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DIALYSIS – TRANSPLANTATION

Clinical impact of preexisting vascular calcifications on mortality after renal transplantation

Domingo Hernández, Margarita Rufino, Sergio Bartolomei, Ana González-Rinne, Víctor Lorenzo, Marian Cobo, and Armando Torres

Nephrology Section, Research Unit, Hospital Universitario de Canarias, Instituto Reina Sofia de Investigación, La Laguna, Tenerife

Clinical impact of preexisting vascular calcifications on mortality after renal transplantation.

Background. Vascular calcifications (VC) are a well-known cardiovascular risk factor (CVRF) in uremic patients. However, their role on mortality after renal transplantation (RT) is unclear.

Methods. In 1117 RT recipients, we investigated the association between long-term survival and the presence of VC, evaluated by preoperative posteroanterior plain radiography from aorto-iliac region, at the time of RT. The primary study outcome was all-cause mortality. Other perioperative CVRF were also collected.

Results. VC were observed in 273 patients (24.4%) before RT; additionally, 132 (12%) patients died during follow-up, due, mainly, to cardiovascular (39%) or infectious (24%) complications. As expected, patients with VC showed a higher age and a greater number of CVRF than those without VC. Overall mortality rate was also higher in VC group (19 vs. 9.5%; $P = 0.0001$), as well as cardiovascular mortality (9.5 vs. 3.1; $P = 0.048$). Multivariate Cox model showed that VC were predictor of overall mortality [relative risk (RR) 1.8; 95% CI 1.1–2.8; $P = 0.015$] and cardiovascular mortality (RR 2.6; 95%CI 1.1–6); $P = 0.033$), independently of other CVRF. An interaction between the presence of VC and diabetes was found. The effect of VC on mortality was evident in nondiabetic patients, that is, those with VC had a significantly higher mortality rate than patients without VC (21 vs. 9%; $P = 0.0001$). By contrast, these differences were not observed in diabetic patients (16.5 vs. 14.3%; $P = 0.656$).

Conclusion. VC evaluated by a simple and inexpensive plain radiography are an independent predictor of cardiovascular and all-cause mortality following RT. This finding may encourage the implementation of appropriate therapeutic strategies after RT.

Vascular calcifications (VC) are frequent among long-term dialysis patients, and this complication by itself is an important predictor of all-cause and cardiovascular mortality in this population [1]. Although the pathogenic mechanisms are not well known, derangement of the calcium/phosphate balance may contribute to the development of this process, especially medial artery calcifications [2, 3]. In addition, previous studies have demonstrated that linear artery calcifications, evaluated by conventional radiographic films, are strong predictors of mortality in both general population and uremic patients [4–6].

Cardiovascular disease (CVD) is prominent in renal transplant recipients. Nearly half of deaths in this population are attributed to CVD [7]. Because this phenomenon is not sufficiently explained by an increased prevalence of traditional risk factors in this population [8], we reasoned that the presence of preexisting VC may be associated with an increased risk of all-cause death after renal transplantation (RT). To date, however, the prognostic implications of VC following RT remain undetermined.

Thus, the aim of our study was to assess the association between long-term survival and the presence of VC, as detected by plain radiography from aorto-iliac region at the time of RT.

METHODS

Study population

We conducted a retrospective cohort study with 1117 consecutive Caucasian patients who received a cadaveric kidney between 1981 and 2001 in a regional transplant center (University Hospital of the Canary Islands, Spain). Immunosuppression consisted of prednisone plus azathioprine until 1986, and thereafter, prednisone plus antilymphocytic antibodies followed by calcineurin inhibitors and azathioprine or mycophenolate mofetil.

Data collection

Patient data were collected at the time of transplantation and during hospitalization until discharge by chart review. The following data were recorded at the time

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of admission: age, gender, primary kidney disease, dialysis modality, time on dialysis, number of transplantation, human lymphocytic antigen (HLA)-mismatches, antilymphocytic antibodies, and comorbidity. The latter was defined as presence or absence of: dyslipidemia, hepatitis B virus, left ventricular hypertrophy determined by echocardiographic [9] or electrocardiographic criteria [10], pretransplant cardiovascular disease (ischemic heart disease, heart failure, stroke, and peripheral artery disease) defined by standard criteria [11], obesity (BMI>30 kg/m^2), hypertension (blood pressure >140/90 mm Hg or need for antihypertensive therapy), and VC evaluated by preoperative conventional radiographs of the aorto-iliac region under standardized conditions. In particular, assessment of arterial calcifications in the abdominal aorta and iliofemoral axis was estimated by 2 nephrologists from posteroanterior fine-detail native radiographs (Eastman Kodak Co., Rochester, NY, USA) of the abdomen and pelvis performed at the time of RT as part of our standard clinical practice. Aortic calcifications were regarded as present if radiodensities were visible in an area parallel to the lumbar spine. Densities overlapping the vertebrae were deemed as present only if they formed a continuity pattern with iliac arteries. Only linear calcifications of aorta, iliac and femoral arteries, with or without patchy calcifications, were considered as VC. Isolated patchy calcifications, which may be associated with intimal calcifications, were not considered because they could be confounded with other types of extravascular calcifications as phleboliths. As previously described, VC were qualitatively determined as absent (score = 0) or present (score = 1) in whichever of the studied zones [12]. Finally, VC were only considered when they were ascertained by both nephrologists without knowledge of any prevalent or incident clinical vascular disease. Discordances (<5%) were evaluated by an independent observer (radiologist) blinded to clinical data, and the samples therefore were classified correctly before final analysis.

We also collected the following data: acute tubular necrosis, acute rejection, and renal function at discharge expressed as serum creatinine (Scr). Additionally, we also recorded immunosuppressants at discharge: antilymphocytic antibodies, anticalcineurin inhibitors, and azathioprine or mycophenolate mofetil.

Outcome

All-cause and cardiovascular mortality were the study outcome. During the period of follow-up, all deaths were accurately recorded. Survival was measured in months from the date of hospital discharge (zero time) to the date of death. Cardiovascular mortality included death associated with a definite myocardial infarction, heart failure, stroke, arrhythmia, and peripheral vascular accident, all of which were defined according to standard clinical criteria, and sudden death, which was defined as unexpected death within 1 hour from the symptom onset and without any prior condition that would appear fatal [13].

Medical record review was performed according to Spanish law with reference to clinical data confidentiality protection. This study was approved by the Ethics Committee of the University Hospital of the Canary Islands, and was conducted in accordance with the provisions of the Declaration of Helsinki.

Statistical analyses

Continuous data were summarized as mean ± SD. Comparisons of continuous variables between patients with and without VC were performed using unpaired *t* test. Categorical data were compared using chi-square test. Cox proportional hazards model was used to identify baseline risk factors for all-cause and cardiovascular mortality. We included covariates potentially unique to transplant recipients along with traditional risk factors. From the time of RT the following variables were included: recipient and donor age, gender, cause of renal disease, type of dialysis, body mass index, pretransplant cardiovascular disease, vascular calcification, cardiac hypertrophy, hepatitis B, hepatitis C, dyslipidemia, hypertension, retransplant, cold ischemia time, HLA-mismatches, peak panel-reactive antibodies, and time on dialysis. The latter was expressed as dichotomous variable (greater or lesser than 48 months) because only waiting time >48 months was a significant predictor of mortality during follow-up when using several categories for duration on dialysis (<12 months, 12–24 months, 24–36 months, 36–48 months, and >48 months) in an univariate Cox analysis of our data ($P = 0.019$). Other transplant-related factors included in the model were: acute tubular necrosis, acute rejection, renal function at discharge, transplant era (1981–1990 vs.1991–2001), and immunosuppressants at discharge. This analysis was performed with a backward elimination procedure, and the final Cox model was built observing the rule that no more than 1 covariate per 10 events should be used in multivariate models. We also examined the validity of the proportionality assumption by testing for significance of covariate-time interaction terms. Covariates included in the Cox proportional hazards analysis did not violate the proportionality assumption. We also determined the interaction between VC and diabetes by introducing a cross product of the 2 dichotomous variables in the Cox regression analyses for all-cause mortality. Survival analysis was performed using Kaplan-Meier method and log-rank test according to the presence or not of VC.

Statistical analyses were performed with SPSS software version 12.0 (SPSS, Inc., Chicago, IL, USA). A *P* value less than 0.05 was considered significant.

Table 1. Demographic and clinical parameters of patients with and without vascular calcifications

	Vascular calcification ($N = 273$)	No vascular calcification ($N = 844$)	P value
Pretransplantation			
Age *years*	51.3 ± 11.7	40 ± 14	0.000
Male gender %	70	66	0.324
Modality dialysis %			
Hemodialysis	85.6	85.3	0.897
Peritoneal dialysis	14.4	14.7	
Time on dialysis >48 months %	15.8	15.3	0.853
Diabetes%	49	10	0.000
BMI >30 kg/m^{2}%	9	6.4	0.308
Dyslipidemia %	36	18	0.000
Hypertension %	87	74	0.000
Pretransplant cardiovascular disease %	40	12.2	0.000
LVH %	64	42	0.000
Retransplant %	10	10.3	0.909
Maximal antibodies %	12 ± 25	10 ± 21	0.347
Post-transplantation			
Acute tubular necrosis %	34	36	0.492
Acute rejections during admission %	15.8	23.4	0.008
Serum creatinine at discharge >2 mg/dL %	23.4	27.3	0.248
Mean follow-up *months*	47 ± 36	65 ± 55	0.000

Conversion factors to SI units: 88.4 (μmol/L).

Table 2. Causes of death in study patients[a]

Cause of death	Total ($N = 1117$)	Patients with VC ($N = 273$)	Patients without VC ($N = 844$)
Cardiovascular disease[b]	52 (4.6)	26 (9.5)	26 (3.1)[c]
Infection	32 (2.8)	10 (3.6)	22 (2.6)
Tumor	17 (1.5)	5 (1.8)	12 (1.1)
Liver disease	7 (0.6)	4 (1.4)	3 (0.3)
Miscellaneous	24 (2.4)	7 (3.6)	17 (2)
Total	132 (11.8)	52 (19)	80 (9.5)[d]

VC, vascular calcification.
[a]Expressed as number (%).
[b]Causes of death from cardiovascular disease include myocardial infarction, heart failure, stroke, arrhythmia, peripheral vascular accident, and sudden death.
[c]$P = 0.048$ and [d]$P = 0.0001$ vs. patients with VC.

RESULTS

Among the 1117 patients included in the study, 273 (24.4%) showed VC prior to RT. Baseline clinical and demographic characteristics of the patients with and without VC appear in Table 1. As expected, patients with VC were older and showed a higher proportion of pretransplant diabetes, dyslipidemia, hypertension, and cardiovascular diseases than those without VC. In addition, patients with VC showed a lower rate of acute rejection during admission (Table 1), but renal function was similar between patients with and without VC at 1 and 5 years after RT (data not shown).

Median follow-up at the time of this analysis (December 31, 2002) was 49 months (interquartile range, 15 to 93 months). One hundred and thirty-two (12%) patients died during follow-up, due, mainly, to cardiovascular (39%) and infectious (24%) complications. As shown in Table 2, patients with VC showed a higher overall mortality rate than patients without VC (19 vs. 9.5%; $P = 0.0001$). Likewise, 9.5% of patients with VC versus 3.1% of patients without VC died from cardiovascular causes ($P = 0.048$). Kaplan-Meier curves revealed significant survival differences between both groups (Fig. 1A and B). As an example, the overall 5-year survival was 77% and 91% for patients with and without VC, respectively (log-rank-test; $P = 0.00001$; Fig. 1A). Similarly, the 5-year cardiovascular mortality was 14% and 3% for patients with and without VC, respectively (Fig. 1B; $P = 0.0001$).

The effects of independent risk predictors for all-cause and cardiovascular mortality, using multivariate Cox regression analysis, are shown in Table 3. VC was predictive of greater all-cause mortality [relative risk (RR), 1.8; 95%CI 1.1 to 2.8; $P = 0.015$] and cardiovascular deaths (RR, 2.6; 95% CI, 1.1 to 6; $P = 0.033$) independently of age, renal function at discharge, diabetes mellitus prior to RT, obesity, time on dialysis, and pretransplant cardiovascular disease (Table 3).

Figure 2 illustrates the result of a significant interaction between VC and diabetes prior to RT, as calculated by the Cox regression analysis. In particular, the effect of VC on mortality was restricted to nondiabetic patients, that is, those with VC had a significantly higher mortality rate than patients without VC (21 vs. 9%; $P = 0.0001$). By contrast, these differences were not observed in diabetic patients (16.5 vs. 14.3%; $P = 0.656$).

DISCUSSION

This cohort study demonstrates for the first time that VC, evaluated by plain radiography, are a strong and independent predictor of long-term all-cause mortality and cardiovascular deaths in RT recipients. Additionally, the effect of VC on mortality was more pronounced in nondiabetic patients. This finding may encourage the implementation of appropriate therapeutic strategies after RT in order to reduce long-term mortality.

Arterial calcifications may develop at 2 places in the arterial wall: the intima and the media [5, 14]. Intimal calcifications have been easily differentiated from medial calcification by plain radiography. In particular, linear calcification corresponds to medial calcification, previously described as railroad calcifications [15]. While intimal calcification can compromise blood flow, leading to tissue ischemia and necrosis, linear calcification is associated with arterial stiffening and reduced vascular compliance. These calcification patterns have been related to adverse clinical outcome in both general population [4, 16] and uremic patients [6, 12]. In this respect, London et al [5]

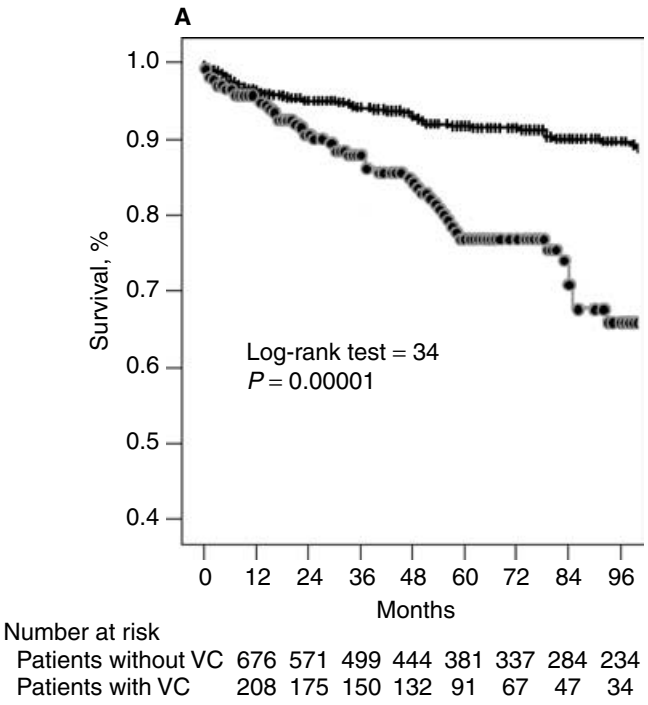

Fig. 1. Kaplan-Meier analysis of (*A*) overall survival and (*B*) cardiovascular event-free survival of 1117 patients with and without vascular calcifications (log-rank analysis: $P = 0.00001$). Dotted line = patients without VC; gray line = patients with VC. Numbers at the bottom refer to patients at risk entering each 12-month interval.

recently demonstrated that both intimal and medial calcification are strong predictors of death in hemodialysis patients. However, to our knowledge this had not been previously investigated in RT population.

CVD is the major cause of death in RT recipients [7, 8]. Because post-transplant CVD mortality is not largely explained by increased prevalence of traditional risk factors, a significant role of other nonmodifiable prognostic factors such as VC appears likely. Our results are consistent with this reasoning. VC, assessed by means of preoperative plain radiography, were an important risk factor of mortality in RT recipients, regardless of other traditional risk factors. The Cox proportional analysis was used to estimate the independent contribution of VC on mortality while controlling for relevant risk factors. We only considered linear calcifications, with or without patchy calcifications. Both calcification patterns (intimal and medial) may coexist in the same patient, contributing to a poor prognosis [5]. Our VC assessment, thus, does not exclude association of intimal and medial calcification, which could explain the strong relationship between VC and long-term survival in our patients. In a previous report, similar assessment of VC was also associated with cardiovascular mortality in hemodialysis patients [6]. Consequently, this inexpensive and readily available radiologic method may be a useful tool to identify RT recipients at higher cardiovascular risk. Although more sensitive methods (helical or electron-beam computed tomography) provide more detailed information about the extension of VC in arterial beds [18–20], they are more sophisticated and require high time consuming and experienced personnel. Additionally, the image resolution of these techniques is insufficient to distinguish between intimal and medial calcifications. In fact, the recent KDOQI clinical practice guidelines include the use of plain radiographic films of bone for VC assessment [21]. Further comparative investigations of different techniques are needed.

VC are now considered an interesting predictive tool for the assessment of atherosclerotic disease. Moreover, VC has been described as a late inflammatory phenomenon in response to lipid oxidation and macrophage infiltration after initial plaque formation in the atherosclerotic process [1]. Medial calcification may also occur with or without intimal lesions. These may lead to arterial stiffening. In addition, chronic inflammation may contribute to both forms of calcifications. Taken together, these factors could explain a higher all-cause and cardiovascular mortality in our patients with VC, as previously suggested [1, 5, 17].

Because accelerated atherosclerosis is the main complication of diabetes, we investigated an interaction between this disorder and VC. Interestingly, we found that the hazard effect of VC was restricted to nondiabetic patients. There are several possible reasons for these results. Of the multiple risk factors analyzed, only a higher age and a longer duration of dialysis were observed in calcified nondiabetic patients compared with diabetic recipients (data not shown), which are strong predictors of

Table 3. Risk factors for all-cause mortality and cardiovascular mortality in 1117 patients following renal transplantation[a]

Variable	All-cause mortality $N = 132$		Cardiovascular mortality $N = 52$	
	Relative risk[b] (95% CI)	*P* value	Relative risk[b] (95% CI)	*P* value
Age *years*				
<40 (41.2)	Reference		Reference	
40–60 (47.1)	1.6 (1.1–2.5)	0.030	1.6 (0.7–3.6)	0.239
>60 (11.7)	3.2 (1.8–5.7)	0.000	3.5 (1.3–9.5)	0.015
Scr >2 mg/dL at discharge (24.7)	1.7 (1.1–2.5)	0.007	5.2 (2.4–11)	0.000
Diabetes prior RT (19.4)	1.7 (1.1–2.8)	0.047	2.8 (1.1–7.1)	0.029
BMI >30 kg/m^2 (4.4)	2.4 (1.1–5.4)	0.037	4.3 (1.1–16)	0.032
Vascular calcifications (24.4)	1.8 (1.1–2.8)	0.015	2.6 (1.1–6)	0.033
Time on dialysis >48 months (18)	1.6 (1.1–2.5)	0.023	2.2 (1–4.7)	0.040
Pretransplant cardiovascular disease (19)[c]	1.7 (1.1–2.6)	0.018	3.1 (1.5–6.3)	0.003

Abbreviations are: BMI, body mass index; Scr, serum creatinine; RT, renal transplantation. Conversion factors to SI units: creatinine 88.4 (μmol/L).

[a]Cox proportional-hazard model.

[b]Adjusted for all risk factors listed in the table. In parentheses are shown the percentage of patients having the characteristics indicated by that variable. A relative risk greater or less than 1.00 indicates a higher or lower risk for death, respectively. Included in the model, but not in the table, were male gender, cardiac hypertrophy, number of transplant, type of dialysis, retransplant, cold ischemia time, donor age, transplant era (1981–1990 versus 1991–2001), hepatitis, B, hepatitis C, dyslipidemia, hypertension, acute rejection, peak panel-reactive antibodies, and immunosuppressants at discharge (each with $P > 0.5$).

[c]Pretransplant cardiovascular disease includes: ischemic heart disease, heart failure, stroke, and peripheral artery disease.

death after RT [22]. Alternatively, it is well known that established cardiovascular risk factors are more prevalent in diabetic than nondiabetic patients, affecting profoundly the pathogenesis of atherosclerosis. Moreover, VC are more severe in diabetic patients than nondiabetic population [23]. Thus, it is plausible that the effect of VC on mortality could have been obscured by diabetes per se among our diabetic recipients.

VC are a common complication of chronic kidney disease. In uremic patients the prevalence of arterial calcifications increases with age, presence of diabetes, higher dose of calcium-based phosphate binders, and duration of dialysis, among others [24]. Waiting time on dialysis has been also associated with worse outcome after RT [22]. Accordingly, our patients with VC at the time of RT showed a higher age and a greater proportion of diabetes prior to RT than those without VC. In addition, a longer time on dilaysis was an independent risk predictor for mortality. Although successful RT may improve some risk factors associated with uremic state, these results suggest that VC may extend or, at least, do not regress in a considerable proportion of renal transplant recipients, as recently reported [25]. In this respect, inherent factors to RT may contribute to the development of VC by increasing traditional risk factors or up-regulating specific genes and transcription factors in the active process of calcification. Future longitudinal studies are needed to clarify these aspects.

Patients with VC showed a lower rate of acute rejection. Similarly, diabetic patients also had less acute rejections during admission than patients without diabetes (data not shown). Why such patients with vascular disease have a reduced risk of immunologic dysfunction is unclear, but deserves further investigation.

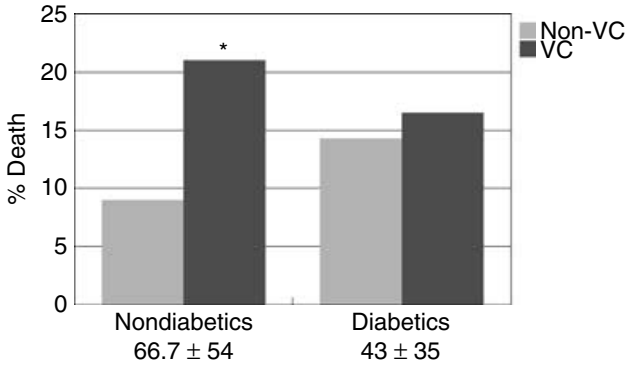

Fig. 2. Percentage of death in nondiabetic and diabetic patients according to the presence or absence of VC. In brackets are shown the mean time of follow-up in months of patients with or without diabetes prior to RT. *$P = 0.0001$ vs. non-VC. VC, vascular calcifications.

The principal limitation of this study is that we did not record important risk factors of comorbidity emerging during follow-up, such as immunosuppressants changes, metabolic disorders, renal function during follow-up, or infections, among others. However, this was consistent with the study aim, that is, to assess the impact of preexisting VC on the prediction of long-term mortality in incident renal transplant recipients.

CONCLUSION

The results of this study showed that preexisting VC, evaluated by plain radiographic film from aorto-iliac region, were by themselves a strong predictor of all-cause and cardiovascular mortality following RT, especially in nondiabetic patients. More attention should be focused on screening for this clinically silent and potentially lethal

complication in RT recipients in order to optimize future therapeutic strategies.

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Reprint requests to Domingo Hernández, M.D., Urbanización San Diego, 51, E-38208, La Laguna, Tenerife, Spain.
E-mail: dhmarrero@hotmail.com

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