Evaluation of intima-media thickness in patients with chronic kidney disease not on dialysis: a prospective study of 24 months

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ABSTRACT

Introduction: Increased carotid intima-media thickness (IMT) is considered a marker of early-onset atherosclerosis and it seems to predict cardiovascular events in general population. The prognostic value of IMT in patients with early-stage chronic kidney disease (CKD) has not been clearly established. **Objective:** We aimed to evaluate the association between IMT and cardiovascular (CV) events and mortality in CKD patients. **Methods:** A cohort of CKD patients in stage 2-4 was evaluated the occurrence of CV events and death in a 24 months follow-up. Laboratory data, carotid ultrasound and coronary computed tomography were performed at baseline. **Results:** A total of 117 patients (57 ± 11 years-old, 61% male) were evaluated. Mean glomerular filtration rate (eGFR) was 36 ± 17 mL/min, 96% of patients had hypertension, 23% diabetes and 27% were obese. Coronary calcification was found in 48% of the patients, with higher prevalence among CKD stage 4 ($p = 0.02$). The median value of IMT was 0.6 mm (0.4-0.7 mm). When compared to patients with IMT ≤ 0.6 mm, those with IMT > 0.6 mm were older ($p = 0.001$), had higher prevalence of male ($p = 0.001$) and had lower eGFR ($p = 0.01$). These patients also had higher prevalence of coronary calcification ($p = 0.001$). During the follow-up, there were no differences in the occurrence of cardiovascular events and deaths between the two groups. **Conclusion:** IMT in early-stage CKD patients was related to coronary calcification, but not with the occurrence of cardiovascular events or death.

Keywords: cardiovascular diseases, carotid intima-media thickness, mortality, renal insufficiency, chronic.

INTRODUCTION

The pathophysiological mechanisms of atherosclerosis in chronic kidney disease (CKD) patients are not yet fully established. However, it is known that in addition to the traditional risk factors described in the Framingham Heart study, other factors related to uremia such as hyperphosphatemia, hyperparathyroidism and increased proinflammatory cytokine play a role in the development of the disease in this population.[1,2]

The measurement of the intima-media thickness (IMT) by ultrasonography (USG) of the carotid artery has been used to identify and monitor preclinical changes caused by atherosclerosis and it is currently recommended for cardiovascular risk assessment.[3,4] In fact, in the general population, the carotid artery IMT is an independent predictor of coronary heart disease after adjustment for the risk of cardiovascular disease factors.[5,6] Some studies have indicated IMT as a predictor of cardiovascular events in patients undergoing hemodialysis.[7-10] However, there are only few studies evaluating the IMT in the early stages of CKD, with inconsistent data.[11-13] This study aimed at evaluating the association between IMT and the occurrence of cardiovascular events and mortality in patients with CKD in the non-dialysis stage.

METHODS

This is a post hoc analysis of a prospective study in which 117 patients were followed

up for a period of 24 months.[2,14] All the patients were over 18 years of age and had been followed up by a nephrologist for at least three months. Exclusion criteria were: chronic inflammatory disease, confirmed neoplasia, HIV, viral hepatitis and chronic use of corticosteroids. Among these patients, 82% were taking angiotensin-converting enzyme (ACE) inhibitors; 77% were on diuretics; 42% were on beta blockers and 42% were taking calcium channel blockers. The use of statins was observed in 34% of the patients; 32% were taking Sevelamer; 5% were on Calcitriol and 5% were taking calcium carbonate. The aforementioned drugs were maintained during the follow-up period.

All the patients signed the informed consent form, and the study was approved by the Ethics Committee of the Federal University of São Paulo.

Study protocol

At baseline, all the patients were submitted to laboratory tests, measurement of calcium score using coronary CT and carotid thickness measurement by USG. Cardiovascular events (angina, myocardial infarction, and stroke) or death were recorded for 24 months.

Laboratory analysis

Blood samples were taken after 12 hours of fasting, and included serum creatinine, hemoglobin, phosphorus, ionized calcium, alkaline phosphatase, intact parathyroid hormone [(iPTH), chemiluminescence immunoassay (Immulite, DPC-Biermann, Bad Nauheim, Germany)], cholesterol and triglycerides. The glomerular filtration rate (eGFR) was estimated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation.[15] Urinary protein was measured after a 24-hour collection, diagnosing proteinuria when the protein concentration exceeded 150 mg/24h.

Hyperphosphatemia, hyperparathyroidism and hypercalcemia were considered when serum levels of calcium, phosphorus and PTH were above the normal range (> 4.6 mg/dL, > 1.40 mmol/L and > 65 pg/mL, respectively) according to the guidelines from the Kidney Disease Improving Global Outcomes (KDIGO) [Guideline on Mineral and Bone Disorder of Chronic Kidney Disease][16]

Coronary artery calcification

Coronary calcification was determined using a 16-channel multislice CT scanner (LightSpeed Pro 16 - GE Healthcare, Milwaukee, USA), 0.4 s gantry rotation, 2.5 mm collimation, six takes per second of reconstruction time. A cutoff point equal to or higher than 130 Hounsfield units (HU) was used to determine the presence of calcium. Image acquisition time was synchronized with the cardiac cycle diastole by electrocardiographic monitoring.

The images were analyzed by a radiologist without access to patient clinical or biochemical information. As per described by Agatston, the calcium score was determined by multiplying the area of each calcified lesion by a numerical factor corresponding to the peak intensity of the pixels for each lesion. For analysis purposes, we used the sum of the lesions of all coronary arteries, represented by its numerical value in Agatston units (AU) [Agatston *et al.*, 1990]. Coronary calcification was defined by having a calcium score above 10 AU.

Ultrasonography

The carotid artery IMT measurement was carried out in all patients by high resolution ultrasonography (Ultramark HDI 3000, ATL Ultrasound Incorporation, Bothell, USA) using a linear probe and a 7.0 MHz variable focus digital transducer, as described previously [Pignoli *et al.*, 1986; Gariepy *et al.*, 1993]. The examinations were performed in the morning by an examiner without access to the patients' clinical or biochemical information. IMT was obtained by measuring the distance between two echogenic lines represented by the artery wall lumen-intima and media-adventitia interfaces. Since the USG is unable to differentiate the intima layer from the media, the measure represents the value of the intima-media complex. According to the VI Brazilian Hypertension Guidelines, an IMT value greater than 0.9 mm was considered abnormal.[17]

Statistical analysis

The variables' values were described as mean ± standard deviation (SD), median and interquartile range or frequency. Due to the small number of patients in stage 5 (n = 5), they were grouped

with those in stage 4. To compare the groups we used the unpaired *t*-test, Mann-Whitney and ANOVA, when appropriate. The Bonferroni test was used as an ANOVA complement when there were differences between the groups. For categorical variables we used the chi-square. The correlation between the IMT and other variables was assessed using the Spearman correlation. The cardiovascular event-free time and survival were assessed by Kaplan-Meier curves. The comparison between the curves was performed using the log-rank test, considering a significance level of 5%. A p value of less than 0.05 was considered significant. The calculations were performed using the SPSS 18.0 for Windows® (SPSS Inc., Chicago, USA).

Results

Table 1 depicts the characteristics of the 117 patients enrolled in the study. The patients were predominantly male; 23% were diabetic and 27% were obese (body mass index greater than 30 kg/m^2). Proteinuria was found in 58% of the subjects. Values above 200 mg/dL of total cholesterol were found in 32% of the individuals. Fifty-six patients (48%) had LDL cholesterol levels above 100 mg/dL, 22% had HDL cholesterol below 40 mg/dL and 43% had triglyceride levels greater than 150 mg/dL. In relation to changes in bone and mineral metabolism, 36% of patients had high concentrations of iPTH, 13% had hyperphosphatemia and 2.5% hypercalcemia.

Seventeen patients (14%) were in stage 2; 46 (39%) in stage 3 and 54 (47%) were in stage 4/5. There were more men in stage 4/5, with higher phosphorus, alkaline phosphatase and PTH; and lower hemoglobin concentrations. There was a lower prevalence of hypertension in stage 3. There were no differences in the other variables.

Fifty-six patients (48%) had coronary artery calcification (CAC), and the calcium score of these patients was 334 AU (108-856 AU). There were no significant differences in the calcium score between different CKD stages; however, the prevalence of patients with calcification was significantly higher in more advanced stages (11 versus 21 versus 42%; p = 0.02; stages 2, 3 and 4/5, respectively).

The median IMT was 0.60 mm (0.47 to 0.72 mm). Only eight patients had values greater than 0.90 mm, two on stage 3 and 6 in stages 4/5. There was a tendency to higher IMT values in CKD stages 4/5 (p = 0.09, Figure 1A). There was a higher ratio of patients with values above the median for IMT in the more advanced stages of CKD (p = 0.03, Figure 1B). There was a correlation between IMT and the calcium score, as shown in Figure 2.

During the study, 20 patients started dialysis, we lost the follow up of nine patients and one patient underwent renal transplantation. There were 15 cardiovascular events and four deaths in this period. The cardiovascular events were angina (n = 4); stroke (n = 3); acute myocardial infarction (n = 3); hypertensive emergency (n = 2); arrhythmia (n = 1); transient ischemic attack (n = 1) and heart failure (n = 1). One patient in stage 2 and three in stages 4/5 died. The deaths were attributed to acute myocardial infarction, pancreatitis, accident and unknown cause. The IMT value did not differ among the patients who had cardiovascular events [0.60 mm (0.46 to 0.72 mm) *vs.* 0.70 mm (0.50 to 0.82 mm), p = 0.75], or who died [0.60 mm (0.53 to 0.70 mm) *vs.* 0.66 mm (0.47 to 0.72 mm), p = 0.60].

Table 2 shows that patients with IMT above the median (≥ 0.60 mm) were older, predominantly males, and had lower glomerular filtration rates, also with a higher ratio of patients with coronary calcification. Cardiovascular events (9% *vs.* 16%, p = 0.26) and death (1.8 % *vs.* 4.8%, p = 0.37) were similar in both groups. As we can see in Figures 3A and 3B, the times free from cardiovascular events and death did not differ between the two groups.

Discussion

In this study, over 90% of patients with CKD in the pre-dialysis stage had carotid IMT values within the normal limits set by the VI Brazilian Guidelines on Hypertension. However, a relationship was found between IMT and the presence of coronary calcification at baseline. Within the 24-month follow up, the IMT was not associated with cardiovascular events or death.

The mean IMT values described in cohorts of patients with CKD are quite large and vary between 0.50 to 1.03 mm.[13,18] This variation can be partly explained by the heterogeneity of the populations studied, with the inclusion of patients on dialysis, higher or lesser ratios of patients with diabetes; and the use of different techniques to measure IMT.[4] The low IMT value found in this population could

Table 1 Population characteristics at the baseline

Characteristic	All	Stage 2	Stage 3	Stages 4-5	*p* value
Number (%)	117	17 (15)	46 (39)	54 (46)	
Age (years)	57 ± 11	56 ± 9	55 ± 12	58 ± 11	0.44
Men (%)	46 (39)	6 (35)	13 (28)	27 (50)	0.11
Hypertension (%)	113 (96)	17 (100)	42 (91)	54 (100)	0.02
Diabetes (%)	27 (23)	4 (23)	10 (22)	13 (24)	0.96
BMI (kg/m^2)	27 ± 5	30 ± 6	26 ± 5	26 ± 5	0.06
Creatinine (mg/dL)	1.8 ± 0.9	0.94 ± 0.24	1.4 ± 0.7	2.3 ± 0.8	0.001a
eGFR (mL/min/1,73m^2)	36 ± 17	69 ± 7	42 ± 9	21 ± 5	0.001a
Proteinuria (mg/24h)	205 (0-650)	0 (0-287)	165 (0-562)	255 (0-822)	0.56
Hemoglobin (g/dL)	12.8 ± 1.8	13.3 ± 1.2	12.9 ± 1.6	11.6 ± 1.7	0.001a
Phosphorus (mg/dL)	3.8 ± 0.7	3.3 ± 0.6	3.6 ± 0.6	4.0 ± 0.8	0.001b
Ion Calcium (mmol/L)	1.3 ± 0.6	1.3 ± 0.5	1.3 ± 0.7	1.3 ± 0.5	0.57
Alkaline Phosphatase (U/L)	81 (66-103)	72 (60-87)	80 (80-103)	83 (68-111)	0.11
Parathormone (pg/mL)	103 (62-192)	56 (39-100)	80 (47-141)	158 (92-257)	0.001b
LDL Cholesterol (mg/dL)	101 ± 28	98 ± 18	105 ± 34	99 ± 24	0.48
HDL Cholesterol (mg/dL)	50 ± 14	51 ± 18	49 ± 12	52 ± 14	0.44
Triglycerides (mg/dL)	127 (98-192)	147 (74-248)	122 (98-203)	127 (102-173)	0.35
Calcium Score (UA)	9 (0-325)	42 (0-223)	0 (0-144)	24 (0-459)	0.26
Intima-media thickness (mm)	0.6 (0.4-0.7)	0.5 (0.4-0.6)	0.6 (0.4-0.7)	0.6 (0.4-0.8)	0.09

Values in mean ± DP, median (interquartile interval) or numbers (percentage). [a] All the stages are different; [b] Only stage 4 is different; BMI: Body Mass Index; GFR: Glomerular Filtration Rate.

Figure 1. Intima-media thickness at the different CKD stages (A) percentage of patients with IMT ≥ 0,6 mm (B).

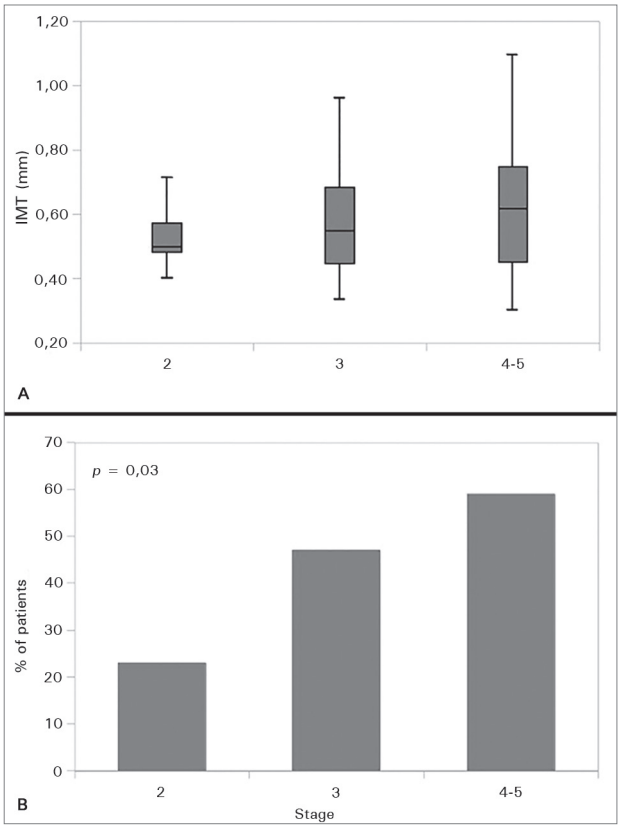
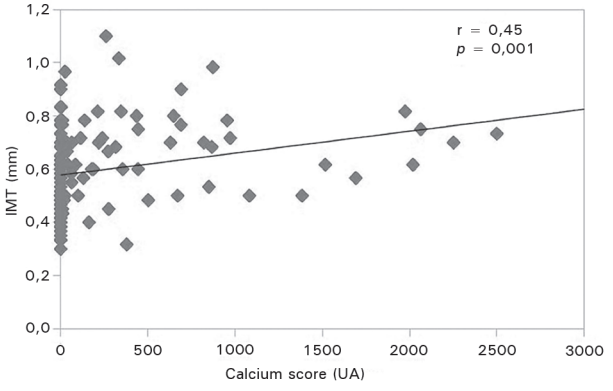


Figure 2. Correlation between intima-media thickness (IMT) and calcium score.



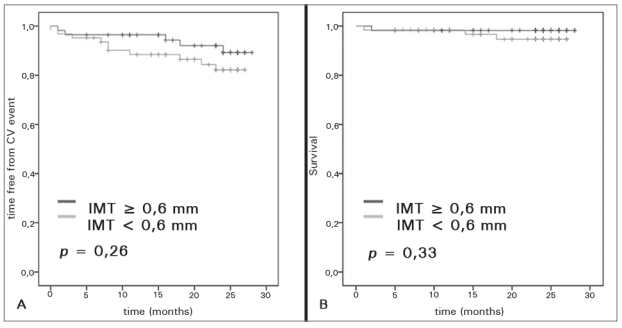
suggest that selected patients in this study had a low cardiovascular risk; however, the measured values are equivalent to those reported by other authors who evaluated patients with similar characteristics.[12,18]

Several factors have been implicated in the genesis of atherosclerosis.[1,3] Men have a higher prevalence of atherosclerosis, and the cause of this increased vulnerability has not yet been fully elucidated. It is suggested that the lower amount of circulating estrogen, to which vasodilation properties are assigned,

Table 2 Population characteristics and analysis of the population broken down according to IMT median value

Characteristic	IMT < 0.6	IMT ≥ 0.6	*p* value
Number (%)	55 (47)	62 (53)	
Age (years)	51 ± 11	62 ± 8	0.001
Men (%)	25 (25)	47 (75)	0.001
Hypertension (%)	52 (94)	61 (98)	0.25
Diabetes (%)	12 (21)	15 (24)	0.76
BMI (Kg/m^2)	27 ± 6	26 ± 5	0.61
Creatinine (mg/dL)	1.6 ± 5.2	1.9 ± 0.2	0.07
eGFR (mL/min/1,73m^2)	41 ± 19	33 ± 16	0.01
Proteinuria (mg/24h)	340 (0-600)	500 (0-500)	0.46
Hemoglobin (g/dL)	12.3 ± 1.8	12.5 ± 1.7	0.67
Phosphorus (mg/dL)	3.2 ± 0.9	3.3 ± 0.7	0.91
Ion Calcium (mmol/L)	1.28 ± 0.06	1.3 ± 0.6	0.58
Alkaline phosphatase (U/L)	77 (36-263)	84.5 (48-260)	0.11
Parathormone (pg/mL)	110 (18-502)	97 (20-1100)	0.65
LDL cholesterol (mg/dL)	100 ± 30	102 ± 26	0.92
HDL cholesterol (mg/dL)	51 ± 13	51 ± 15	0.93
Triglycerides (mg/dL)	159 (48-680)	156 (41-467)	0.83
Calcium score (UA)	0 (0-18)	138 (1-639)	0.22
Calcified patients (%)	16 (29)	42 (67)	0.001

Figure 3. Time free from cardiovascular events and patient survival, according to the intima-media thickness value.



can be an explanation.[19,20] The association between age and atherosclerosis reflects the degeneration the endothelium undergoes over the years - probably a consequence of the exposure to risk factors such as hypertension, oxidative stress, and hyperglycemia among others.[2] In the present study, the IMT was associated to both age and male gender.

An association between loss of renal function and increased IMT has been described;[18,21-23] however, we have a study that does not report such association.[12] In our study, we found more patients with IMT above the median value in the later stages of CKD - suggesting that uremia, and related factors, such as hypertension, diabetes, dyslipidemia, disorders of bone and mineral metabolism, inflammation and increased oxidative stress may induce or aggravate the atherosclerotic process in this population.[24-27]

Studies on the relationship between IMT and vascular calcification in CKD are scarce. Kurnatowska *et al.*,[28] upon assessing dialysis patients, found a direct correlation between the IMT and the calcium score. This data is similar to what we found in our study that evaluated patients in the early stages of CKD. Vascular calcification is prevalent and early, being found in all stages of kidney disease.[29,30] Coronary calcification is associated with a significant increased risk of cardiovascular events in this population.[14,31]

Different studies have investigated the relationship between IMT and cardiovascular events.[1] In agreement with our study, Zoungas *et al.*[13] found no association. However, Szeto *et al.*[11] found that the IMT was a strong predictor of cardiovascular events in a cohort of patients with CKD stages 3 and 4. It is noteworthy in this study that the median IMT was 0.8 mm, indicating a population with more advanced lesions than those found in our population. In addition, a longer study time (48 months) allowed the occurrence of a greater number of cardiovascular events. It is noteworthy that, like our study, Szeto *et al.*[11] found no association between IMT and mortality. However, the association between IMT and mortality has been

described in patients undergoing dialysis.[32] In this study, the authors report the occurrence of death in 30% of patients at 2 years follow-up. In our study, with the same follow-up period, we had only 3% of death, suggesting a greater severity of cardiovascular lesions in patients undergoing dialysis.

Despite the relatively small sample and reduced occurrence of cardiovascular events and deaths during follow-up, our study confirms that the IMT is a marker of cardiovascular disease - having seen its relationship with the calcification score. Further studies are needed to evaluate the IMT in patients with CKD.

Conclusion

The intima-media thickness in patients with CKD not requiring dialysis is associated with coronary calcification, but not to the occurrence of cardiovascular events and death in a 24-month follow-up.

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