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Inflammation and oxidation: do they improve after kidney transplantation? Relationship with mortality after transplantation

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Abstract
Summary Patients with chronic kidney disease (CKD) are characterized by a state of inflammation and oxidative stress that seems to improve after kidney transplantation (KT). Nevertheless, there is controversy regarding what is the best marker that better define inflammation and specially oxidative stress.
Objective To evaluate the biomarkers which are associated with improvements in inflammation and lipid peroxidation in patients who have undergone KT. To evaluate the relationship between inflammation, lipid peroxidation and mortality in KT.
Patients 196 KT (between 2003 and 2008). 67.9% men; median age: 51.9 years. Inflammation markers analyzed previous KT and 3 months after KT: c-reactive protein(CRP), interleukin 6(IL-6), tumor necrosis factor alpha(TNFα), soluble tumor necrosis factor receptor alpha(sTNFRα), soluble interleukin-2 receptor (sIL-2R). Lipid peroxidation markers analyzed: oxidized low-density lipoprotein (oxLDL) and anti-oxLDL antibodies. Calculation of glomerular filtration rate after KT: MDRD equation.
Results Following KT, there is a significant decrease in CRP ($p = 0.006$), IL-6 ($p = 0.0037$), TNFα ($p < 0.0001$), sTNFRα ($p < 0.0001$) and sIL-2R ($p < 0.0001$), while levels of oxLDL increase after KT ($p < 0.0001$) and there is not a significantly difference in anti-oxLDL. 12.8% of the patients had died in 2012. These patients had higher levels of IL-6 ($p = 0.011$) and sTNFRα ($p < 0.006$) after KT and a lower MDRD ($p < 0.0001$), hemoglobin ($p = 0.012$) and albumin ($p = 0.007$). We observed no statistically differences in the levels of markers previous KT. Of the patients who died, the 43.5% of them had anti-oxLDL antibody levels greater than 75th percentile (P_{75}: 3781 UI/ml, $p = 0.028$). In the multivariate analysis, age (OR:1.12; $p = 0.0129$), MDRD (OR:0.92; $p = 0.013$) and P_{75} of anti-oxLDL(OR: 5.19; $p = 0.026$) were independent risk factors for mortality. Independent risk factors for survival were: P_{75} of IL-6 (HR: 2.45; $p = 0.027$), oxLDL (HR:19.85; $p = 0.002$) and anti-oxLDL (HR: 9.55; $p = 0.003$).
Conclusions KT improved inflammation but not lipid oxidative state. KT patients who died had a higher inflammatory state (with higher levels of IL-6 and sTNFRα), a worse lipid oxidative state and a worse renal function 3 months after KT. Age, anti-oxLDL and renal function at 3 months after KT were independent risk factors for mortality.

Keywords Immunosuppression · Inflammation biomarkers · Lipid peroxidation biomarkers · Kidney transplant · Mortality

Introduction

Chronic kidney disease (CKD) is an independent risk factor for morbidity and mortality [1]. Among the main causes of this increase in morbidity and mortality are cardiovascular disease (CVD) [2], infections [1, 3, 4], and cancer [5].

CVD and infections have been shown to be associated with changes in the immune system. In uremia, a decreased immune defense contributes to a greater prevalence of

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Table 1 Baseline characteristics of renal transplanted patients

Months on dialysis	23.0 (12.0–38.0)
Type of graft	88.6% cadaveric donor
	7.4% living donor
	4% kidney-pancreas
Cold ischemia time (hours)	19.3 (15.26–22.0)
Immunosuppressant treatment	100% corticosteroids, 96.9% mycophenolate, 4,7% rapamycin, 65.6% basiliximab
Calcineurin inhibitors	80.2% tacrolimus
	19.8% cyclosporine
Etiology of kidney disease	12.4% poliquistosis, 12.4% nephroangiosclerosis, 6.5% tubulointerstitial, 22.4% glomerulonephritis, 14.9% diabetic nephropathy, 19.4% unknown, 11.9% others
Hepatitis status (%)	8.6% Hepatitis C
Diabetes mellitus status (DM) (%)	21% pre-transplant DM
	22.8% DM at 3 months post-transplant
Hypertension (%)	91.5% pre-transplant hypertension
	84.8% post-transplant hypertension

infections [6], while the pre-activation and proliferation of immune system cells lead to inflammation and CVD [7].

Both oxidative stress and inflammation are common in patients with CKD, and the two conditions are related [8, 9] although it remains unclear whether chronic inflammation is the cause of oxidative stress or whether oxidative stress is responsible for the activation of inflammatory stimulators associated with uremia and dialysis.

Numerous studies have documented that an increase in proinflammatory cytokines and markers of oxidative stress [10] contributes to pathologic conditions such as cancer, atherosclerosis and hypertension, both in the general population and in patients with CKD [11–16].

Elevated levels of c-reactive protein (CRP), as well as other inflammatory cytokines such as interleukin 6 (IL-6) and tumor necrosis factor alpha (TNFα), have been associated with general morbidity and mortality, as well as with cardiovascular morbidity and mortality, in healthy subjects [11, 17, 18]. Our group [19] previously demonstrated an association between CRP and general mortality in a group of patients undergoing hemodialysis.

Oxidized low-density lipoprotein (oxLDL) has been proposed as a prognostic marker of lipid oxidative stress [20] in coronary heart disease associated with kidney transplantation (KT) [21], although this molecule has also been associated with a risk of various types of cancer [22, 23]. The presence of antibodies directed specifically against oxLDL could be a useful marker of lipid oxidative stress [24, 25].

The objective of this study was to evaluate the relationship between inflammation biomarkers and mortality, lipid peroxidation biomarkers and mortality before kidney transplantation and at 3 months after kidney transplantation and also the evolution of the inflammation and oxidation at 3 months after KT.

Patients, materials and methods

We conducted a prospective study of 196 patients with chronic kidney disease (CKD) who underwent KT between January 2003 and November 2008.

The main characteristics of patients are listed in Table 1. The 11.3% of the patients included in the study had pre-transplant cardiovascular disease as stroke, acute myocardial infarction and peripheral vascular disease.

All patients underwent a study with Doppler ultrasound of the carotid before kidney transplant, and the 50.5% of them had atheroma plaque. The 21.5% of the atheroma plaques were unilateral, and the 29% of the atheroma plaques were bilateral.

Pre-KT blood samples were obtained 6–8 h prior to KT, and post-KT samples were obtained 3 months after the procedure, both under fasting conditions. Blood samples were collected when patients were in a stable clinical condition, with no signs of acute infection, inflammation or rejection. All samples were stored at −80 °C until processed.

The following were analyzed: CRP, IL-6, TNFα, soluble tumor necrosis factor receptor alpha (sTNFRα) and soluble interleukin-2 receptor (sIL-2R) as markers of inflammation; oxLDL and anti-oxLDL as a marker of lipid peroxidation; hemoglobin, albumin, total cholesterol, LDL cholesterol and glomerular filtration (GF) using the MDRD equation [30]:

Table 2 Evolution of the markers pre and at 3 months after KT

Biomarkers	Pre-KT	3 months post-KT	*p*
Hemoglobin (g/dL)	12.47 ± 1.61	12.46 ± 2.06	0.789
Albumin (g/L)	39.21 ± 5.95	40.49 ± 4.77	0.008*
Total cholesterol (mmol/L)	4.09 ± 1.03	4.89 ± 1.05	0.0001*
LDL cholesterol (mmol/L)	2.73 ± 0.90	3.98 ± 1.03	<0.0001*
MDRD (ml/min/1.73 m^2)	10.39 ± 6.11	44.32 ± 16.26	0.009
Markers of immflamation			
CRP (mg/L)	4.24 (1.48–8.72)	2.86 (1.14–8.13)	0.006*
IL-6 (pg/mL)	5.37 (3.6–7.86)	4.53 (3.13–7.10)	0.037*
TNFa (pg/mL)	14.4 (11.1–19.5)	11.6 (8.95–15.85)	<0.0001*
sTNFRa (ng/mL)	32.82 (26.07–42.26)	3.56 (2.58–5.32)	<0.0001*
sIL-2R (U/mL)	1760 (1352.5–2385)	934 (619–1321)	<0.0001*
Markers of lipid peroxidation			
oxLDL (U/L)	54.04 (41.86–71.93)	72.58 (48.4–91.21)	<0.0001*
Anti-oxLDL (U/mL)	2493 (1659–3854)	2398 (1458–3781)	0.095

Results expressed as median (interquartile range) or median ± SD

CRP c-reactive protein, *IL-6* interleukin 6, *TNFα* tumor necrosis factor alpha, *sTNFRα* soluble tumor necrosis factor receptor alpha, *sIL-2R* soluble interleukin 2 receptor, *oxLDL* oxidized low-density lipoprotein, *anti-oxLDL* anti-low-density lipoprotein antibodies

* Statistical significance

Table 3 Relationship between biomarkers at 3 months after KT and mortality in kidney transplant patients

	Patients living	Patients who died	*p*
Hemoglobin (g/dL)	12.7 ± 1.93	11.59 ± 2.07	0.012*
Albumin (g/L)	40.85 ± 4.83	38.20 ± 3.64	0.007*
Total cholesterol (mmol/L)	4.88 ± 0.97	4.99 ± 1.49	0.697
LDL cholesterol (mmol/L)	3.92 ± 0.97	3.95 ± 1.99	0.951
MDRD (ml/min/1.73 m^2)	47.59 ± 15.83	33.9 ± 12.73	<0.0001*
Markers of immflamation			
CRP (mg/L)	2.85 (1.09–7.73)	3.02 (1.75–14.20)	0.14
IL-6 (pg/mL)	4.33 (3.05–6.73)	6.45 (4.45–10.30)	0.011*
TNFa (pg/mL)	11.5 (8.92–14.80)	13.65 (9.33–19.30)	0.365
sTNFRa (ng/mL)	3.33 (2.50–4.61)	4.9 (3.41–9.56)	0.006*
sIL-2R (U/mL)	894 (617–1249)	1149 (740–1732)	0.105
Markers of lipid peroxidation			
oxLDL (U/L)	70.87 (48.49–0.38)	77.49 (47.69–98.55)	0.719
Anti-oxLDL (U/mL)	2383 (1518–3599)	2726 (968–8119)	0.645

Results expressed as median (interquartile range) or median ± SD

CRP c-reactive protein, *IL-6* interleukin 6, *TNFα* tumor necrosis factor alpha, *sTNFRα* soluble tumor necrosis factor receptor alpha, *sIL-2R* soluble interleukin 2 receptor, *oxLDL* oxidized low-density lipoprotein, *anti-oxLDL* anti-low-density lipoprotein antibodies, *MDRD* glomerular filtration

* Statistical significance

$$FG_{estimated} = (180 \times 0.0113[\text{serum creatinine}])^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if black ethnicity})$$

Serum CRP (mg/L) was determined by nephelometry using the analyzer BN-ProSpect (Dade Behring, GMBH, Marburg, Germany). IL-6 (pg/ml), TNFα (pg/mL) and sIL-2R (U/mL) were determined using automated chemiluminescent immunoassay with the analyzer Immulite 1(DPC, Los Angeles, CA, USA). Concentrations of sTNFRα (ng/mL), oxLDL (U/L) and anti-oxLDL (U/mL) were determined using ELISA (BKline, Mercodia and Inmunodiagnostika GMBH, respectively).

Table 4 Univariate logistic regression analysis of risk factors for mortality in kidney transplant patients

	Mortality		
	OR	CI [95%]	*p*
Age (years)	1.09	1.04–1.14	<0.0001*
Months in dialysis	1.00	0.98–1.02	0.870
DM pre-KT (yes)	3.60	1.45–8.94	0.006*
CVD pre-KT (yes)	1.53	0.52–4.47	0.435
Hemoglobin (g/dL)	0.7	0.58–0.94	0.015
Albumin (g/L)	0.89	0.81–0.97)	0.09
MDRD (mL/min/1.73 m^2)	0.93	0.89–0.97	<0.0001*
Markers of inflammation			
CRP (P75: 8.13 mg/L)	2.15	0.86–5.37	0.100
IL-6 (P75: 7.10 pg/mL)	2.86	1.14–7.17	0.025*
TNFα (P75: 19.50 pg/mL)	1.88	0.73–4.84	0.188
sTNFRα (P75: 5.32 ng/mL)	2.72	1.10–6.74	0.030*
sIL-2R (P75: 1321U/mL)	2.32	0.92–5.88	0.074
Markers of oxidation			
oxLDL (P75: 91.21 U/L)	1.36	0.52–3.53	0.533
Anti-oxLDL (P75: 3781 U/mL)	2.73	1.11–6.75	0.029*

DM diabetes mellitus, *CVD* cardiovascular disease, *MDRD* glomerular filtration, *CRP* c-reactive protein, *IL-6* interleukin 6, *TNFα* tumor necrosis factor alpha, *sTNFRα* soluble tumor necrosis factor receptor alpha, *sIL-2R* soluble interleukin 2 receptor, *oxLDL* oxidized low-density lipoprotein, *anti-oxLDL* anti-low-density lipoprotein antibodies

* Statistical analysis

All of the data were analyzed using the statistical program SPSS V 15.0. Initially, the type of distribution of the variables was studied using the Kolmogorov–Smirnov test. The means of the variables analyzed pre-KT and post-KT were compared using the Wilcoxon test for paired samples if the distribution was nonparametric and student's t test for paired data if the distribution was normal. The comparison of means between patients who were alive and those who had died was carried out using the nonparametric Mann–Whitney U test.

To study the association between two categorical variables, we used the Chi-squared test. To evaluate the variables predicting mortality, we used a logistic regression model using a confidence interval for the odds ratio of 95%. The goodness for fit for the multivariate logistic regression model was determined using the Hosmer and Lemeshow test. Statistical significance was considered when $p < 0.05$. The survival analysis was carried out using the Kaplan–Meier estimator. To evaluate the variables predictive of survival, we used a Cox proportional hazards regression model with a confidence interval for the hazard ratio of 95%.

Table 5 Multivariate logistic regression analysis of the risk factors for mortality in kidney transplant patients

	Mortality		
	OR	CI [95%]	*p*
Age (years)	1.124	1.03–1.13	0.012*
MDRD (mL/min/1.73 m^2)	0.916	0.86–0.95	0.013*
Markers of oxidation			
Anti-oxLDL (P75: 3781 U/mL)	5.19	1.78–17.60	0.026*

Dependent variable: mortality; Covariables: age, hypertension, diabetes mellitus, cardiovascular disease, hemoglobin, albumin, MDRD, hemoglobin, albumin, IL6, sTNFαR, anti-oxLDL P75

MDRD glomerular filtration, *anti-oxLDL* anti-low-density lipoprotein antibodies

* Statistical significance

Results

We studied 196 patients (67.9% ($n = 133$) men, 32.1% ($n = 63$) women). The mean age was 51.89 ± 12.54 years. The mean time in dialysis was 23 (12–38) months, 21% ($n = 41$) were diabetic and 14.8% ($n = 29$) had pre-KT CVD.

The number of patients who had died by January 2012 represented 12.8% ($n = 25$) of the total number of patients who underwent KT, with the main causes of mortality being cancer (3.1%), CVD (2.6%), infections (1.5 %) and other causes (3.1%).

Evolution of the markers pre- and post-KT

Of the markers of inflammation analyzed, we observed that CRP ($p = 0.006$), IL-6 ($p = 0.037$), TNFα ($p < 0.0001$), sTNFRα ($p < 0.0001$) and sIL-2R ($p < 0.0001$) decreased significantly post-KT, while oxLDL increased significantly ($p < 0.0001$) and also the total cholesterol ($p = 0.0001$) and the LDL cholesterol ($p < 0.0001$). Regarding anti-oxLDL, there were no statically significant differences observed between pre-KT and post-KT ($p < 0.095$). The serum albumin ($p = 0.008$) and the glomerular filtration ($p = 0.009$) increase significantly. The median post-KT GF was 43.89 (35.16–53.94) mL/min/1.73 m^2 (Table 2).

Relationship between post-KT markers and mortality

Pre-transplant markers studied do not correlate with mortality in transplant patients. However, of the markers of inflammation analyzed three months after KT, we observed that IL-6 ($p = 0.011$) and sTNFRα ($p = 0.006$) were significantly more elevated in patients who had died. Also,

Table 6 Multivariate Cox proportional hazards model for survival in kidney transplant patients

	Mortality		
	HR	CI [95%]	*p*
Age (years)	1.10	1.02–1.20	0.021*
MDRD (mL/min/1.73 m^2)	0.93	0.86–0.99	0.045*
Markers inflammation:			
Il-6 (P75:7.10 pg/mL)	2.45	1.12–9.86	0.027
Markers of oxidation:			
oxLDL (P75: 91.21 U/L)	19.85	2.94–134.19	0.002*
Anti-oxLDL (P75: 3781U/mL)	9.56	2.13–42.89	0.003*

MDRD glomerular filtration, *IL-6* interleukin-6, *oxLDL* oxidized low-density lipoprotein, *anti-oxLDL* anti-low-density lipoprotein antibodies

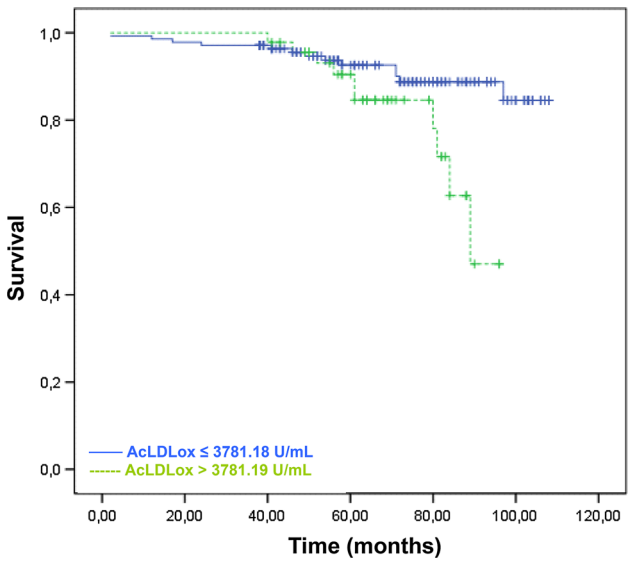

Fig. 1 Kaplan–Meier survival curves with anti-oxLDL (P75) in serum at 3 months after KT. *anti-oxLDL* anti-low-density lipoprotein antibodies. Equivalence and statistical significance determined using log-rank test, $p = 0.016$

the age was significantly higher in patients who died (60.29 ± 8.96 vs. 50.91 ± 12.61 years; $p < 0.0001$). The hemoglobin ($p = 0.012$), albumin ($p = 0.007$) and the GF 3 months post-KT were significantly lower in patients who had died ($p < 0.0001$). With respect to the markers of lipid peroxidation, there were no differences between patients who were alive and those who had died (Table 3). On the other hand, we observed that 21.7% of the patients with anti-oxLDL greater than P_{75} (P_{75} = 3.781 U/mL) died, compared with 9.2% who died with anti-oxLDL less than this percentile (Chi-squared = 5.04; $p = 0.028$).

The univariate analysis evaluated the markers of inflammation and oxidation three months after KT in relation to mortality as dependent variable (Table 4) and also other variables related with mortality as age, hemoglobin, albumin, glomerular filtration (MDRD), DM pre-KT, HTA pre-KT, previous cardiovascular disease and presence of carotid plaques.

In the multivariate analysis, using as covariables, those variables that in the univariate analysis were statistically significant (Table 5), we observed that age ($p = 0.012$), GF ($p = 0.013$) and P_{75} of anti-oxLDL ($p = 0.026$) were independent markers of mortality.

Relationship between post-KT markers and survival

Figure 1 shows the survival curves for the kidney transplant patients in relation to the P_{75} of anti-oxLDL. Patients with a lower serum concentration of antibodies showed greater survival ($p = 0.016$).

The results obtained in the Cox proportional hazards regression model are highlighted in Table 6 and show that age ($p = 0.021$), MDRD ($p = 0.045$), P_{75} of oxLDL ($p = 0.002$) and P_{75} of anti-oxLDL ($p = 0.003$) were predictors of mortality.

Discussion

One of the objectives of this study was to evaluate whether KT could improve inflammation and oxidative stress, and to what extent, in kidney transplant patients. The results obtained show that following KT, there is a significant decrease in circulating levels of proinflammatory cytokines such as CRP, IL-6 or TNFα. These results are in agreement with what has been reported to date in the literature [8, 28, 29, 31].

There is some controversy surrounding the effect of KT on markers of lipid oxidative stress. Some studies have shown that the re-establishment of renal function improves the oxidative stress associated with uremia [8, 27, 29]. However, other studies have reported that patients who undergo KT have a pattern of increased lipid peroxidation oxidative stress that would be offset by an increase in antioxidant mechanisms [32, 33]. Despite the fact that these mechanisms could counteract oxidative stress in KT patients, it is known that the resulting injury would accumulate during the cellular cycle, and the effect on DNA, proteins and lipids is key in the development of diseases such as cancer and atherosclerosis [34], which increases the risk of death in these patients. Nevertheless, in this study, we have only studied the lipid perioxidation, not the proteins or DNA oxidation.

The data obtained in this study show a significant increase in oxLDL three months post-KT. A possible explanation for this increase in the oxidative stress is that the

immunosuppressive treatment causes dyslipidemia post-transplant as evidenced by our results with increases in total cholesterol and LDL cholesterol and therefore an increase in the substrate for oxidation. In the other, Cofan et al. [35] and Bakar et al. [36] have shown that treatment with cyclosporine and tacrolimus increase oxidation of LDL in vitro compared with healthy subjects. Ghanem et al. [37] also observed an increase in oxidation of LDL in vivo and in vitro in patients who underwent KT, although the mechanism by which immunosuppressive treatment exerts this effect is still unknown.

Owing to the increase in oxLDL at 3 months post-KT, an increase in anti-oxLDL as a compensatory mechanism would be expected. However, the data do not show differences in the serum concentrations of these antibodies 3 months post-KT. A possible explanation could be that, owing to the restoration of renal function, there would be a greater clearance of these antibodies and immune complexes. Another possible explanation would be the direct [38, 39] or indirect [40] influence of immunosuppressive treatment on the production of these antibodies.

In the present study, we observed that patients who died not only had a significantly lower GF, but also an elevation in all of the proinflammatory cytokines analyzed, with significant increases in IL-6 and sTNFRα. In the multivariate cox proportional hazards regression model, we observed that patients with serum concentrations of IL-6 above 7.1 pg/mL had a relative risk ratio of death of 2.45. IL-6 is a pleiotropic cytokine with a large variety of biologic functions in the regulation of the immune system, hematopoiesis, inflammation and oncogenesis [41], exerting diverse effects on proliferation, differentiation and cell maturation according to the nature of the target cell [42]. It has also been found to be a mediator of inflammation in atherosclerosis [43] and vascular disease. sTNFRα is secreted in response to an increase in TNFα. Experimental data show that sTNFRα contributes to the pathogenesis of atherosclerosis and vascular disease [44]. Other authors, however, have shown a relationship between elevated levels of TNFα and its receptor and the risk of developing endometrial cancer [45]. This suggests an implication of these molecules in the development of CVD and cancer, and as such, could explain why the main causes of death in the study population were cancer and CVD.

We previously stated that among the risk factors associated with greater mortality in KT patients is the increase in oxidative stress that accompanies a decrease in GF. As a marker of oxidative stress, oxLDL has been associated with a poor prognosis in coronary heart disease associated with kidney transplantation [21]. On the other hand, some authors have shown the relationship between this molecule and risks of several types of cancer [22, 23]. In this study, the Cox proportional hazards model revealed an increase in oxLDL, which in concentrations over 91.21 mg/L represented a 19.85 relative risk rate of death.

The presence of specific antibodies against oxLDL have been suggested to be a useful marker for a higher lipid oxidative stress [24, 26], but there is controversy as to whether these antibodies play a protective role or a pathogenic one [46]. Some authors have found an inverse relationship between anti-oxLDL levels and the development of certain types of cancer [47] or the development of cardiovascular disease [48]. In a previous study by our group [49], we found that, in patients on hemodialysis, elevated levels of anti-oxLDL would be predictors of risk of cardiovascular death. Following this same line of work, the current data in KT patients reflect that serum levels of anti-oxLDL greater than 3.781 U/ml not only increase in 9.56 the probability of death, but are also significantly associated with an earlier death in KT patients, reaffirming the pathogenic effect of these antibodies.

One of the limitations of this study is the small number of patients who died in terms of distribution by causes of death. For this reason, it was not possible to evaluate clinical factors and markers of inflammation and oxidation with distinct causes of death, such as cancer, CVD and infections. This is one of the possible explanations for which classic pre-KT risk factors such as diabetes or CVD did not yield statistically significant results in the multivariate analysis for global mortality.

In summary, the results obtained validate, for the most part, the objectives described in the beginning of the study: KT results in an evident improvement in inflammation, although the same expectations were not achieved for oxidative stress. Strategies to improve these "potentially correctible" factors such as MDRD and anti-oxLDL, which are independent risk factors for mortality, could improve patient survival and lower morbidity and mortality in KT.

Compliance with ethical standards

Conflict of interest Dr. Eva Iglesias, Dr. Laura Cañas, Dr. María Cruz Pastor, Dr. Jaume Barallat, Dr. Javier Juega, Dr. Ioana Bancu, Dr. Ricardo Lauzurica declare that they have no conflict of interest.

Human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

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