Impact of Cardiovascular Calcification in Nondialyzed Patients after 24 Months of Follow-up

Renato Watanabe, Marcelo M. Lemos, Silvia R. Manfredi, Sérgio A. Draibe, and Maria Eugênia F. Canziani

Department of Internal Medicine, Division of Nephrology, Federal University of São Paulo, São Paulo, Brazil

Background and objectives: Coronary artery calcification (CAC) is highly prevalent among patients with chronic kidney disease (CKD), and it has been described as a strong predictor of mortality in the dialysis population. Because there is a lack of information regarding cardiovascular calcification and clinical outcomes in the earlier stages of the disease, we aimed to evaluate the impact of CAC on cardiovascular events, hospitalization, and mortality in nondialyzed patients with CKD.

Design, setting, participants, & measurements: This is a prospective study including 117 nondialyzed patients with CKD (age, 57 ± 11.2 years; 61% male; 23% diabetics; creatinine clearance, 36.6 ± 17.8 ml/min per 1.73 m^2). CAC was quantified by multislice computed tomography. The occurrence of cardiovascular events, hospitalization, and death was recorded over 24 months.

Results: CAC >10 Agatston units (AU) was observed in 48% of the patients [334 (108 to 858.5) AU; median (interquartiles)], and calcification score ≥400 AU was found in 21% [873 (436–2500) AU]. During the follow-up, the occurrence of 15 cardiovascular events, 19 hospitalizations, and 4 deaths was registered. The presence of CAC >10 AU was associated with shorter hospitalization event-free time and lower survival. CAC ≥400 AU was additionally associated with shorter cardiovascular event-free time. Adjusting for age and diabetes, CAC ≥400 AU was independently associated with the occurrence of hospitalization and cardiovascular events.

Conclusions: Cardiovascular events, hospitalization, and mortality were associated with the presence of CAC in nondialyzed patients with CKD. Severe CAC was a predictor of cardiovascular events and hospitalization in these patients.

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Cardiovascular mortality is up to 20 times more common in patients with chronic kidney disease (CKD) than in the general population (1). Actually, cardiovascular injury is the main clinical problem among patients with CKD, accounting for ~50% of all deaths. Cardiovascular calcification is a severe vascular alteration, and it has shown to be highly prevalent, particularly among patients undergoing dialysis (2–4). Recent studies have shown an association of vascular calcification with cardiovascular events, hospitalization, and all-cause mortality in these patients (5–8).

The higher rate of cardiovascular death has been increasingly shown in studies including the nondialyzed CKD population. Actually, cardiovascular events, hospitalization, and risk of death have been associated with the progression of renal failure (9). Keith *et al.* (10) showed in a large cohort that the 5-year mortality rates of patients with CKD in stages 2, 3, and 4 were 19.5, 24.3, and 45.7%, respectively. In the last few years, several studies has been published addressing the high prevalence of cardiovascular calcification in nondialyzed patients with CKD as well (11,12). However, the impact of this condition on clinical outcomes in this population has thus far not been studied. Thus, the aim of this study was to evaluate the impact of coronary artery calcification (CAC) on cardiovascular events, hospitalization, and mortality in the nondialyzed CKD population followed for 24 months.

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Correspondence: Dr. Maria Eugênia Fernandes Canziani, Rua Pedro de Toledo 282, CEP 04039–000, São Paulo SP, Brazil. Phone: 55-11-5904-8499; Fax: 55-11-5572-1862; E-mail: dialisefor@uol.com.br

Materials and Methods

Patients

A total of 117 nondialyzed patients with CKD stages 2 to 5 were recruited from the outpatient clinic of the Federal University of São Paulo, Sao Paulo, Brazil. Patients on therapy for at least 3 months were approached to participate in the study. Exclusion criteria were age less than 18 years, presence of chronic inflammatory disease, active malignancy, HIV, viral hepatitis, and chronic use of steroids. The majority of the patients were on regular use of angiotensin-converting enzyme inhibitors (82.2%) and diuretics (77.1%). Patients were also taking β-blockers (42.2%), calcium channel blockers (41.5%), statins (34.4%), angiotensin receptor blockers (22.9%), and human recombinant erythropoietin (4.2%). Thirty patients (32.3%) were using sevelamer, six patients (5%) were taking calcium-based phosphate binders, and six patients (5%) were taking calcitriol.

This study was reviewed and approved by the Ethics Advisory Committee of the Federal University of São Paulo. All patients gave written informed consent.

Study Protocol

In this prospective study, all patients underwent clinical history evaluation, laboratory tests, and assessment of CAC at baseline. The

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occurrence of cardiovascular events (acute myocardial infarction, angina, arrhythmia, uncontrolled BP, stroke, and cardiac failure), hospitalization, and death were recorded during a period of 24 months.

Laboratory Tests

Blood samples were drawn in a fasting state. Biochemical parameters included serum creatinine, ionized calcium, phosphate, alkaline phosphatase, lipid profile, hemoglobin, albumin, and intact parathyroid hormone (iPTH). High-sensitivity C-reactive protein was determined by immunochemiluminescence (CRP Immunolite; Immunometric Assay), and IL-6 was measured using a commercially available enzyme-linked immunosorbent assay (BD Biosciences Pharmingen).

Creatinine clearance and proteinuria were measured by obtaining 24-hour urine samples. Abnormal proteinuria was defined as urinary protein excretion >150 mg/24 h. The diagnosis and classification of CKD were established according to the criteria from the Kidney Disease Outcomes Initiative (K/DOQI) guidelines (13). Anemia was defined as hemoglobin <11 g/dl (14). Hyperparathyroidism, hyperphosphatemia, and hypercalcemia were defined according to bone metabolism K/DOQI guidelines (15).

Coronary Computed Tomography

Patients underwent CAC quantification using a multislice computed tomography scanner (LightSpeed Pro 16; GE Healthcare, Milwaukee, WI), using a gantry rotation of 0.4 seconds, collimation of 2.5 mm (slice thickness), and reconstruction time of six frames per second. A calcium threshold of 130 or more Hounsfield Units was used. The images were scored by a single radiologist blinded to the clinical and biochemical aspects of the patient. As described by Agatston *et al.* (16), the calcium score was determined by multiplying the area of each calcified lesion by a weighting factor corresponding to the peak pixel intensity for each lesion. The sum of each lesion of all coronary arteries was used for analysis. Presence of calcification was defined as CAC score >10 Agatston units (AU) and severe calcification as CAC score ≥400 AU.

Statistical Analysis

Mean and SD, median, and interquartiles values or frequencies (proportions) were calculated for all variables. The distribution of calcification score was markedly skewed; as such, it was resistant to normalization by log transformation and other techniques. Therefore, the calcification score values were grouped into a dichotomous variable first according to the presence or absence of any calcification (CAC > 10) and, second, according to the presence or absence of severe calcification (CAC ≥ 400). Comparisons of continuous variables were done by *t* test and the Mann-Whitney *U*-test for normally distributed data and skewed data, respectively. The comparison of median calcification score in the different stages of CKD was performed using the Kruskal-Wallis test. Comparisons of proportions were done by χ^2 analysis or by the Fisher exact test, when appropriate. Event-free survival curves were estimated by the Kaplan-Meier method and compared by log-rank test in univariate analysis. The Cox regression model was used, considering age and diabetes as covariates and CAC >10 or CAC ≥400 as the independent variable (or control variables). Associations were tested using the Wald test and described through the hazard ratios and 95% confidence intervals. In situations where all observations were censored (no event was observed), the inferential tests were not performed because they are general biased estimators. $P < 0.05$ was considered statistically significant. All statistical analysis was performed using SPSS for Windows (version 13; SPSS, Chicago, IL).

Results

Table 1 shows the demographic and clinical characteristics of the patients. The patients were predominantly middle-aged men. Twenty-three percent of the patients had diabetes. Obesity (as described by body mass index ≥ 30 kg/m^2) was found in 27.4%, overweight (body mass index ≥ 25 kg/m^2) in 60.7%, and none had body mass index indicative of malnutrition (≤18.5 kg/m^2). According to the CKD classification, 17 patients (14.5%) were in stage 2, 46 (39.3%) were in stage 3, 49 (41.3%) were in stage 4, and 5 (4.3%) were in stage 5. Proteinuria was found in 58% of the patients. A small proportion of patients had anemia (14.5%). Total cholesterol levels >200 mg/dl were found in 32.5% of the patients, LDL cholesterol >100 mg/dl was found in 48%, HDL cholesterol <40 mg/dl was found in 22%, and triglycerides >150 mg/dl were found in 42.7%. Overall, 70% of the patients had at least one lipid profile abnormality. Increased C-reactive protein (>1.1 mg/dl) was found in 12% of the patients. Concerning bone mineral metabolism, 36% of the patients had increased levels of iPTH, 13% had hyperphosphatemia, 2.5% had hypercalcemia, and 12% had increased levels of alkaline phosphatase.

CAC >10 AU was observed in 56 patients (48%), and their median calcification score was 334 (108 to 858.5) AU. CAC ≥400 AU was found in 25 patients (21%), and their median calcification score was 873 (436 to 2,500) AU. The prevalence of CAC and severe CAC according to the stages of CKD is presented in

Table 1. Baseline characteristics of the patients studied ($n = 117$)

Age (years)	57 ± 11.2
Gender males (%)	46 (61)
Chronic kidney disease etiology	
Hypertension (%)	31 (26)
Diabetes (%)	27 (23)
Polycystic kidney disease (%)	18 (15)
Smoking (%)	14 (12)
Body mass index	27.1 ± 5.2
Laboratory parameters	
Creatinine (mg/dl)	2.2 ± 5.2
Creatinine clearance (ml/min per 1.73 m^2)	36.6 ± 17.8
Proteinuria (g/24 h)	0.67 (0–0.76)
Hemoglobin (g/dl)	12.8 ± 1.8
Phosphorus (mg/dl)	3.7 ± 0.73
Ionized calcium (mM)	1.28 ± 0.6
Alkaline phosphatase (U/L)	90.2 (66–103)
iPTH (pg/ml)	103 (62.5–190.5)
Total cholesterol (mg/dl)	183.9 ± 36.7
LDL-cholesterol (mg/dl)	101.5 ± 28
HDL-cholesterol (mg/dl)	50.9 ± 14
Triglycerides (mg/dl)	127 (98–192.5)
C-reactive protein (mg/dl)	0.58 (0.1–0.7)
Interleukin-6 (pg/ml)	4.6 (2.6–8.8)

Values expressed as mean ± SD, median (range), or number (percent).

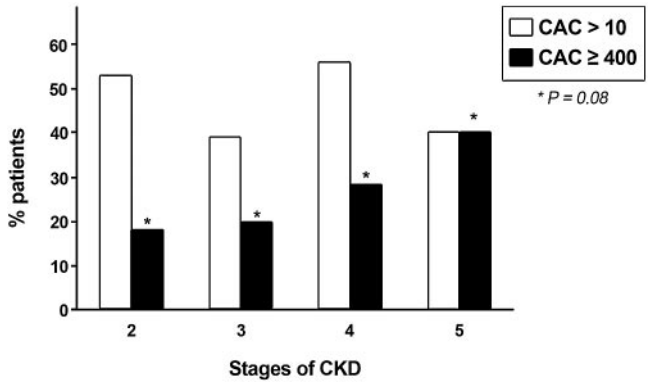

Figure 1. Proportion of patients with CAC score >10 and ≥400 AU according to the stages of CKD (170 × 127 mm; 300 × 300 DPI).

Figure 1. Although no differences were found regarding the overall prevalence of CAC >10 AU, there was a trend toward an increase in the prevalence of CAC ≥400 AU according to the progression of renal failure ($P = 0.08$). The calcification scores of patients with CAC ≥400 AU according to CKD stages were as follows: 131 (83–1127.5) AU in stage 2; 200.5 (52.2 to 999.5) AU in stage 3; 436 (240–850) AU in stage 4; and 779 (691–867) AU in stage 5.

Follow-Up

At the end of the study period of 24 months, 20 patients had started dialysis, 8 patients had withdrawn, 1 patient had received a kidney transplant, and 1 patient had changed hospitals. During the follow-up, the occurrence of 15 cardiovascular events, 19 hospitalizations, and 4 deaths were registered. The cardiovascular events occurred were characterized as follows: angina ($n = 4$), stroke ($n = 3$), acute myocardial infarction ($n = 3$), hypertensive emergence ($n = 2$), arrhythmia ($n = 1$), transient ischemic attack ($n = 1$), and cardiac failure ($n = 1$). The hospitalizations were for the following reasons: cardiovascular events ($n = 9$), surgeries ($n = 5$), infection ($n = 1$), and other ($n = 4$). The deaths were attributed to acute myocardial infarction, pancreatitis, accident, and unknown causes; three of them occurred in patients in stage 4 and one in a patient in stage 2 of CKD.

Data on the occurrence of cardiovascular events, hospitalization, start of dialysis, and mortality according to the baseline CAC scores of the patients are shown in Table 2. Although only hospitalization was significantly higher in the group of patients with CAC >10 AU, the occurrence of cardiovascular events, hospitalization, and mortality was markedly higher in the group with CAC ≥400 AU. Of note, there was a trend toward a higher incidence of death among patients with CAC >10 AU. Patients with CAC were older regardless of the severity of the calcification (62.7 ± 8.7 *versus* 51.6 ± 10.7 years; $P = 0.0001$ for CAC >10 AU and ≤10 AU, respectively, and 62.8 ± 8.4 *versus* 55.4 ± 11.4 years; $P = 0.003$ for CAC ≥400 AU and <400 AU). In addition, IL-6 tended to be higher among patients with severe calcification [7.0 (2.8 to 16.6) *versus* 4.3 (2.3 to 8.4) pg/ml; $P = 0.07$]. There were no differences regarding gender, diabetes, and laboratory parameters between the groups.

During the 2-year follow-up, a shorter hospitalization event-free period and lower survival were observed in patients with CAC >10 AU (Figure 2). The presence of CAC ≥400 AU was associated with shorter cardiovascular events-free periods, shorter hospitalization event-free periods, and lower survival (Figure 3). Clinical outcomes were not predicted by CAC >10 AU when adjusting for age and diabetes. However, the presence of CAC ≥400 AU was associated with cardiovascular events (hazard ratio = 3.53; 95% confidence interval, 1.03 to 12.06; $P = 0.04$) and hospitalization (hazard ratio = 4.05; 95% confidence interval, 1.42 to 11.56; $P = 0.009$). The Cox regression analysis was not conducted for mortality rate, because no deaths were observed in the group of patients without calcification.

Discussion

Herein we described a high prevalence of CAC in nondialyzed patients with CKD. Cardiovascular events, hospitalization, and mortality rate were all associated with the presence of CAC in nondialyzed patients with CKD. Severe calcification was a predictor of cardiovascular events and hospitalization in these patients.

Cardiovascular calcification scores have shown to be 10-fold higher among patients with CKD than in the general population. In this study, the presence of CAC (defined as CAC > 10 AU) was observed in almost one half of the patients, and the presence of severe CAC (defined as CAC ≥ 400 AU) was found in 21%. Accordingly, previous studies have shown that CAC is highly prevalent in dialysis patients and in nondialyzed patients with CKD (4,11). In the latter, the prevalence of CAC varies from 40 to 83.2% (11,12,17–19). Such wide variability could be partially explained by the characteristic of the studied

Table 2. Occurrence of cardiovascular events, hospitalization, start of dialysis, and mortality during the 2-year follow-up according to the baseline CAC scores

	CAC > 10 ($n = 56$)	CAC ≤ 10 ($n = 61$)	P	CAC ≥ 400 ($n = 25$)	CAC < 400 ($n = 92$)	P
Cardiovascular events [n (%)]	10 (18%)	5 (8%)	0.16	7 (28%)	8 (8%)	0.017
Hospitalization [n (%)]	14 (25%)	5 (8%)	0.02	10 (40%)	9 (9%)	0.001
Start of dialysis [n (%)]	11 (19%)	9 (14%)	0.62	5 (20%)	15 (16%)	0.76
Mortality [n (%)]	4 (7%)	0	0.05	4 (16%)	0	0.002

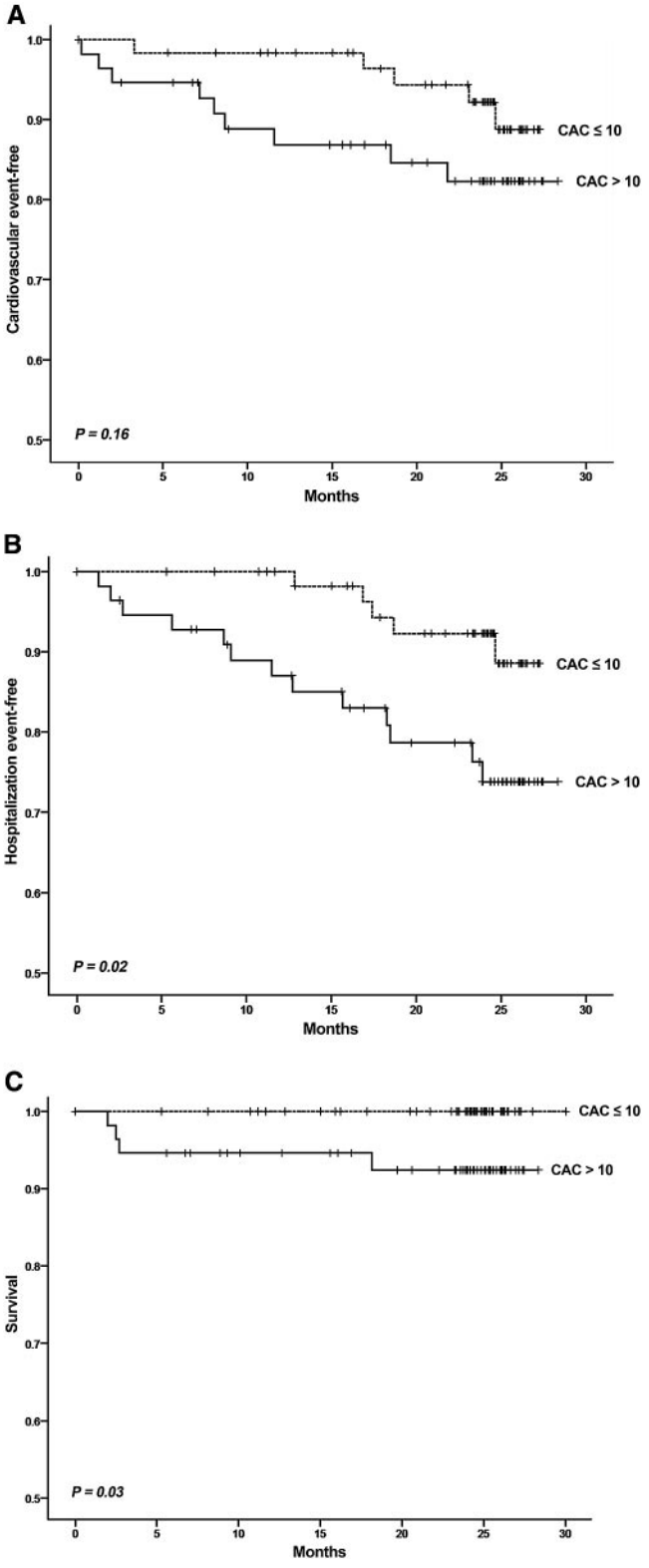

Figure 2. Cardiovascular event-free (A), hospitalization event-free (B), and survival (C) periods in 117 nondialyzed patients with CKD according to the presence of CAC score ≤10 or 10 AU (170 × 127 mm; 300 × 300 DPI).

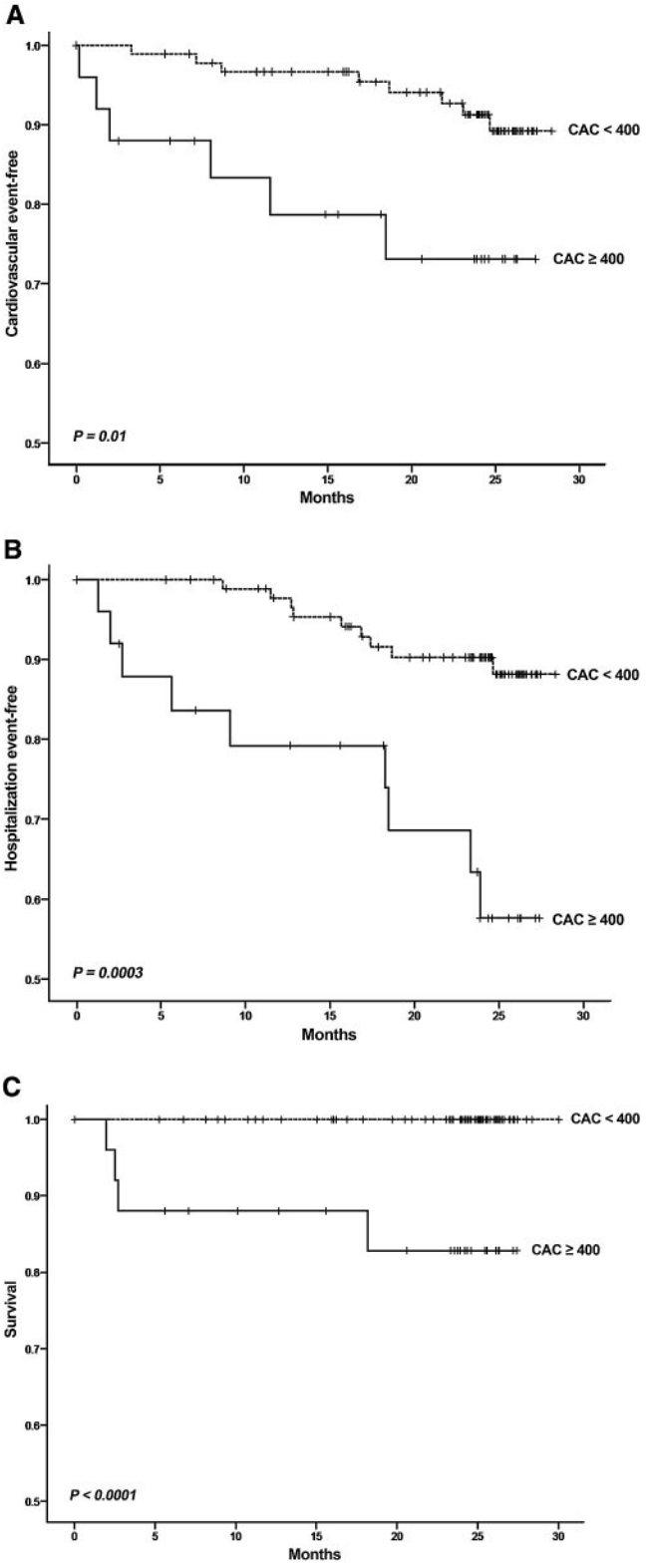

Figure 3. Cardiovascular event-free (A), hospitalization event-free (B), and survival (C) periods in 117 nondialyzed patients with CKD according to the presence of CAC score <400 or ≥400 AU (170 × 127 mm; 300 × 300 DPI).

population but also by the different cut-off values used for diagnosing CAC. For instance, Garland *et al.* (12) studied predominantly male patients in stage 4 CKD and, when defining CAC as calcium score greater than zero, they found that CAC prevalence was >80%. On the other hand, a lower prevalence of CAC has been reported when patients with diabetes or a history of cardiovascular disease were excluded (11).

The development of CAC in patients with CKD is much likely associated with traditional and nontraditional cardiovascular risk factors. In this study, age was the known factor that differentiated patients with CAC from those without and patients with severe CAC from those with a lower degree of calcification. Accordingly, previous studies in the general population have shown that CAC progresses with aging. Moreover, there is evidence that the prevalence of atherosclerotic plaque is increased among the elderly (20). The relationship between age and CAC can be at least in part explained by the lifetime exposure of individuals to cardiovascular risk factors. Within nontraditional factors, we observed that IL-6 tended to be higher among patients with severe CAC. In fact, inflammation along with other clinical conditions such as hypertension, dyslipidemia, proteinuria, and especially disturbances in the mineral metabolism have been pointed out as additional important factors associated with CAC in patients with CKD (18,21). However, the investigation of the physiopathology of CAC was not under the scope of this study.

Renal function may have an important role in the incidence and progression of CAC. It has been suggested that CAC initiates early in the course of CKD and progresses further with deterioration of renal function. In this study, although significance was not reached ($P = 0.08$), we observed that the prevalence of severe CAC increased gradually according to the progression of CKD. This observation is of special interest because, as far as we are concerned, no study has shown the relationship between CAC and kidney dysfunction.

It is of note that the main cause of hospitalization in our patients was cardiovascular events. Vascular injury is probably the key link among CAC, hospitalization, and cardiovascular events. Actually, the relationship between CAC and obstructive atherosclerosis has been previously shown in patients with CKD (3,22). Vascular damage includes intimal arterial site and medial wall. The former is an alteration often related to atherosclerotic processes, and the latter is frequently associated with diabetes and CKD (23–25). Although lesions in the intimal site induce ischemia as a consequence of stenosis and thrombosis, lesions in the medial site result in left ventricular hypertrophy, a decrease in diastolic pressure and diastolic pressure time integral, and alterations in coronary perfusion caused by arterial stiffening (26). Therefore, damage in different arterial sites leads to different clinical consequences. Unfortunately, coronary computed tomography is unable to differentiate lesions in such arterial compartments. Nevertheless, the presence of arterial calcification in both intimal and medial sites has been shown to be associated with an increased mortality rate in the dialysis population (23).

The association between CAC and the risk of mortality in dialysis patients has become a common finding in the last years (3,5,27). These data showed that this association starts in the earlier stages of CKD. This study has some limitations that should be considered. First, the studied sample size was relatively small. Second, it was not possible to apply the Cox modeling analysis for mortality rate because no deaths occurred in the group of patients without CAC. However, to the best of our knowledge, this is the first study to show the prevalence of different degrees of CAC and their relationship with increased risk of composite outcomes in nondialyzed patients with CKD.

In conclusion, the prevalence of CAC was elevated in nondialyzed patients with CKD, and this condition was associated with increased cardiovascular events, hospitalization, and mortality rate. In addition, severe CAC was an independent predictor of cardiovascular events and hospitalization in these patients. Therapeutic interventions are warranted in the earlier stages of the disease to attenuate the high morbidity and mortality rates observed in the CKD population.

Disclosures

None.

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