Pre-Transplant Assessment of Vascular Calcification as a Risk Factor of Mortality, Graft Loss, and Cardiovascular Events in Renal Transplant Recipients

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ABSTRACT

Background. Vascular calcification (VC) is known as an independent predictor of mortality in patients undergoing hemodialysis; nevertheless, there is a lack of studies about the impact of vascular calcification in renal transplant recipients, and none of them use the Kauppila Index (KI) as a predictor of patient and graft prognosis.

Methods. We conducted an observational, retrospective study of 119 renal transplants, evaluating abdominal aortic calcifications (L4-S1) with the KI. We established 2 categories: absence (KI = 0–2) and presence (KI = 3–24) of VCs before transplantation. We analyzed the impact of calcification in graft and patient survival, new-onset diabetes mellitus, hypertension, cardiovascular events, renal function, and mineral metabolism.

Results. VCs were observed in 50 patients (42%) before renal transplantation. Patients with VCs were older, but no statistical differences were found in the pre-transplant study between sex, diabetes, body mass index, and cardiovascular events. We found a major patient survival (limited to first 2 years after transplantation), graft survival, and death-censored graft survival in those without VCs ($P = .037$, $P = .015$, and $P = .023$, respectively). In line with results, a higher incidence of major cardiovascular events (MACE) and cardiovascular death was observed in the group with preexisting calcification ($P = .016$/$P = .019$). In the multivariable analysis, VCs were not an independent predictor for graft loss, death-censored graft loss, or major cardiovascular events.

Conclusions. Simple evaluation of VCs with the use of the KI at the time of transplantation relates with graft and patient survival and with MACE after renal transplantation.

MINERAL and bone disorders and finally vascular calcification (VC), are the predominant causes of cardiovascular morbidity and mortality in the chronic kidney disease population. The best screening for cardiovascular calcification and optimization of such management are still an ongoing debate [1–9].

The increased risk of cardiovascular events after transplantation could be attributed to an over-representation of traditional risk factors as well as transplant-specific factors, such as side effects of immunosuppressive drugs. However, vascular damage accumulated before transplantation probably increases the risk of cardiovascular events, and the implications and prognosis on the principal outcomes of the graft and survey of the renal transplant recipients (RTR) are not well known. Few studies have been made about this matter, but none of them used the Kauppila Index (KI) to measure the VCs.

METHODS

All RTRs from July 2011 to September 2013 with a lateral lumbar radiography obtained immediately before transplantation were included (119 of 169; 70%). Abdominal aortic calcifications

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Table 1. Baseline Demographics According to VC Group

	Without VCs (n = 69)	With VCs (n = 50)	*P*
Men	43 (62.3%)	35 (70%)	.384
HD/DP/preemptive	52/15/2	38/11/1	.958
PRA >10%	26.1%	24.4%	.684
CMV IgG neg	12/55 (21.82%)	3/43 (6.98%)	.043
DC/DV (%)	66/3 (4.35%)	49/1 (2.0%)	.483
Diabetes (%)	11.8%	24.5%	.17
MACE pre-transplant	18.6%	30.6%	.143
Second transplant	9/60 (13.04%)	8/42 (16.0%)	.649
Recipient age, years	52.5 ± 1.8	64.4 ± 1.2	<.001
Recipient BMI	26.0 ± 0.5	26.8 ± 0.6	.3334
Months on dialysis	28.4 ± 2.3	30.9 ± 2.9	.3037
Donor age, years	53.5 ± 2.1	64.1 ± 1.6	.0002
Donor creatinine	0.91 ± 0.1	0.97 ± 0.1	.3150
Donor BMI	26.4 ± 0.5	26.8 ± 0.7	.9812
Cold ischemic time, h	14.24 ± 0.7	15.79 ± 0.6	.1273
iPTH pre-transplant, pg/mL	340 ± 28	351 ± 38	.9347
Pre-transplant, mg/dL	4.99 ± 0.21	4.74 ± 0.21	.6157

(L1–L4) were evaluated by use of the KI. Patients were classified in 2 groups: absence (KI = 0–2) and presence (KI = 3–24) of VCs before transplantation.

We analyzed the impact of calcification on patient and graft survival, major cardiovascular events (MACE), new-onset diabetes mellitus (NODAT), arterial hypertension, glomerular filtration rate, and mineral metabolism.

The Student *t* test and the χ^2 test were used for the statistical comparison of means and proportions between groups. Variables not distributed normally were compared by use of the Wilcoxon rank-sum test. Unadjusted patient and allograft survival were estimated by means of the Kaplan-Meier method, with comparison between groups performed with the use of the log-rank test. Cox proportional-hazards analysis was used to identify factors independently associated with patient and allograft survival. All statistical analyses were performed with the use of STATA 12.1 software (Stata Corporation, College Station, Tex, United States). All reported *P* values are 2-sided.

RESULTS

VCs were observed in 42% of the patients and were not statistically associated with hyperphosphatemia, PTH levels, nor months on dialysis previous to the transplant. However, RTRs with more calcifications were older and were more proportional of cytomegalovirus (CMV) immunoglobulin (Ig)G-negative. There were no statistical differences in the pre-transplant study between sex, diabetes, body mass index (BMI), and cardiovascular events and calcification (Table 1).

Table 2. Post-Transplant Events According to VC Group

	Without VCs (n = 69)	With VCs (n = 50)	*P*
DGF	12.7%	24.5%	.106
Acute rejection	7.9%	12.2%	.447
NODAT	4.8%	17.4%	.031
HTA	90.5%	85.1%	.388
MACE	4.8%	19.6%	.016
MACE or cardiovascular death	6.5%	21.7%	.019
SBP, mm Hg	125.4 ± 1.3	133.4 ± 1.6	.0002
DBP, mm Hg	72.4 ± 1.0	71.8 ± 1.3	.7309
Creatinine m1, mg/dL	1.90 ± 0.13	1.79 ± 0.10	.9437
Creatinine m3, mg/dL	1.63 ± 0.06	1.69 ± 0.10	.9568
Creatinine m1 2, mg/dL	1.57 ± 0.07	1.55 ± 0.11	.5895
U-Alb/U-Cr m12, mg/g	105 ± 40	70 ± 34	.5916
iPTH m3, pg/mL	170 ± 37	213 ± 77	.6394
iPTH m12, pg/mL	135 ± 24	167 ± 32	.4150

We found statistically differences in the proportion of those patients with VCs and NODAT when they were compared with patients with absence of calcification. The systolic blood pressure (SBP) 1 year after transplant was also increased in the group with VCs (Table 2).

Graft loss and death-censored graft loss were higher in RTRs with VCs ($P = .0155$ and $P = .0231$, respectively) (Fig 1). Major cardiovascular events or the composite endpoint of MACE and/or cardiovascular death were also higher in the group with preexisting calcification ($P = .016$, $P = .019$, respectively). Patient mortality was higher in the group with VCs, but only within the first 2 years after transplantation ($P = .037$, Fig 1), with such difference disappearing from the second year onward. In the multivariable analysis, VC was not an independent predictor for mortality (hazard ratio [HR], 3.46; $P = .074$; 95% CI: 0.9–13.6), graft loss (HR, 1.81 ± 1.10; $P = .329$; 95% CI: 0.55–5.97), death-censored graft loss (HR, 7.08 ± 6.80; $P = .076$; 95% CI: 0.85–61.46), or non-fatal cardiovascular events.

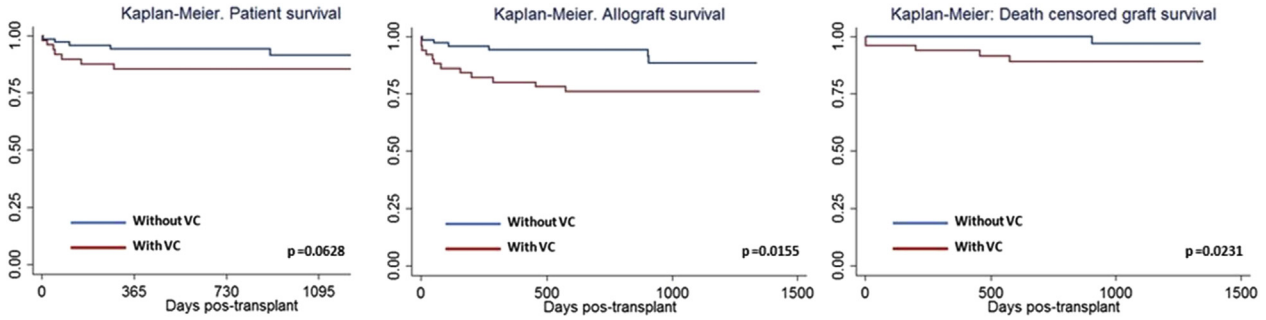

Fig 1. Graft loss and death-censored graft loss were higher in RTRs with VCs.

DISCUSSION

It is remarkable that some factors, such as cardiovascular events, serum PTH, or phosphatemia have no statistical association with calcification, but there are some items, such as CMV IgG serostatus, that were found to be correlated. Although the age differences between two groups may explain the different proportion of negative-CMV IgG patients, this last finding is surprising because no relationship between the two events has been stablished in chronic kidney disease before.

It is not a novelty that VC in transplantation is related to cardiovascular events and deaths in the post-transplantation period, but we describe in this study that baseline KI on incident RTR is a useful measure to discriminate the degree of VCs that results in worse clinical outcomes in the post-transplant period.

This test also has some other implications because of its association between calcification and NODAT and higher SBP after transplantation. Even more relevant were the findings of a higher graft loss, death-censured graft loss, and major cardiovascular events in the group that demonstrate the presence of vascular calcification. The mortality rate was also increased in the first 2 years in the group mentioned, but this difference disappeared after this period; possibly some other factors begin to play a more intensive role at this time. Another interpretation of the data is that calcification is mainly established in the pre-transplant period, and their consequences should become patent in the early post-transplant outcomes.

We could not find that VCs represent an independent predictor for mortality or non-fatal cardiovascular events—except for diabetes—but this result could be explained by the limited number of events. We consider it of interest to amplify this study sample to obtain more meaningful results.

CONCLUSIONS

We propose the use of the KI for VC measure, not only because of its simplicity and low price but also as an additional tool to estimate the cardiovascular risk and surveillance of kidney graft and kidney transplant receptors.

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