

The impact of donor age on the results of renal transplantation

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Abstract

Background. The use of elderly donors is becoming more frequent. An increase in the donor's age is associated with a greater incidence of delayed graft function (DGF), chronic allograft nephropathy (CAN) and worse graft survival. Poor renal graft function is a risk factor for cardiovascular (CV) complications and, finally, for mortality of the patients.

Methods. A total of 3365 adult patients transplanted in 1990 ($n = 824$), 1994 ($n = 1075$) and 1998 ($n = 1466$) with a functioning graft after the first year were included. The impact of donor age on renal function, DGF, acute rejection and other clinical factors was evaluated according to two donor and recipient age categories: young (<60 years old) and elderly (≥ 60 years old). Additionally, donor age was categorized by decades for the analysis of patient and graft survival, acute rejection and CV mortality.

Results. Donor mean age significantly increased during the three transplantation periods. A total of 478 out of 3365 donors were older than 60 years. Elderly donors showed an increased risk of DGF (38.9 vs 28.8%) and CAN (56.8 vs 46.2%). Mean serum creatinine at 3 and 12 months and proteinuria were significantly higher in the old donor group. Incidence and severity of acute rejection were similar in both groups. Graft and patient survival were significantly lower in the old donor group. Also, risk of mortality due to CV events was also significantly higher. A linear increase in risk of graft loss, patient death or CV mortality was observed when donor age was divided into 10 year increase subsets.

Conclusions. Donor age is a strong predictor of CAN and graft loss. Patient survival is also affected by

donor age, particularly by a higher risk of CV mortality.

Keywords: cardiovascular risk; donor age; kidney transplant; survival

Introduction

Use of elderly donors has been progressively increasing in recent years. In Spain, where cadaver donor transplants predominate, the increase in donor age has been especially significant [1]. Many studies show that elderly donors more frequently present risk factors for the development of chronic allograft nephropathy (CAN): have a higher incidence of delayed renal function, susceptibility to anti-calceineurin caused nephrotoxicity, arterial hypertension and loss of functional renal reserve [2–7]. An increased risk of acute rejection has also been described [8–10] and the fact that elderly donor kidneys are more immunogenic has been suggested among the possible causes of this observation [11]. All these factors associated with the elderly age of the donors contribute either individually or synergistically to the fact that elderly donors offer worse long-term renal function [12,13].

It has recently been described that deterioration of renal graft function is associated with an increase in risk of CV complications [14]. CV complications represent the first cause of death in recipients with a long-term functioning graft. It could be postulated that the advanced age of the donors could also contribute to this greater mortality.

This present study analyses the influence of the advanced age of the donor as an independent risk factor on the time-course of renal function, patient and graft survival and CV mortality.

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Subjects and methods

Donor and recipient age was divided into two categories: young (<60 years old) and elderly (\geq 60 years old).

The distribution of donor and recipient clinical characteristics was compared according to donor age category and transplantation year: donor and recipient age, sex, bodyweight and HCV and HBV serologies; recipient height, BMI, end-stage renal disease aetiology, first and second transplants, HLA antibodies, HLA mismatches, smoking, type of dialysis (HD or PD) and time on dialysis; donor cause of death, donor source (living or cadaveric), non-heart beating donors, cause of brain death (trauma or stroke).

In this study, CAN was defined using histological criteria (tubular atrophy, interstitial fibrosis, fibrous intimal thickening in the arteries, and a variety of glomerular lesions) or clinical criteria (a slowly progressive graft dysfunction ultimately leading to chronic renal failure in the absence of a particular reason).

When analysing graft and patient survival, acute rejection and CV mortality, donor age was categorized in a different way: <20; 20–30; 30–40; 40–50; 50–60; 60–70; >70 years old, respectively.

Kruskall–Wallis and chi-square tests were employed for the comparison of the different study endpoints between donor age groups.

Cox's proportional hazards regression was used to analyse graft and patient survival and time to first acute rejection. A backward procedure was used to exclude those not showing a significant effect. Survival models were based on variables available at the moment of transplantation, so that the models obtained could be used to predict a prognosis at that moment.

Simple linear regression was employed for analysing creatinine predictors at the first year, without follow-up variables.

Results

Increase in donor age over one decade

Donors were older than 60 years in 478 (14.8%) of the 3365 transplants analysed. Prevalence of elderly donor age progressively increased in the three periods studied: 4.8% in 1990, 14.1% in 1994 and 20.8% in 1998. Elderly donors presented a somewhat lower predominance of males (57.5%) than young donors (67.2%) ($P < 0.001$), more frequent stroke as cause of death (78.1 vs 41.1%, $P < 0.001$), greater age average of the recipients (53.7 ± 12.3 vs 44.4 ± 12.5 years, $P = 0.0223$), lower proportion of male recipients (58.8 vs 63.8%, $P = 0.0369$), and of retransplantations (9.0 vs 13.2%, $P = 0.011$). Other clinical factors of the donor, such as organ origin (living or cadaveric), non-heart beating donors, HBV, HCV, or body weight did not show significant differences in relationship to the age group of the donors. In the same way, there were also no differences between young and elderly donors regarding the characteristics of the recipients, such as: bodyweight and height, peak panel reactive antibodies (PRA), HBV, HCV, smoking or previous time on dialysis.

Cold ischaemia time (19.7 vs 19.5 h) and number of HLA mismatches (3.1 vs 3.0) were similar in elderly and young donors, respectively. Differences were also not observed in the type of immunosuppressive drugs used over time in relationship to the donor age.

Impact of donor age on the post-transplantation clinical course

The incidence of delayed graft function (DGF) decreased during the three periods studied but was more frequent in elderly donors (Table 1). On the contrary,

Table 1. Post-transplantation renal function according to donor-age groups

	1990	1994	1998	Overall
% DGF				
Donor age (<60)	30.6	29.8	26.9	28.8
Donor age (\geq 60)	31.4	40.1	39.3	38.9
<i>P</i>	0.9133	0.0158	<0.0001	<0.0001
Creatinine at 3 months (mg/dl)				
Donor age (<60)	1.57 \pm 0.64	1.66 \pm 0.70	1.57 \pm 0.60	1.60 \pm 0.65
Donor age (\geq 60)	1.87 \pm 0.59	2.12 \pm 0.85	2.02 \pm 0.75	2.04 \pm 0.77
<i>P</i>	0.0002	<0.0001	<0.0001	<0.0001
Creatinine at 1 year (mg/dl)				
Donor age (<60)	1.61 \pm 0.73	1.68 \pm 0.75	1.53 \pm 0.57	1.60 \pm 0.68
Donor age (\geq 60)	2.19 \pm 1.20	2.13 \pm 0.74	2.01 \pm 0.74	2.06 \pm 0.79
<i>P</i>	0.0004	<0.0001	<0.0001	<0.0001
Proteinuria at 3 months (g/24 h)				
Donor age (<60)	0.25 \pm 0.59	0.31 \pm 0.92	0.29 \pm 0.70	0.29 \pm 0.75
Donor age (\geq 60)	0.48 \pm 0.85	0.35 \pm 0.66	0.36 \pm 0.47	0.36 \pm 0.56
<i>P</i>	0.0202	0.0414	<0.0001	<0.0001
Proteinuria at 1 year (g/24 h)				
Donor age (<60)	0.35 \pm 0.98	0.33 \pm 0.94	0.30 \pm 0.70	0.32 \pm 0.86
Donor age (\geq 60)	0.95 \pm 1.91	0.40 \pm 0.69	0.40 \pm 0.69	0.44 \pm 0.83
<i>P</i>	0.0003	0.0098	<0.0001	<0.0001

P-values obtained from chi-square tests for categorical variables, with the exact *P*-value calculated using the Monte Carlo method when appropriate. For continuous variables, Kruskal–Wallis tests were employed.

donor's age did not affect the risk of acute rejection or its severity. It was also not possible to observe a different influence in relationship to CMV infection or in the development of surgical complications.

When the causes of transplant failure were studied, we observed that CAN was predominant in both groups (56.8% in elderly donors, 46.2% in young donors), without significant differences between both during the three periods analysed. The second cause of transplant failure is death of the patient with functioning graft (31.8% in elderly donors vs 33.3% in young donors). CV complications were the predominant cause of death with elderly donors (32.5%) and young donors (28.4%).

Impact of donor age on renal function

Elderly donors present significantly higher serum creatinine and proteinuria levels at 3 months and 1 year in the three periods (Table 1). Overall data show that the following factors were associated with an increase in mean serum creatinine: recipient gender (male), recipient age (<60 years), donor gender (female), donor age (>60 years) and donor cause of death (stroke). A more detailed analysis of the impact of donor age, by progressive increases of decades also shows a relationship between donor age and the mean increase of serum creatinine levels (Figure 1).

Graft and patient survival, and time to first acute rejection

Figure 2 shows the progressive impact of donor age on long-term graft survival. Similar results were obtained for patient survival (data not shown). Table 2 and Figures 3 and 4 provide the results of graft survival, patient survival and acute rejection multivariate analysis in terms of relative risk. Donor age had a significant effect on graft and patient survival, but not on the risk of acute rejection. A further analysis was performed in order to check whether the effect of donor age on graft and patient survival was linear: i.e. if there was a steady increase in risk for elder donors. Deviation from linearity was not found to be significant. Instead,

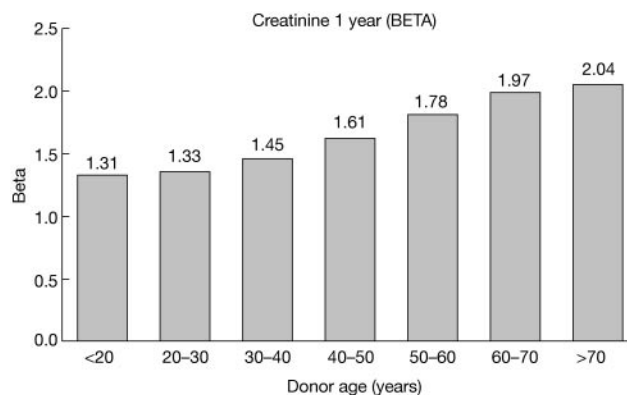


Fig. 1. Effect of donor age on serum creatinine.

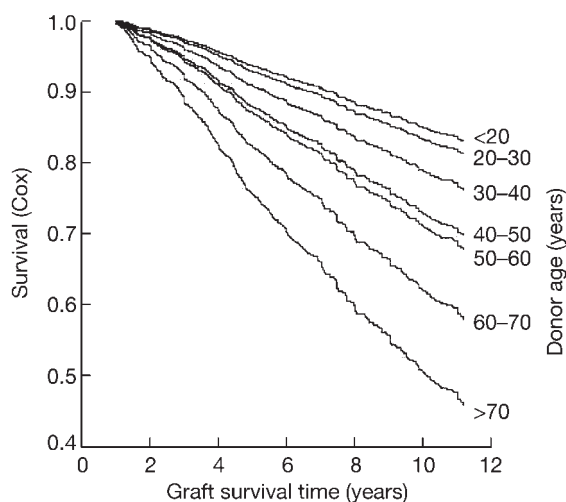


Fig. 2. Effect of donor age on long-term graft survival.

regardless of the actual donor age, each 10 year increase was associated with a similar increase of relative risk.

Cardiovascular mortality

As shown in Figure 3, donor age significantly predicted death due to CV disease. Although the influence of donor age on CV mortality was higher for recipients >60 years than for <60 years, no significant differences were found (Figure 5).

Discussion

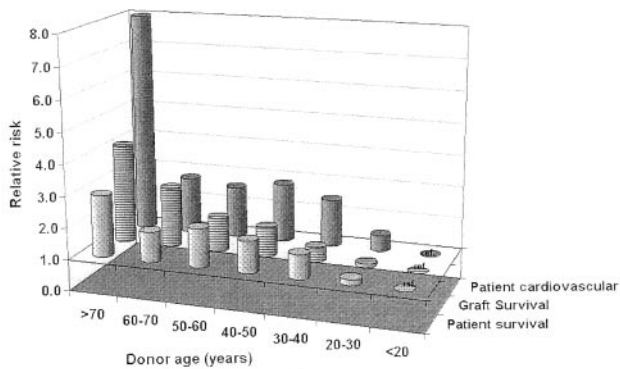
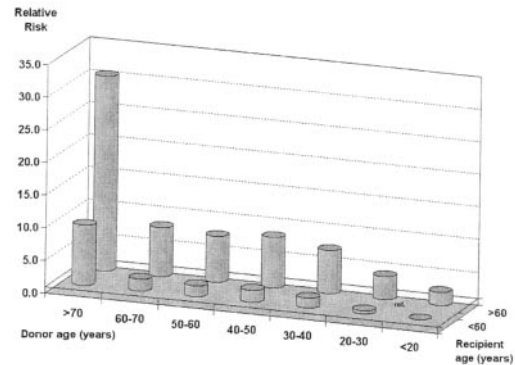
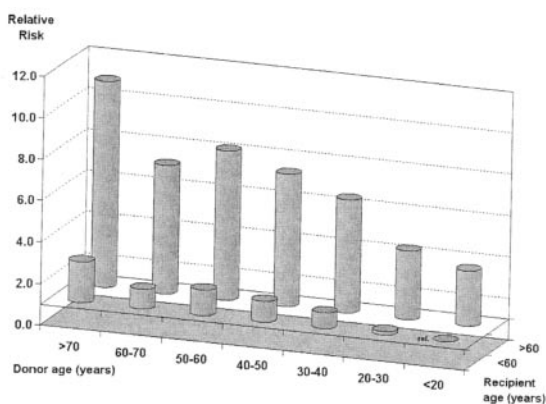
The present study, analyses the interaction between donor age and CAN. Progressive ageing of the cadaveric donors is one of the clinical aspects that has evolved most in recent years, and this is especially relevant in Spain, which is characterized by a high rate of donations of this type [1]. In the present study, it is observed that donor age has been significantly increasing over the years, up to the point that in 1998 more than 20% of the transplants came from donors over 60 years. Increase in donor age has been parallel to the age of the recipients and to the predominance of stroke compared with cranioencephalic trauma as cause of brain death.

In our study, CAN is the first cause of transplant failure in both the young as well as elderly donor group. However, several clinical factors that are classically associated with CAN appear to affect the two donor groups differently. One of them is DGF, which, as predictable, is more frequent in elderly donors. This finding agrees with that already published in another series and has great clinical relevance, since DGF has a negative prognostic value on graft survival [7]. In addition, the 3 month and 1 year serum creatinine values were significantly higher in the elderly donor group in the three periods studied, although renal function remained stable between 3 months and 1 year.

Table 2. Risk factors for acute rejection, graft and patient survival (multivariate analysis)

	Graft survival			Patient survival			Acute rejection		
	RR	95% CI	P	RR	95% CI	P	RR	95% CI	P
Recipient age (ref. '<60 years')	NS	NS	NS	3.680	(2.772, 4.885)	<0.0001	0.632	(0.512, 0.781)	<0.0001
Recipient HCV (ref. 'no')	1.507	(1.227, 1.851)	<0.0001	NS	NS	NS	NS	NS	NS
Donor age (ref. '<20 years')	1.000		<0.0001	1.000		0.0014	NS	NS	NS
Donor age (20–30 years)	1.119	(0.822, 1.523)	0.4754	1.172	(0.760, 1.808)	0.4728	NS	NS	NS
Donor age (30–40 years)	1.452	(1.063, 1.984)	0.0192	1.752	(1.153, 2.663)	0.0086	NS	NS	NS
Donor age (40–50 years)	1.921	(1.438, 2.565)	<0.0001	2.002	(1.331, 3.010)	0.0009	NS	NS	NS
Donor age (50–60 years)	2.074	(1.534, 2.805)	<0.0001	2.226	(1.453, 3.409)	0.0002	NS	NS	NS
Donor age (60–70 years)	2.895	(2.070, 4.048)	<0.0001	1.952	(1.191, 3.200)	0.0080	NS	NS	NS
Donor age (>70 years)	4.132	(2.011, 8.490)	0.0001	2.972	(1.175, 7.519)	0.0214	NS	NS	NS
Cause of death (ref. 'CET')	NS	NS	NS	NS	NS	NS	NS	NS	NS
Peak PRA (ref. '≤15%')	NS	NS	NS	NS	NS	NS	1.173	(1.009, 1.365)	0.0380
DGF (ref. 'no')	NS	NS	NS	NS	NS	NS	1.417	(1.233, 1.629)	<0.0001
Cytomegalovirus infection (ref. 'no')	NS	NS	NS	NS	NS	NS	1.260	(1.069, 1.487)	0.0060

These results were obtained via Cox's proportional hazards regression, adjusting for year of transplantation and centre effect. Significance level was 0.05 for all statistical tests. Donor age effect did not deviate significantly from linearity on CV mortality, neither for graft survival nor patient survival. Ref., reference.

**Fig. 3.** Relative risk associated with donor age (graft survival, patient survival and patient cardiovascular survival).**Fig. 5.** Risk of cardiovascular mortality according to donor and recipient age (multivariate analysis).**Fig. 4.** Risk of patient survival according to donor and recipient age (multivariate analysis).

Initial poor renal function is also associated with increased risk of CAN [15]. Worse initial renal function could be due to the fact that this was already present in the donor (in a more or less detectable way) [16] or, on the contrary, because the different noxae that affect a transplant (ischaemia, high blood pressure, diabetes,

drugs, etc.) would accelerate the physiological process of renal ageing [17], making elderly donors more susceptible.

It is interesting that the cold ischaemia time, HLA mismatching or type of immunosuppression used do not differ from those observed in the young donors. Although each transplant centre probably adopts its own strategies, the data obtained in the present study suggest that the progressive acceptance of older donors has not been accompanied by an effort to minimize other clinical factors, such as the ischaemia-reperfusion syndrome or nephrotoxicity, that could contribute to an improvement of the initial renal function.

The use of living donors makes it possible to prevent ischaemic lesions. The age effect in living donors seems to be less important than in cadaveric donors [18]. In our study, the low number of living donor transplants prevents us from analysing this aspect.

The incidence and severity of the acute rejections in the older donors have been similar to that observed with younger donors. Both groups of patients have been treated with the same immunosuppressive drugs

and do not present differences in HLA mismatching. Some authors suggest that the elderly donor kidneys are more immunogenic and that it is a mistake to use less potent immunosuppressive regimes, despite the lower immunological response capacity of the elderly patients, in whom these types of kidneys are generally used [11].

In these series, donor age had a marked negative prognostic value on long-term graft survival. It is interesting to observe that when the donor age is subdivided into 10 year increases, we have been able to show that the deterioration in graft survival increases linearly. This detrimental effect of age is independent of recipient age, HCV serology of the patient, cause of donor death, presence of DGF or CMV infection. Most authors recognize donor age as an independent risk factor of graft survival [7,19]. Controversy exists on the potential benefit of selecting recipients with age-matched criteria (old for old) [19,20].

One result that is surprising to a certain point has been that increase in donor age influences long-term patient mortality. As occurs in the graft survival, survival analysis by increases of 10 years of donor age makes it possible to observe that the risk increase is linear. The greater mortality associated with donor age is independent of the recipient age. It is possible that part of the explanation for this observation may be found in the increase of CV caused mortality in relationship to the donor age that we have been able to observe in our study. The risk increase is linear here again when the age increase of the donors is subdivided into decades. It is worthy of note that the risk of CV mortality also affects the group of young patients. Our results would agree with those recently published by Meier-Kriesche *et al.* [14], who analysed the data of 58 900 patients of the United States Renal Data System (USRDS) and observed that there is a close relationship between CV mortality and donor age. Other authors have already previously suggested that there exists a close relationship between the degree of deterioration of the renal function and CV events [5]. In our study, as in others, the advanced age of the donors is associated with worse renal function.

In conclusion, we have observed that donor age has a clear influence on the development of CAN, on graft survival, on patient survival and on mortality risk of CV origin. These data show the need to search for new alternatives for the clinical management of elderly donors: minimization of ischaemia times, use of drugs with sufficient immunosuppressive potency lacking nephrotoxic effects, primary prevention strategies of the CV risk factors, etc.

Conflict of interest statement. None declared.

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