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Original Paper

Long-Term Progression of Coronary Artery Calcification Is Independent of Classical Risk Factors, C-Reactive Protein, and Parathyroid Hormone in Renal Transplant Patients

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Keywords
Coronary calcification · Coronary artery disease · Kidney transplantation

Abstract
Aims: Compared to the general population, mortality is significantly increased in renal transplant recipients. In the general population, coronary artery calcification (CAC) and its evolution over time are associated with cardiovascular and all-cause mortality, and the study of this biomarker could provide useful information for describing the long-term progression of coronary heart disease in renal transplant recipients. ***Methods:*** We followed up a cohort of 113 renal transplant patients by performing three multi-detector computed tomography studies over 83.6 ± 6.8 months. Data analysis was performed by logistic regression analysis and by mixed linear modelling. ***Results:*** Progression was observed in 34.5% of patients. Baseline CAC and time-to-transplantation were the sole variables that predicted CAC evolution over time. Neither classical nor nontraditional risk factors, biomarkers of renal function (GFR) and kidney damage (albuminuria) or biomarkers of bone mineral disorder (BMD), such as serum phosphorus, calcium, and PTH, were associated with the long-term progression of coronary calcification. Serum triglycerides predicted CAC progression only in logistic regression analysis, while in addition to baseline CAC, time to transplantation was the sole variable predicting CAC progression when the data were analyzed by mixed linear modelling. These data suggested that, in addition to the background calcification burden, other unmeasured factors play major

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roles in promoting the evolution of coronary calcification in the transplant population. ***Conclusion:*** CAC progression continued over the long-term follow-up of renal transplant patients. This phenomenon was unaccounted for by classical and nontraditional risk factors, as well as by biomarkers of renal dysfunction and renal damage. © 2017 S. Karger AG, Basel

Introduction

It is well established that renal transplantation is the best renal replacement therapy in that it provides longer survival than dialysis therapies [1]. Nevertheless, mortality in renal transplant patients is substantially higher than in the comparable sex-matched general population [2]. Cardiovascular disease is the leading cause of death in kidney transplant recipients, with a 3.5–5% annual risk of fatal or nonfatal cardiovascular events, which is much higher than the same risk in the general population [3, 4].

Coronary artery calcification (CAC) is an established prognostic marker for cardiovascular events and all-cause mortality in the general population [5–7]. CAC progression adds incremental value over the baseline CAC score in predicting all-cause mortality, and it is considered a more accurate predictor of the risk of cardiovascular events than baseline CAC alone [8].

We previously examined the extent and progression of CAC in renal transplant recipients in 2 separate studies and found that CAC was highly prevalent and progressive in this population [9, 10]. Progression of CAC is a nonlinear phenomenon, and individuals without coronary calcification at baseline have a low probability of developing measurable levels of coronary calcification over 4 years. Because our previous study describing the progression of CAC had a follow-up of 2.8 years [10], we could have underestimated the full potential for the progression of CAC in the same cohort. Therefore, we designed the present study to assess the long-term progression of CAC in transplant patients by extending the follow-up of the original cohort that we enrolled between 2006 and 2007 [10].

Patients and Methods

Study Design

Between March 2006 and December 2007, we enrolled 178 consecutive adult (older than 18 years of age) renal transplant recipients in a study to measure CAC [10]. In this study, the data on angina (Rose questionnaire) and background coronary artery disease events (myocardial infarction, coronary revascularization procedure or coronary artery disease documented by angiography) were collected from the patient files. The CAC score was measured using multidetector computed tomography (MDCT), and myocardial perfusion scintigraphy (MPS) was performed in patients with a CAC score >100 [9]. Following the baseline MDCT, patients with angina pectoris, abnormal MPS, or CAC scores >400 were referred to the cardiology department for further cardiovascular workup and treatment. The scope of our previous study on CAC progression was that of estimating the risk for de novo CAC in patients without coronary artery disease at baseline; therefore, 12 patients with documented coronary artery disease were not eligible for follow-up MDCT scans. Details of the follow-up in outpatient clinics and management using drug therapy were described in detail previously [10]. A second MDCT scan was performed in 150 patients between March 2009 and June 2010 and a third MDCT scan in 113 patients between 2013 and December 2014. The study design and patient follow-up are summarized in Figure 1. The study protocol was approved by the local medical ethics committee (protocol No.: 18578).

Data Collection

Definitions and methods used for the clinical and laboratory assessment were previously described in detail [9]. The data on drugs, blood pressure, and biochemical parameters were collected from patient files.

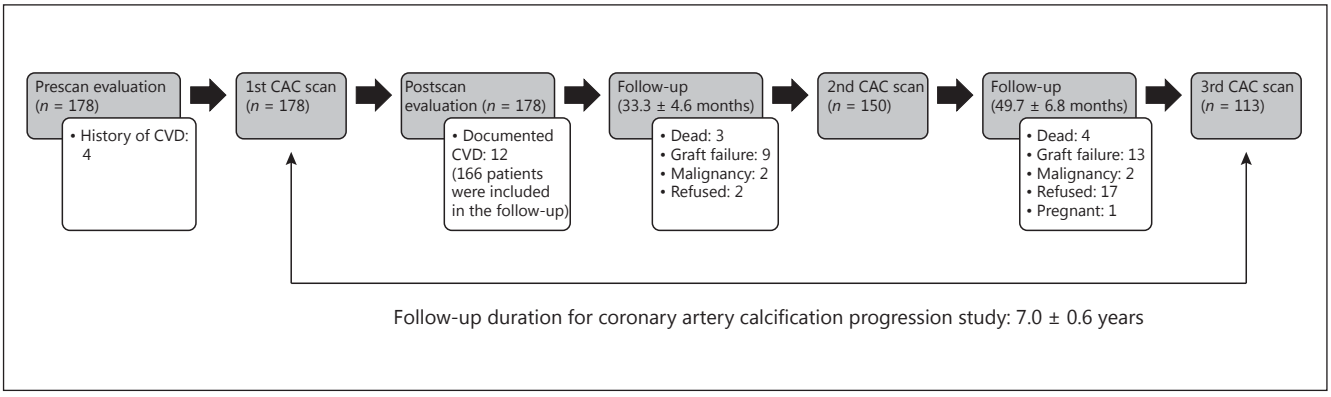

Fig. 1. Study design and patient follow-up.

The average values for the entire follow-up period were calculated, and these mean values were used to represent follow-up data.

Imaging Procedures

All of the MDCT scans were performed with the same equipment (SOMATOM Sensation 16 Cardiac; Siemens AG, Erlangen, Germany) using the same procedures [10]. CAC scores were calculated according to the Agatston method. The presence of CAC was defined by a CAC score of ≥1. All of the follow-up MDCT scans were scored by the same radiologist (D.C.O.). Intraobserver variability was calculated previously and was described in detail [10].

Evaluation of CAC Progression

Measurement of CAC progression depends on accurate reproducibility of CAC scores. Therefore, minimizing the variability between scans is paramount to quantify progression accurately [11]. Recently, it was proposed to use the transformed square-root method of Hokanson et al. [12] to quantify progression [11]. In contrast, the method proposed by Sevrukov et al. [13] has the advantage of including definitions for Agatston scoring. We chose to analyze our data according to both methods. First, the progression of calcification was defined as the difference between the follow-up square-root transformed score (SRC) and the baseline SRC ≥2.5 [13]. Second, in subjects with detectable CAC at baseline, the smallest statistically significant interval change was defined as ± (4.93 × √ baseline CAC score) in subjects with a CAC score of 0. A follow-up CAC score >11.6 indicated progression [13].

Statistical Analysis

Data are expressed as the mean ± standard deviation if not stated otherwise. Categorical variables were compared using the χ^2 test, and two-sided exact significances were reported. Continuous variables were first analyzed for normality by examining normal Q–Q plots and then compared using Student's *t* test or the Mann-Whitney U test, when appropriate. The distribution of CAC scores was nonnormal; therefore, logistic regression analyses were performed using log-transformed (ln [1 + absolute CAC score]) CAC scores [14]. Multivariate logistic regression analysis was used to evaluate the determinants of CAC progression. Forward selection was used in multivariate models. In addition to standard statistical methods, because of the relatively limited number of observations, we used mixed linear modelling (MLM) to maximize the exploitation of available data. This approach is ideal for the analysis of nonequally spaced serial observations with a variable number of repetitions within the subjects, such as our data [15]. Moreover, in this method, the normality or otherwise of residuals did not affect the parameter estimates in multivariate models. Therefore, MLM could be used when the dependent variable was not normally distributed [16].

All of the tests were performed using SPSS software, version 22.0 for Windows (SPSS Inc., Chicago, IL, USA). The figures were prepared using Microsoft® Office for Mac 2011 software (Microsoft Corp., Redmond, WA, USA). *p* values >0.05 were considered statistically significant.

Table 1. Characteristics of all (n = 178) study subjects

	Mean ± SD	Median (range)
Age, years	36.5±11.2	35.0 (20.0–68.0)
Male sex, %	67.4	
Time to transplantation, months	70.6±59.5	53.5 (3–295)
Living donor, %	83.1	
Dialysis vintage, months	24.4±23.5	16.0 (0–120)
History of coronary artery disease, %	2.2	
Rose angina pectoris, %	7.3	
Family history of cardiovascular disease, %	9.0	
Smoking history, %	51.1	
Smoking, pack-years	4.8±9.6	0.15 (0–80)
Body mass index	25.7±4.3	25.2 (16.5–39.0)
Diabetes mellitus, %	6.2	
Systolic BP, mm Hg	122.6±16.3	120.0 (80.0–170.0)
Diastolic BP, mm Hg	79.9±11.1	80.0 (40.0–115.0)
Hypertension, %	80.9	
Total cholesterol, mg/dL	188.8±41.6	184.0 (96.0–387.0)
HDL cholesterol, mg/dL	49.1±12.3	48.0 (28.0–95.0)
LDL cholesterol, mg/dL	111.8±33.2	107.5 (27.0–240.0)
Triglycerides, mg/dL	151.6±76.1	132.5 (36.0–581.0)
GFR, mL/min/1.73 m^2	61.0±20.5	61.4 (8.6–144.0)
Albuminuria, mg/day	250.9±586.7	45.0 (4.0–3978.0)
Calcium, mg/dL	9.6±0.5	9.6 (7.9–11.2)
Phosphorus, mg/dL	3.4±0.7	3.4 (1.8–5.5)
Calcium phosphorus product, mg^2/dL^2	32.2±6.3	32.4 (16.9–53.4)
Parathyroid hormone, pg/mL	114.6±113.6	76.1 (13.0–856.0)
CRP, mg/L[a]	3.1±3.7	1.76 (0.15–18.9)

NA, not applicable; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; GFR, glomerular filtration rate; CRP, C-reactive protein. [a] CRP measurements were available for 146 patients.

Results

Baseline Characteristics of the Study Population

The demographic characteristics, cardiovascular risk factors, and laboratory data of the 178 renal transplant recipients were described previously [9]. In summary, the study participants were predominantly male and mostly young or middle-aged, and they had received living donor transplants (Table 1). Preemptive transplantation was performed in 3 (1.7%) patients. A history of previous coronary artery disease was present in 4 patients (2.2%). Rose questionnaire angina pectoris was reported by 13 (7.3%) patients, and all of the patients with a previous history of coronary artery disease were reported to have angina pectoris.

The GFR was >30 mL/min/1.73 m^2 in 93.8% of the patients; microalbuminuria was present in 40.4%, and overt proteinuria was present in 19.7%. Other characteristics of the patients are presented in Table 1.

Aspirin was used by 16.3%, statins by 41.0%, antihypertensive medications by 77.5%, bisphosphonates by 19.1%, calcium supplements by 29.2%, and vitamin D supplements by 25.8% of the patients.

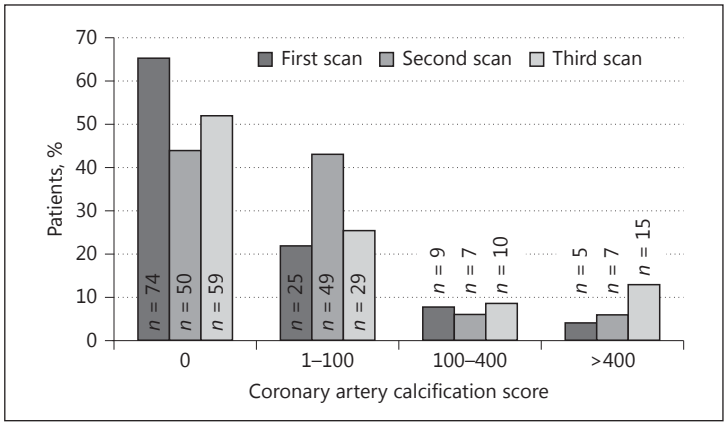

Fig. 2. Frequency of coronary artery calcification scores for kidney transplant recipients at the first, second, and third scans.

Table 2. CAC scores and progression of CAC

CAC scores (n = 113)	Mean ± SD	Median (range)	CAC frequency	
First CAC score	47.08±135.25	0 (0–904.0)	34.5%	
Second CAC score	78.12±204.29	1.8 (0–952.6)	55.8%	
Third CAC score	140.18±332.11	0 (0–1876.7)	47.6%	
Time between scans	**Mean ± SD**	**Median (range)**	**Progression[a]**	**Progression[b]**
1st–2nd scan, months	33.3±4.6	33.0 (25–50)	26.5%	27.4%
2nd–3rd scan, months	49.7±6.8	48.0 (36–66)	27.4%	25.7%
1st–3rd scan, months	83.6±6.8	82.0 (71–100)	34.5%	32.7%

[a] Progression according to the definitions used by Sevrukov et al. [13]. [b] Progression according to the definitions used by Hokanson et al. [12].

Changes in CAC

One hundred and sixty-six patients without coronary heart disease were eligible for the progression study. Nineteen patients refused to undergo follow-up MDCT scans, and follow-up scans could not be performed in 34 patients for various reasons (Fig. 1). Compared to the 113 patients who underwent three scans, the 53 patients who did not complete the whole follow-up had lower GFR and serum calcium and higher creatinine and phosphorus levels (online suppl. Table 1; see www.karger.com/doi/10.1159/000475999 for all online suppl. material). The CAC scores and frequencies are shown in Table 2, and annual CAC progression (ACP) rates are shown in online supplementary Table 2. Mean CAC scores increased during the follow-up. In patients with baseline CAC, the mean and median ACPs were higher than those of the patients without baseline CAC (Table 2). The distribution of CAC scores among the patients is shown in Figure 2.

Changes in CAC scores were evaluated following transformation of raw CAC scores using different methods that consider high interscan variability of CAC scores [12, 13]. At the end of the whole follow-up period (scan 1 to scan 3), progression was observed in 37 (32.7%) and 39 (34.5%) patients according to the methods used by Hokanson and Sevrukov, respectively. Regression of CAC was observed only in 2 (1.7%) patients with both methods. Because the results with both methods were similar (kappa = 0.907; p = 0.000), and the method of Sevru-

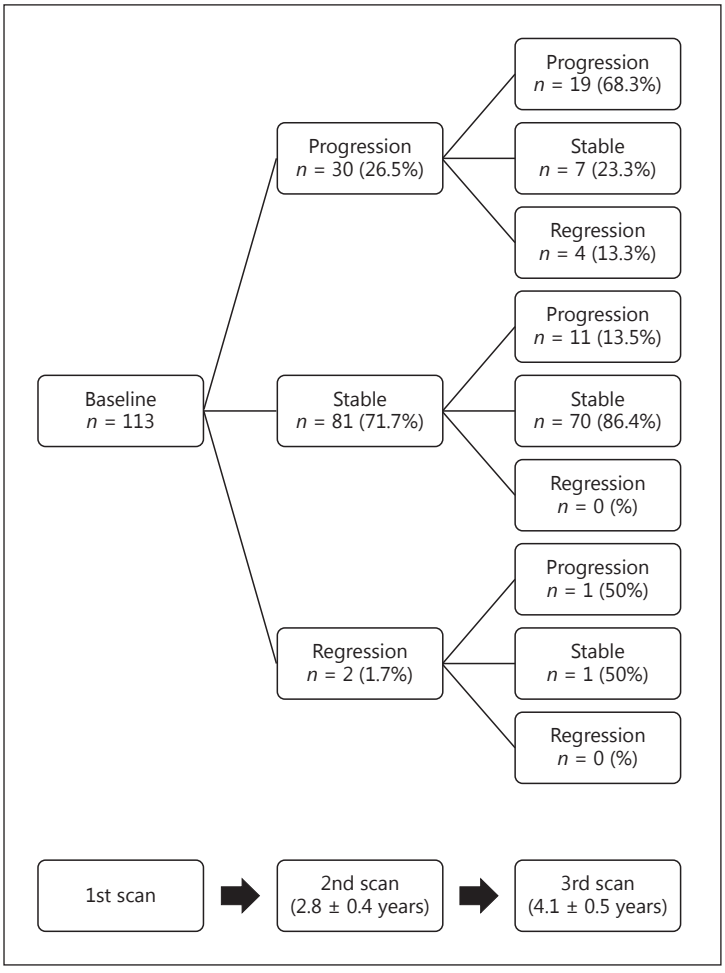

Fig. 3. Changes in individual CAC scores.

kov et al. [13] included definitions for Agatston scoring, we used them to define progression for subsequent analysis.

To visualize better the changes in individual CAC scores, we prepared a flow-chart (Fig. 3). It can be seen that the probability of CAC progression on the third scan was higher in patients who had already shown evidence of CAC progression on the second scan.

Determinants of CAC Progression

We compared the clinical and biochemical characteristics and drug use of 113 renal transplant recipients according to the presence or absence of CAC progression. Based on univariate analysis, age, presence of baseline CAC, high baseline CAC score, and high body mass index were significantly associated with CAC progression, defined according to both the Hokanson and Sevrukov methods. Moreover, HDL cholesterol levels were significantly associated with CAC progression when progression was defined according to Hokanson's method, and donor type, high triglyceride levels, and systolic blood pressure were significantly associated with CAC progression when progression was defined according to Sevrukov's method (online suppl. Table 3).

We constructed two multivariate logistic regression models; in both models, variables were selected based on the comparison of progressors with nonprogressors, and variables that were associated with CAC at a significance level of $p < 0.05$ were used. In the first model,

Table 3. Logistic regression analysis showing patient characteristics associated with coronary artery calcification progression

Analysis	Odds ratio (95% CI)	*p*
Multivariate[a]		
CAC presence, %	0.097 (0.041–0.232)	0.000
Triglycerides, mg/dL	1.005 (1.001–1.008)	0.009
Multivariate[b]		
CAC presence, %	0.233 (0.130–0.416)	0.000
CAC score	1.186 (1.002–1.404)	0.047

[a] Progression according to Sevrukov (R^2 = 0.408). [b] Progression according to Hokanson (R^2 = 0.356).

progression was defined according to the Sevrukov method; in the second model, progression was defined according to the Hoakson method. In both models, baseline CAC was a determinant of CAC progression. Triglyceride levels were a determinant of CAC progression according to the first model, and CAC score was a determinant of CAC progression according to the second model (Table 3). Neither classical risk factors (age, sex, smoking, diabetes, blood pressure, cholesterol), emerging risk factors, such as C-reactive protein (CRP), nor CKD-related risk factors, such as GFR, albuminuria, or PTH serum phosphorus, predicted CAC progression in this analysis.

MLM analysis was performed in 2 steps. First, a univariate linear mixed model was used to select the variables that were presented in Table 4. A second multiple linear mixed model was constructed using the variables that were associated ($p \leq 0.10$) with CAC evolution over time in the univariate mixed linear model.

According to univariate MLM analysis, age, time to transplantation, cadaveric donor, RRT duration, diabetes, and CAC presence at baseline were associated with increasing CAC scores. Finally, multivariate MLM analysis showed that time to transplantation and CAC presence at baseline were independently associated with CAC evolution. Again, in this analysis, classical and emerging risk factors and CKD-related risk factors did not predict CAC progression in renal transplant patients.

Discussion

In this study, which is the sole report of the long-term evolution of coronary calcification in transplant patients, we found that coronary calcification continued to progress relentlessly in this population and that the presence and extent of previous coronary calcification were the main determinants of the evolution of this alteration. Importantly, neither demographic, classical or nontraditional risk factors, nor biomarkers of renal function (GFR) and kidney damage (albuminuria) were explanatory factors for the long-term progression of coronary calcification. This phenomenon suggested that, in addition to the background calcification burden and perhaps serum triglycerides, other unmeasured factors play major roles in promoting the evolution of coronary calcification in the transplant population.

In studies evaluating CAC progression, two important methodological issues related to CAC scoring have demanded attention. First, because of the high interscan variability of CAC measurements, an appropriate method of transformation should be introduced to the raw data before analyzing progression. Second, it was shown that CAC does not increase at a constant rate, and progression is usually detected following a lag period of 4 years [17]. In

Table 4. Univariate and multivariate linear mixed model analyses of CAC evolution over time

Variable	Univariate analysis		Multivariate analysis	
	slope ± SE	*p*	slope ± SE	*p*
Age (years)	6.3±1.7	<0.001	2.8±1.8	0.12
Sex (male, female)	–6.7±40.6	0.90		
Time to transplantation (months)	1.3±0.34	<0.001	0.9±0.4	0.01
Donor type (cadaveric donor)	107.3±50.6	0.04	59.5±47.7	0.22
RRT duration (months)	1.67±0.84	0.05	1.44±0.80	0.07
Smoking (pack-years)	–7.9±38.4	0.84		
Family history of CVD (%)	35.1±66.7	0.60		
Statin use	12.9±39.0	0.74		
Acetylsalicylic acid use	61.1±54.7	0.27		
Antihypertensive treatment	40.4±45.2	0.37		
Bisphosphonate use	72.6±48.4	0.14		
Calcium supplements	–74.0±41.7	0.08	–65.1±37.7	0.09
Vitamin D use	20.0±44.0	0.65		
BMI	4.5±4.5	0.32		
SBP (mm Hg)	1.3±1.2	0.27		
DBP (mm Hg)	1.3±1.7	0.45		
Pulse pressure (mm Hg)	1.5±1.7	0.39		
Hypertension	27.4±48.1	0.57		
Angina	–52.8±96.5	0.59		
Diabetes	197.7±84.2	0.02	95.4±79.0	0.23
eGFR (mL/min/1.73 m^2)	1.01±0.97	0.30		
Total cholesterol (mg/dL)	–0.11±0.47	0.82		
Triglycerides (mg/dL)	–0.07±0.25	0.77		
LDL cholesterol (mg/dL)	–0.63±0.58	0.28		
Calcium (mg/dL)	28.2±39.0	0.47		
Phosphate (mg/dL)	40.9±30.1	0.18		
CRP (mg/L)	–2.9±4.6	0.52		
PTH (pg/mL)	–0.06±0.18	0.72		
Albuminuria	0.002±0.03	0.95		
CAC presence at baseline	94.3±22.4	<0.001	69.0±22.7	0.003

In the multivariate model, we adjusted for all of the univariate correlates of CAC evolution over time (with $p < 0.10$).

agreement with this contention, Gopal et al. [18] suggested that, in patients without detectable calcification, a second scan should not be repeated before 5 years. Herein, we used appropriate methods to control for interscan variability and followed up with the patients for as long as 7.0 ± 0.6 years. To the best of our knowledge, this was the longest follow-up in a cohort of renal transplant recipients.

We found independent associations of CAC progression with baseline CAC score and triglyceride levels, although the second factor was related to only one of the two metrics of CAC progression (Table 3). Triglyceride levels have been associated with CAC progression in previous studies in renal transplant patients [10], as well as in a large cohort of men and women in six US communities [19]. High triglyceride levels are one of the five components of metabolic syndrome [20], and they interact with abdominal obesity in the risk of all-cause and cardiovascular death in the dialysis population [21]. However, evidence that triglycerides are causally implicated in high risk for cardiovascular disease and death in the transplant population has been lacking. The presence of CAC was per se a strong predictor of further CAC

progression over time in previous studies in renal transplant recipients and non-kidney disease patients [10, 22–24]. In the present long-term study, we confirmed the paramount role of background coronary calcification in the progression of the same alteration by two statistical approaches: first, by standard logistic regression analysis; and second, by the multivariate mixed linear model, which is a technique that is well suited for the analysis of clinical studies with unevenly spaced time points [25], such as our progression study. The risk of death and cardiovascular complications in renal transplant patients is lower than that in the comparable population maintained on chronic dialysis, and this is mainly attributed to better control of CKD-related risk factors [26]. Systemic inflammation, as measured by CRP, is related to the progression of atherosclerosis in dialysis patients [27]. However, in the present study, CRP largely failed to consider the progression of CAC in our cohort of transplant patients. In general, biomarkers of CKD-mineral bone disorder improve dramatically after transplantation, and PTH does not seem to play a major role in arterial disease in this population [28], which is in agreement with the lack of prediction power of baseline PTH levels with CAC progression in the present study. Novel biomarkers of CKD-mineral bone disorder, such as fibroblast growth factor 23 (FGF23), are among the most indicated risk factors for the high rate of cardiovascular events in dialysis patients [29], and FGF23 seems to play a major role in the progression of atherosclerosis in renal transplant patients [28]. Furthermore, FGF23 was a strong predictor of cardiovascular mortality in stable renal transplant patients [30] and was associated with the severity and extent of coronary artery disease in patients undergoing coronary angiography [31], as well as with coronary calcification in African-Americans with type 2 diabetes [32]. Thus, FGF23, a biomarker that we did not measure in the present study, might be a risk factor for CAC and CAC progression in renal transplant patients, and the link between FGF23 and coronary disease progression should be addressed in future studies in transplant patients.

Our study has limitations. We excluded patients with documented coronary artery disease at the baseline screening; therefore, we might have underestimated the progression rate of CAC, which is a possibility emphasized by the strong predictive power of coronary calcification for the evolution of the same alteration emerging in the present analysis. Second, the majority of the patients in our unit were living donor transplant recipients; therefore, our findings might not apply to the general transplant population, which is mainly composed of patients who receive cadaveric renal transplants. Finally, lack of an age- and sex-matched control group that can be used to compare the rate of progression is a limitation. However, in our previous report we compared our CAC progression rates with those of 2 large-scale studies and concluded that CAC progression is higher in our renal transplant recipients [10, 17, 19].

In conclusion, our study documented that, in renal transplant recipients, CAC progressed, especially in patients with baseline CAC, and CAC progression was associated with time to transplantation but was largely independent of the main classical and nonclassical risk factors, including factors related to the function and integrity of the renal graft, such as GFR and albuminuria.

Acknowledgements

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Statement of Ethics

The study protocol was approved by the local medical ethics committee (protocol No. 18578). This study was conducted in accordance with the principles of the Declaration of Helsinki. The clinical and research activities reported were consistent with the Principles of the Declaration of Istanbul as outlined in the "Declaration of Istanbul on Organ Trafficking and Transplant Tourism." Subjects have given their informed written consent.

Disclosure Statement

The authors declare no conflicts of interest.

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