcium, phosphorus and parathormone (PTH) did not reach statistical significance involving both groups. Otherwise, statistical significance was found when comparing the prevalence of angina at rest (33.3 *versus* 6.9%; $p < 0.025$), level of low density lipoprotein (LDL) cholesterol (110.6 ± 25.8 *versus* 75.5 ± 43.1 mg/dL; $p < 0.005$), level of hemoglobin (10.8 ± 1.5 *versus* 12.0 ± 1.9 g/dL; $p < 0.05$) and hematocrit (32.8 ± 4.7 *versus* 36.2 ± 5.4%; $p < 0.05$).

Eleven patients were studied with IVUS. They provided 16 different coronary lesions, which were compared to IVUS images of lesions from patients with confirmed CAD and with no renal dysfunction. These patients or lesions were successfully matched by age, presence of Framingham risk factors, and lesion location at the coronary artery tree (Table 2). Lesions from patients with end-stage renal disease (ESRD) presented a significantly larger proximal reference diameter and a smaller cross sectional area when compared to the ones of CAD patients with normal renal function (4.1 ± 0.6 *versus* 3.7 ± 0.5 mm; $p < 0.01$ and 4.2 ± 1.6 *versus* 5.2 ± 1.8 mm^2; $p < 0.05$). There were no significant differences when comparing their distal reference diameter and minimal lumen diameter (Table 3). In addition, there were no differences in the prevalence of calcified lesions or in the extent of calcification in the CKD Group (81%) when compared to the Controls (69%). Finally, the extent of calcium was not statistically significant after comparison; however, the site of calcification was significantly more frequent in the deep layer in ESRD patients (69%) when compared to patients with CAD

Table 1 Distribution of clinical variables among patients enrolled in the study, those patients evaluated in cardiology clinic with noninvasive tests and the ones submitted to angiography

Population	Total	Noninvasive evaluation	Submitted to angiography
Number of patients	139	70	18
Age (years)	53 ± 13	53 ± 10	55 ± 7
Male gender (%)	86 (62)	49 (70)	10 (56)
Weight (kg)	64 ± 16	64 ± 21	67 ± 19
Height (m)	1.64 ± 0.10	1.64 ± 0.08	1.65 ± 0.08
Angina Pectoris (%)	67 (48)	46 (65)	15 (78)
Hypertension (%)	120 (86)	62 (88)	17 (89)
Smoking habit (%)	22 (16)	16 (23)	02 (10)
Diabetes mellitus type II (%)	38 (27)	28 (40)	12 (63)
Insulin therapy (%)	20 (14)	14 (20)	06 (36)
Family history of CAD (%)	64 (46)	39 (56)	09 (47)
Dyslipidemia (%)	21 (15)	13 (19)	03 (19)
Sedentary lifestyle (%)	66 (48)	40 (58)	11 (61)

Table 2 Clinical variables between patients with ESRD, with CAD, and patients with CAD without kidney dysfunction

Clinical Variable	ESRD Group	CAD Group	p-value
Age	55 ± 7	55 ± 8	ns
Male gender (%)	62	62	ns
Family history of CVD (%)	25	25	ns
Smoking (%)	18	12	ns
Hypertension (%)	93	93	ns
Diabetics (%)	50	50	ns
Dyslipidemia (%)	25	25	ns

ns: nonsignificant.

Table 3 Comparisons of the IVUS measurements in end-stage renal disease patients compared to patients with coronary artery disease without renal dysfunction

Variable	ESRD Group	CAD Group	p-value
Proximal reference diameter (mm)	4.1 ± 0.6	3.7 ± 0.5	0.007
Distal reference diameter (mm)	3.4 ± 0.5	3.3 ± 0.5	ns
Cross sectional area (mm^2)	4.2 ± 1.6	5.2 ± 1.8	0.020
Minimal lumen diameter (mm)	2.0 ± 0.5	2.2 ± 0.5	ns

ns: nonsignificant.

and no renal failure (9%; $p < 0.005$), as it can be seen in Figures 1 and 2).

Discusssion

Patients with ESRD present very high mortality, mainly due to atherosclerotic CAD. Although this group of patients is exposed to several nontraditional risk factors, there is little information in the literature regarding the characteristics of the coronary lesions in dialysis patients. In this study, ESRD patients, when compared to those with CAD and normal renal function, presented lesions with a larger proximal diameter, a smaller cross sectional area, and intense calcification in the deeper vessel layer.

In the present study, only 14% of the screened patients (19 of 139 subjects) were considered eligible to coronary angiography. Since ESRD patients are exposed to a very high cardiovascular burden, the low number of patients with indication of angiographic study most likely underestimates patients with lesions. Potential reasons for this underestimation are distinct tolerance to pain and high prevalence of diabetes. In addition, the poor discrimination value of noninvasive tests, particularly the exercise test, leads to a low prevalence of patients with indication for angiographic investigation.[17,24-28] It points out to the need of identifying the value of additional noninvasive screening, which could more effectively recognize a population with angiography indication in this patient group.

The present study also sheds light on the potential role of traditional and nontraditional risk factors for CAD in the ESRD population. In this cohort, higher LDL levels were present in patients with CAD confirmed by angiography. Interestingly, intervention studies performed in this population do not confirm the impact of dyslipidemia in the development of CAD. The Die Deutsch Diabetes Dialysis study, 4D Study,[29] demonstrated that the treatment with atorvastatin did not reduce the composite incidence of death from cardiac causes, nonfatal myocardial infarction, and stroke, but it lowered the incidence of death due to CAD. The recently published AURORA Trial[30] also shows no significant effects of rosuvastatin on the composite primary endpoint of death from cardiovascular causes and nonfatal myocardial infarction or stroke in patients undergoing hemodialysis. The findings of the present study suggest that LDL may indeed play a role in the development of CAD and that larger and randomized trials should more carefully look for this specific population, when comparing the clinical use of statins. The largest SHARP trial enrolled 9,270 patients with CKD (3,023 of them in dialysis), and provided data showing that aggressive lipid modifying therapy can safely reduce the incidence of major atherosclerotic events in a wide range of patients with advanced CKD.[31]

Figure 1. Calcium deposits – distribution and location at the arterial wall. Extension and site for calcification.

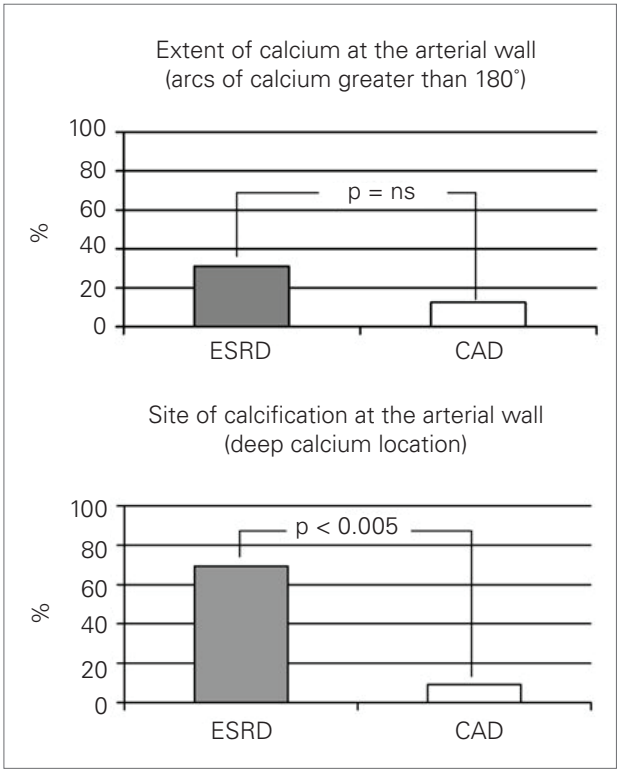
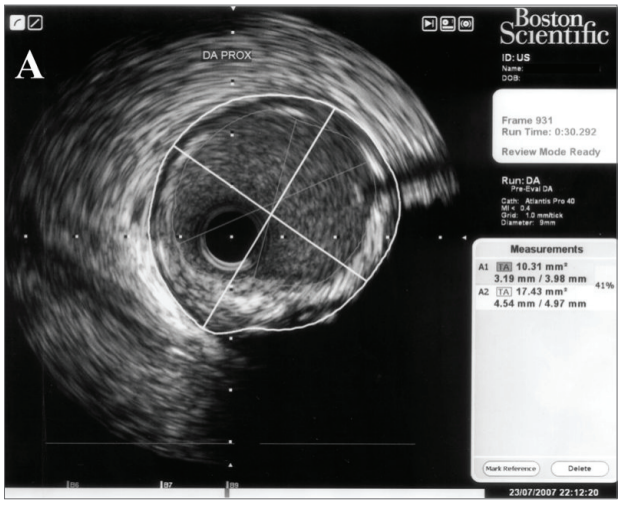
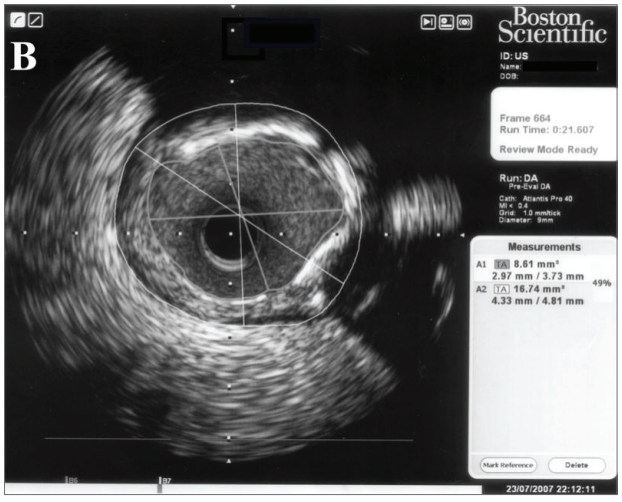
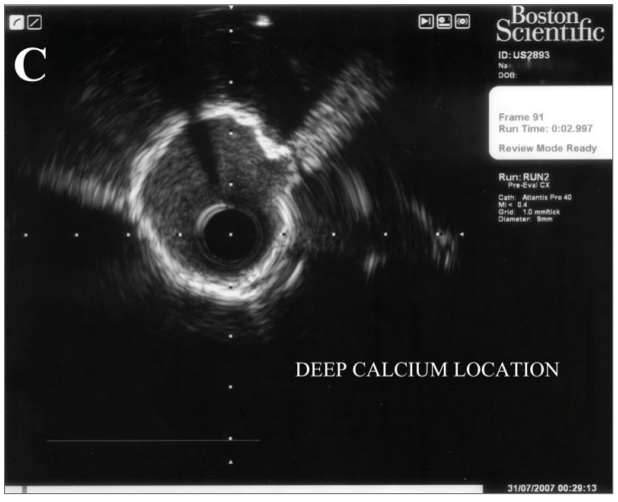


Figure 2. Images obtained from IVUS. A – presence of an arc of calcium at 3 to 6 o'clock in the proximal segment of the left descending artery (LAD); B – presence of an arc of calcium at 11 to 4 o'clock in middle segment of the LAD; C – deep circumferential deposit of calcium at the proximal segment of the circumflex branch.







We also identified that an ERSD related risk factor for CVD was also present in patients with confirmed CAD. Some published clinical and laboratory data suggest that anemia, congestive heart failure (CHF), and ESRD are interrelated resulting in a "vicious cycle" of disease progression, which has been labeled as Cardio-Renal Anemia Syndrome. In this condition, ESRD can cause and be caused by CHF and *vice-versa*.[32] It has been reported that erythropoietic stimulating agents often result in improvement of the left ventricular systolic and diastolic functions and hypertrophy, stabilization or improvement in renal function, reduced plasma volume, heart rate, and inflammatory markers C-reactive protein and interleukin 6. In addition, an improvement in New York Heart Association (NYHA) functional classification system, exercise capacity, oxygen utilization during exercise, depression, and quality of life occurs.[33] Nevertheless, it has also been stated that patients with renal failure develop anemia due to mechanisms associated with chronic inflammation[34] and that reduced production of erythropoietin (EPO) in patients with ESRD may accelerate diabetic angiopathy and that replacing therapy with EPO might inhibit endothelial cell apoptosis and diabetic angiopathy.[35]These might reflect on the reason why we found lower levels of hemoglobin among patients presenting CAD. The impact of anemia correction on the reduction of atherosclerotic events in ESRD patients deserves further investigation.

Studies analyzing the peculiar characteristics of the coronary lesions in ESRD patients compared to lesions of patients with normal renal function are clearly lacking, and they represent an important tool to investigate potential underlying mechanisms and management strategies. The only report published utilizing IVUS in ESRD patients – until the time of manuscript preparation – showed an intense calcified process with a large lesion plaque area and calcium in patients under hemodialysis.[36] Unlike the present study, Gruberg *et al*. did not include a Control Group in their analysis. When comparing artery measurements from ESRD patients and CAD Group, we demonstrated a significant difference between proximal reference diameter and cross sectional area suggesting an exacerbated positive arterial remodeling process, which refers to the changes in vascular geometry during the advance of the atherosclerotic process.[37] As initially thought, this enlargement of the artery wall could reflect a compensatory mechanism to preserve lumen size, explaining the underestimation of the disease severity by angiography.[38] However, histological

studies have established that the arterial remodeling is more complex than only a compensatory process, and positive remodeling is associated with features of plaques vulnerability, such as infiltration of inflammatory cells, expression of pro-inflammatory cytokines, and increased protease activity.[39,40]

More recently, novel technologies were able to demonstrate the association between positive remodeling and plaque vulnerability, also *in vivo*. Using optical coherence tomography (OCT), Raffel *et al*. have shown that coronary plaques with positive remodeling are more commonly associated with lipid-rich plaque and plaques with thin fibrous cap.[41] Together, these ex vivo and *in vivo* findings may explain the link between positive remodeling of culprit lesions and unstable clinical presentation, whereas negative remodeling is associated with more stable disease.[42] The fact that a positive remodeling process seemed to be intensified in ESRD patients may imply that even those individuals who do not present detectable CAD in coronary angiography are at higher risk of plaque instability and its consequences. Whether or not the positive remodeling accounts for higher cardiovascular event rates in ESRD patients remains to be defined.

Another important finding of this study is related to the intense and deep calcification process in coronaries of ESRD patients. Intense calcification of the medium layer of the vessel has been reported as one of the reasons for such elevated mortality rates among ESRD patients.[14-16,43] An autopsy study[44] assessed the morphology of coronary arteries in patients with ESRD and compared them with coronary arteries of matched nonuremic control patients, concluding that coronary plaques in patients with end-stage renal failure are characterized by increased media thickness and marked calcification.

A study applying the high-resolution electron beam computed tomography scanning described a coronary artery calcium score from 2.5 to 5-fold higher in dialysis patients than in nondialysis patients.[45] The pathology and physiology of these calcifications are not yet completely understood. Some factors seem to be related to them as follows: hyperphosphatemia, hypercalcemia, longer periods of uremia and dialysis, dyslipidemia (mainly higher levels of LDL) and the presence of inflammatory markers.[46] Unfortunately, the cross-sectional design of this study is a major limitation to evaluate the causal effect between metabolic disorders and coronary calcification. In the same way, we can only speculate about mechanisms involved in coronary calcification. The presence of bone proteins in the calcification areas of both peripheral and coronary arteries, as demonstrated in other studies,[47-49] directs to the discussion about the role of the smooth muscle cells (SMC) in the genesis of these morphologic alterations. The SMC and the osteoblasts have a very similar mesenchymal precursor cell, which made some authors[50] suggest a differentiation pathway from those into osteoblast-like cells. The fact that our data show a greater appearance of calcium at the deeper layer of the arterial wall in the ESRD Group seems to be reasonable based on the above-mentioned arguments.

It must be emphasized that the present study, although it shows several novel information, has some limitations. The small number of patients submitted to coronary angiography and the difficulty in detecting CAD in the ESRD, due to the screening methods available in our center, may have underscored the prevalence of CAD. In addition, this small number of patients turns the subgroup analysis inappropriate under a statistical point of view, preventing that associations between calcium deposits were made with blood levels of phosphorus, calcium and PTH, for instance. In the same way, some lesions were not accessed by IVUS due to high risk of acute complications.

In conclusion, we found that the lesions of ESRD patients differ from the controls presenting a larger proximal reference diameter and intense calcification in the deeper vessel layer, which suggest a greater positive remodeling effect in response to a more aggressive atherosclerotic process in the medial portion of the artery. In addition, these data show that mechanisms, evaluation, diagnosis and therapeutic approaches for CAD should be reevaluated in ESRD patients that present clinical and structural peculiarities.

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