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Clinical impact of preexisting vascular calcifications on mortality after renal transplantation

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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.