Coronary Artery Calcification in Kidney Transplant Recipients With Long-term Follow-up

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ABSTRACT

Objectives. Kidney transplantation (KT) is associated with increased incidence of hypertension, hyperlipidemia, metabolic syndrome, and posttransplant diabetes mellitus that promote the development of coronary artery calcification (CAC). The aim of the current study was to elucidate the extent of CAC and its risk factors among KT patients.

Methods. A cross-sectional study was performed to evaluate the severity of CAC in our KT patients. Multidetector computed tomography was performed to assess the coronary artery calcium score (CACS). Patients were further stratified according to the CACS as: group 1: 0–10, group 2: 11–100, group 3: 101–300, group 4: 301–1000, and group 5: >1000. Clinical as well as demographic data were compared among groups. Linear regression analysis was performed to determine factors that were associated with CAC.

Results. A total of 99 patients were enrolled in the study. The mean age was 53.5 ± 11.8 years and duration of follow-up post-KT was 11.2 ± 5.9 years. The distribution of CACS in groups 1 through 5 was: 41.4%, 20.2%, 11.1%, 15.2%, and 12.1%, respectively. A significantly higher CACS was found in males, patients with pretransplant diabetes mellitus, older current age, older age at KT, hypertension, higher body weight, higher fasting plasma sugar level and lower high-density lipoprotein (HDL) cholesterol. Twenty-nine (29.3%) patients fulfilled criteria for metabolic syndrome (MS). The CACS was significantly higher in patients with MS than in those without MS. An incremental CACS was found to be correlated with increasing number of MS components ($P = .003$). Multivariate linear regression revealed that female gender, current age, hypertension, and HDL cholesterol were associated with CAC.

Conclusion. KT was associated with high CACS in a significant proportion of patients with long-term follow-up. Several risk factors were identified. Some of them were potentially treatable and should be taken into consideration in the management of KT recipients.

PATIENTS with chronic kidney disease (CKD) are associated with increased risk of cardiovascular diseases (CVD), which is a result of multiple traditional and nontraditional factors.[1,2] Kidney transplantation (KT) may ameliorate several of these factors, such as hyperphosphatemia, anemia, and uremic toxins, but in the meantime

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Partly supported by the research grants from Taichung Veterans General Hospital (TCVGH-993603C) and the National Science Council (99-2314-B-075A-001-MY3).

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0041-1345/–see front matter
doi:10.1016/j.transproceed.2011.11.031

Table 1. Comparison of Clinical Features in Patients With Different Degree of Coronary Artery Calcification

CAC Score	0–10 (n = 41)	11–100 (n = 20)	101–300 (n = 11)	301–1000 (n = 15)	> 1000 (n = 12)	*P* Value
Sex, % male	29.3	65.0	63.6	53.3	66.7	.027*
Age at KT (y)	39.6 ± 12.8	44.1 ± 12.5	37.5 ± 11.8	43.0 ± 14.4	52.1 ± 9.7	.042*
Current age (y)	49.8 ± 11.9	56.1 ± 11.3	50.3 ± 10.9	55.8 ± 11.8	62.0 ± 7.82	.015*
Duration post KT (y)	10.2 ± 5.3	12.0 ± 6.4	12.8 ± 5.0	12.8 ± 6.6	7.9 ± 6.8	.277
BW (kg)	56.2 ± 10.7	63.7 ± 11.7	60.4 ± 12.9	64.2 ± 13.2	68.3 ± 8.8	.01*
Pre-KT DM (%)	0	0	11.1	7.1	36.4	.001**
PTDM (%)	8.8	5.9	11.1	21.4	18.2	.206
HTN (%)	40.9	69.2	100.0	71.4	77.8	.001**
Number of HTN drugs	0.59 ± 0.80	1.23 ± 1.17	1.80 ± 0.84	1.29 ± 1.14	1.56 ± 1.24	.042*
Cr (mg/dL)	1.47 ± 0.71	1.53 ± 0.38	1.11 ± 0.34	1.69 ± 0.82	1.34 ± 0.51	.154
eGFR (mL/min)	52.8 ± 22.4	51.4 ± 16.4	48.9 ± 16.6	45.4 ± 15.2	60.4 ± 22.5	.266
Total-C (mg/dL)	194.9 ± 33.5	190.9 ± 31.9	201.8 ± 34.7	199.5 ± 32.9	182.3 ± 43.9	.660
HDL-C (mg/dL)	70.8 ± 20.2	57.7 ± 13.8	65.5 ± 25.0	58.5 ± 16.3	51.8 ± 14.3	.015*
LDL-C (mg/dL)	112.5 ± 31.4	118.1 ± 20.5	124.4 ± 38.5	130.4 ± 28.8	114.2 ± 37.0	.381
FBS (mg/dL)	106.6 ± 71.8	108.6 ± 43.5	109.0 ± 29.4	101.5 ± 16.9	129.6 ± 35.6	.009*
Uric acid (mg/dL)	6.98 ± 1.97	7.44 ± 1.34	8.33 ± 2.61	7.03 ± 1.64	8.07 ± 2.03	.290
TG (mg/dL)	110.9 ± 42.8	134.2 ± 64.2	142.3 ± 66.6	151.9 ± 92.8	157.5 ± 92.6	.264

Abbreviations: KT, kidney transplantation; BW, body weight; DM, diabetes mellitus; PTDM, posttransplantation DM; HTN, hypertension; Cr, creatinine; e-GFR, estimated glomerular filtration rate; Total-C, total cholesterol; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; FBS, fasting blood sugar; TG, triglyceride.
*$P < .05$.
**$P < .005$.

may aggravate other factors such as hypertension, hyperglycemia, and metabolic syndrome. Thus, as in the case of uremia, the leading cause of death remains CVD among KT patients.[1] Coronary artery calcification (CAC) may represent a burden of coronary atherosclerosis.[3] The aim of the current study was to elucidate the extent of CAC and its risk factors among KT patients.

METHODS

KT patients currently followed up at our institution were recruited for the study. This study was approved by the Institutional Review Board of Taichung Veterans General Hospital (IRB TCVGH No: C09255). Multidetector computed tomography (MDCT; Brilliance™ CT [64 MDCT], Phillips Medical System, Cleveland, USA) was performed to assess the coronary artery calcium score (CACS). Patients were stratified according to the CACS as: group 1: 0–10, group 2: 11–100, group 3: 101–300, group 4: 301–1000, and group 5: >1000. A modified Asian version of the Adult Treatment Panel III criteria was adopted for the definition of metabolic syndrome (MS), in which the abdominal obesity was defined as a waist circumference of > 90 cm for males and > 80 cm for females. Clinical as well as demographic data were compared among groups. Multivariate logistic regression analysis was performed to identify independent risk factors that were associated with calcification.

Table 2. Univariate Linear Regression Showing Factors That Were Associated With CAC

	β	*P* Value	95% CI
Female gender	−1.75	.0003	0.07 to 0.45
Current age	0.06	.0039	1.02 to 1.10
Transplantation age	0.03	.0416	1.00 to 1.07
Body weight	0.05	.0234	1.01 to 1.09
Body height	0.07	.0323	1.01 to 1.13
Hypertension	0.66	.0051	1.22 to 3.06
HDL cholesterol	−0.03	.0047	0.95 to 0.99

Abbreviations: CAC, coronary artery calcification; CI, confidence interval; HDL, high-density lipoprotein.

RESULTS

A total of 99 patients (male:female, 48:51) were enrolled for the study. The mean age was 53.5 ± 11.8 years and the duration of follow-up posttransplant was 11.2 ± 5.9 years. Six patients had pretransplantation diabetes mellitus (DM) whereas 10 cases had posttransplantation DM. Forty (63.5%) patients had hypertension. The distribution of CACS in groups 1 through 5 was: 41.4%, 20.2%, 11.1%, 15.2%, and 12.1%, respectively. A comparison of the clinical features among patients with different CACS is shown in Table 1. Statistically significant parameters that were associated with higher CACS were: male sex ($P = .027$), older age at KT ($P = .042$), older current age ($P = .015$), higher body weight ($P = .01$), hypertension ($P = .001$), higher severity of hypertension (represented as number of antihypertensive agents used, $P = .042$), pretransplantation DM ($P = .001$), higher fasting plasma sugar ($P = .009$), and lower high-density lipoprotein (HDL) cholesterol ($P = .015$). There was a borderline association of CACS with the

Table 3. Parameters Associated With CAC by Multivariate Linear Regression

	β	*P* Value	95% CI
Female gender	−1.61	.0021	0.07 to 0.59
Hypertension	0.56	.0424	1.02 to 3.03
Current age	0.07	.0021	1.03 to 1.12
HDL cholesterol	−0.02	.0382	0.96 to 1.00

Abbreviations: CAC, coronary artery calcification; CI, confidence interval; HDL, high-density lipoprotein.

Table 4. Calcium Score According to Number of Components of Metabolic Syndrome (MS) and Patients With or Without MS

No. of MS Components	0 (n = 21)	1 (n = 32)	2 (n = 17)	3 (n = 23)	> 3 (n = 6)	MS (n = 29)	Non-MS (n = 70)
CAC score Mean ± SD	117.9 ± 240.0	247.6 ± 687.6	528.8 ± 1014.0	967.0 ± 1401.6	741.0 ± 1086.1	920.2 ± 1327.7	277.0 ± 700.9
Median	2.3	5.25	242.5	261	319.1	261.0	11.8
Range	0–789	0–3409	0–4276	0–4276	0–2805	0–4276	0–4277
P value			.003				.001

following parameters: higher hemoglobin A1c ($P = .051$), higher body mass index ($P = .053$) as well as higher waist circumference ($P = .08$). MS was found in 29 patients (29.3%). Univariate linear regression analysis revealed that male gender, transplant age, current age, body weight, body height, hypertension, and HDL cholesterol were associated with CAC (Table 2). In multivariate analysis, male gender, hypertension, current age, and HDL cholesterol were independently associated with CAC (Table 3). Patients with MS had a significantly higher CACS (920.2 ± 1327.7 versus 277.0 ± 700.9; $P = .001$) than patients without MS (Table 4). An incremental CACS was found to be correlated with an increasing number of MS components ($P = .003$; Table 4).

DISCUSSION

CACS measured by MDCT is a noninvasive procedure used to assess coronary artery disease and has been found to correlate well with coronary angiography in the general population[4] and in patients with CKD.[5] The procedure is relatively safe, takes 10 to 15 minutes with no need of radiocontrast infusion and the total radiation exposure is only 1.5 mSV in our examinations. Recent studies have shown that CACS is closely related with coronary event [6] and all-cause mortality.[7] Although the presence of CAC does not necessarily indicate the presence of coronary artery stenosis, it is the current consensus that CAC can identify a high-risk group of patients rather than a vulnerable vessel or plaque.[3] The present study revealed that only 41.4% of KT patients had a zero or negligible (<10) CACS, which was significantly lower than the 57% obtained during a study on general population with a similar mean age.[7] Given the fact that CVD remains the leading cause of death in KT recipients, our finding highlights the potential role of MDCT coronary scan in the long-term care of KT patients. Several factors have been identified to be associated with a higher CACS, namely, male sex, older age, higher body weight, hypertension, hyperglycemia, pretransplantation DM, and lower HDL cholesterol (Table 1), many of which are modifiable through adjustment of immunosuppressive agents, therapeutic intervention, and lifestyle modification. Patients with DM are known to be associated with excessive coronary artery calcification. Higher CACS was also found in patients with pre-KT DM but not posttransplantation DM in our series. This may be simply due to a shorter duration of DM in the latter group, because the process of calcification is likely time-dependent. We further analyze factors that would be associated with CAC. By univariate linear regression, male gender, older current age, older age at transplant, higher body weight and body height, hypertension, and lower HDL cholesterol were associated with CAC (Table 2). However, in the multivariate analysis, only current age, male gender, hypertension, and HDL cholesterol were independently associated with CAC (Table 3). Unexpectedly, DM and MS were not found to be independent risk factors of CAC. The small sample size and relatively low proportion of DM patients might render the statistics underpowered to detect an association. Moreover, the different components of MS might contribute differently to CAC. In our study, of the five components of MS, only hypertension and low HDL cholesterol were independently associated with CAC. Nevertheless, the current study did show that patients with MS had a significantly higher CACS than did those without MS (Table 4). This is consistent with the findings of a recent report in which both baseline and follow-up CACS in MS renal transplant patients were significantly higher as compared with those in non-MS recipients.[8] Moreover, with the increase of number of MS components, an incremental CACS was also shown in the current study (Table 4). In view of the high prevalence (29.3%) of MS in our series and even higher (55.4%) in the aforementioned report,[8] measures to ameliorate the adverse effects of MS components are mandatory in preventing CVD in KT recipients.

Recently, a strong and graded relationship between lower glomerular filtration rate (GFR) and CAC, independent of traditional risk factors, were found in the Chronic Renal Insufficiency Cohort (CRIC).[9] However, we were not able to find a significant difference in estimated GFR among patients with different grades of CAC (Table 1). Determinants of CAC in KT recipients may be more complicated than those in the general population with CKD. Moreover, pretransplantation CAC may not be resolved after a successful KT, thus, a high CACS may coexist with a good GFR.

In conclusion, we have shown that more than half of our KT patients were associated with CAC. Therapies that target those modifiable risk factors should be a crucial part of management for KT recipients.

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