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Original Article

Age-matching in renal transplantation

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Abstract

Background. So far, the combined influence of donor age and recipient age on renal allograft survival has not been investigated sufficiently. In this retrospective single-centre study we analysed whether the influence of donor age and recipient age on renal allograft survival are dependent on each other.

Methods. Data from 1269 cadaveric renal allograft transplantations were evaluated. Paediatric donors (<15 years) and paediatric recipients (<15 years) were excluded. Donors and recipients were divided by age: young donors (yd, ⩽55 years, $n=1093$), old donors (od, >55 years, $n=176$), young recipients (yr, ⩽55 years, $n=1058$), and old recipients (or, >55 years, $n=211$). Functional and actual long-term graft survival (8 years) within the four resulting groups was determined: yd/yr ($n=926$), yd/or ($n=167$), od/yr ($n=132$), and od/or ($n=44$).

Results. Univariate analysis showed that long-term graft survival of both, kidneys from young donors (functional, 66.1 *vs* 52.2%, $P=0.004$; actual, 53.3 *vs* 46.2%, $P=0.065$) and kidneys from old donors (functional, 68.7 *vs* 22.5%, $P=0.07$; actual, 57.1 *vs* 20.8%, $P=0.15$) was better in old recipients as compared to young recipients. Multivariate regression analysis revealed that actual graft survival of kidneys from old donors was significantly reduced in young recipients (od/yr) as compared to all other groups ($P=0.001$; RR, 1.97; 95% CI, 1.32–2.94). In this group of patients, graft loss was mainly due to acute (33.7%) and chronic (24.0%) rejection.

Conclusion. Transplantation of kidneys from 'old' donors into 'young' recipients should be avoided, and these kidneys should be given to age-matched recipients.

Keywords: age-matching; graft survival; renal transplantation

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Introduction

Expanding inclusion criteria for renal allograft recipients have generated an increasing number of patients waiting for kidney transplantation. In an attempt to close the widening gap between supply and demand, transplant physicians nowadays accept organs from older donors that might have been considered inappropriate in the past [1]. As a consequence, the question has become of growing importance, to what extent donor age and recipient age influence long-term outcome after renal transplantation. The influence of donor age and recipient age on renal allograft survival has been investigated in numerous studies. Meanwhile, it is well established that graft survival of kidneys from old donors (>50–60 years) is significantly reduced as compared to kidneys from younger donors [2–9]. Concerning recipient age, graft survival has been shown to be equal in old recipients and in young recipients [8,10,11]. Unfortunately, the influence of donor age and recipient age on renal allograft survival was analysed separately from each other in most of these studies. So far, there are only a few investigations in which the combined influence of donor age and recipient age on renal allograft survival was analysed [3,12–16]. In addition, the results of these studies are controversial. As there is an ongoing discussion about the question of whether the influence of donor age and recipient age on long-term renal allograft survival are dependent on each other, we performed the following study.

Subjects and methods

Patients

Data from 1269 cadaveric renal allograft recipients transplanted between 1979 and 1989 at the University of Erlangen-Nuremberg were analysed, in order to have a complete 8-year follow-up for all patients. Paediatric donors (<15 years) and paediatric recipients (<15 years) were excluded.

Only patients receiving standard double immunosuppression were included. Patients transplanted between 1979 and

1984 ($n=567$) received methylprednisolone (MP) and azathioprine (AZA), patients transplanted between 1984 and 1989 ($n=702$) received MP and cyclosporin A (CsA). MP was given as a bolus of 250 mg i.v. before transplantation, 100 mg on day 1, 60 mg for the next 3 days, and 40 mg within the first week. Thereafter, the drug was tapered down in a stepwise procedure to 4 mg/day, 6 months after transplantation. AZA was adjusted to the white blood cell count to range between 4000 and 8000 cells/μl (50–150 mg daily). CsA was adjusted according to whole-blood monoclonal trough levels between 100–150 ng/ml (TDX, Abbott Co., Wiesbaden, Germany).

Both donors and recipients were divided into two different groups by age: young donors (yd, $\leqslant 55$ years, $n=1093$); old donors (od, >55 years, $n=176$); young recipients (yr, $\leqslant 55$ years, $n=1058$); and old recipients (or, >55 years, $n=211$). Based on this regimen, four groups were generated, representing the four possible age-match combinations: group 1 = yd/yr ($n=926$), group 2 = yd/or ($n=167$), group 3 = od/yr ($n=132$), and group 4 = od/or ($n=44$).

Statistical analysis

Renal allograft survival was defined as the interval between transplantation and either resumption of dialysis or retransplantation. Both actual graft survival and functional graft survival were analysed. Death with functioning graft was considered as allograft failure in the analysis of actual graft survival, but as a censoring event in the analysis of functional graft survival. Renal allograft survival was analysed according to Kaplan–Meier plots with a log-rank test. In order to assess the unadjusted relationship of other relevant predictors for actual graft survival, an univariate regression analysis was performed. In this analysis the following parameters were included: the number of prior transplants, the percentage of panel reactive antibodies, HLA match, CMV match, cold ischaemia time, warm ischaemia time, primary graft function, diabetes mellitus, and the type of immunosuppression. All variables that were predictive ($P<0.20$) in the univariate analysis were candidates for subsequent multivariate analysis. Controlling for these relevant predictors, actual graft survival according to the age-match between donor and recipient was analysed by multivariate, stepwise Cox proportional hazards regression analysis. All data are expressed as mean $\pm$ standard deviation. A probability of less than 0.05 was considered as statistically significant.

Results

Mean donor age was 37.2 ± 14.9 years (median 36.2, minimum 15.0, maximum 74.6 years), mean recipient age was 42.4 ± 12.3 years (median 43.7, minimum 15.1, maximum 72.7 years). The age difference between donors and recipients (donor age–recipient age) was -6.2 ± 15.6 years in group 1, -23.7 ± 11.3 years in group 2, 22.3 ± 10.8 years in group 3, and 2.6 ± 6.5 years in group 4. At any time-point, functional renal allograft survival was best in group 4 (8 years, 68.7%) and in group 2 (8 years, 66.1%). In contrast, the lowest functional graft survival was found in group 3 (8 years, 22.5%). Functional graft survival of kidneys from young donors was significantly better in old recipients (group 2) as compared to young recipients (group 1) (8 years, 66.1 *vs* 52.2%, $P=0.004$). Concerning kidneys from old donors, there was a statistically non-significant trend towards an improved functional graft survival in old recipients (group 4) as compared to young recipients (group 3) (8 years, 68.7 *vs* 22.5%, $P=0.07$).

Actual graft survival according to Kaplan–Meier is shown in Figure 1. Again, the best graft survival was found in group 4 (8 years, 57.1%) and in group 2 (8 years, 53.3%). As before, the lowest graft survival was found in group 3 (8 years, 20.8%). Concerning kidneys from young donors, there was a statistically non-significant trend towards an improved actual graft survival in old recipients (group 2) as compared to young recipients (group 1) (8 years, 53.3 *vs* 46.2%, $P=0.065$). Concerning kidneys from old donors, there was a statistically non-significant trend towards an improved graft survival in old recipients (group 4) as compared to young recipients (group 3) (8 years, 57.1 *vs* 20.8%, $P=0.15$).

The relevant patient characteristics of the four patient groups are shown in Table 1. In order to evaluate the unadjusted relationship of each of these variables with regard to actual graft survival, an univariate regression analysis was performed. From this analysis it turned out that prior transplantation, the percentage of panel reactive antibodies, CMV match, cold ischaemia time, primary graft function, diabetes mellitus, and maintenance immunosuppression were predictive for renal allograft survival ($P<0.20$), whereas HLA match and warm ischaemia time were not ($P>0.20$). To further evaluate these relevant predictors, a multivariate, stepwise Cox proportional hazards regression analysis was performed. This analysis revealed that actual renal allograft survival was significantly influenced by age-match, prior transplantation, cold ischaemia time, and the type of maintenance immunosuppression (Table 2). Subdivision of both, donors and recipients into three groups (young, 15–39 years; medium, 40–55 years; old, >55 years)

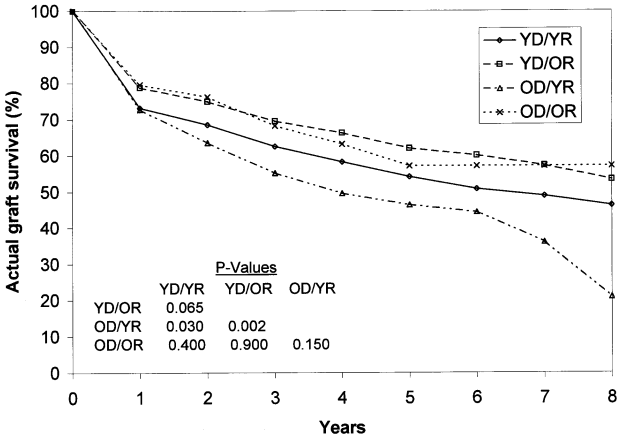

Fig. 1. The influence of age-match on actual graft survival (Kaplan–Meier plot with a log-rank test). YD, young donors ($\leqslant 55$ years); OD, old donors (>55 years); YR, young recipients ($\leqslant 55$ years); OR, old recipients (>55 years).

Table 1. Patient characteristics according to the age match

Characteristic	YD/YR ($n=926$)	YD/OR ($n=167$)	OD/YR ($n=132$)	OD/OR ($n=44$)
Donor age: mean/median (years)	32.9/31.9	35.5/35.3	60.9/60.2	63.0/61.2
Recipient age: mean/median (years)	39.1/41.0	59.2/58.4	38.6/40.8	60.4/59.5
Patients $\geqslant 2$ transplants (%)	14.5	10.8	20.5	9.1
PRA (%)	5.6 ± 15.8	2.5 ± 10.6	2.9 ± 9.2	0.5 ± 2.2
HLA mismatches (n)	2.5 ± 1.0	2.6 ± 1.2	2.4 ± 1.0	2.5 ± 1.2
CMV D+/R− (%)	15.0	19.8	24.2	22.7
Cold ischaemia time (h)	25.3 ± 7.1	23.3 ± 6.5	24.5 ± 7.7	21.4 ± 7.3
Warm ischaemia time (min)	37.8 ± 11.9	35.7 ± 11.4	36.4 ± 11.7	36.2 ± 11.0
Primary graft function (%)	23.1	41.3	30.9	36.4
Diabetes mellitus (%)	3.8	7.2	5.3	13.6
Immunosuppression: MP+CsA (%)	53.2	62.0	59.1	64.1

PRA, panel reactive antibodies; MP, methylprednisolone; CsA, cyclosporin A.

Table 2. Stepwise multivariate regression analysis

Characteristic	*P* value	RR	95% CI
Age-match:			
yd/or *vs* yd/yr	0.94	1.02	0.66–1.58
od/yr *vs* yd/yr	0.001	1.97	1.32–2.94
od/or *vs* yd/yr	0.80	0.90	0.39–2.05
Prior transplant (any *vs* none)	0.02	1.51	1.06–2.16
PRA (>0 *vs* 0%)	0.27	0.83	0.61–1.15
CMV D+/R− (yes *vs* no)	0.07	1.32	0.98–1.75
Cold ischaemia time (>24 h *vs* <24 h)	0.04	1.32	1.01–1.75
Primary graft function (no *vs* yes)	0.15	1.27	0.92–1.72
Diabetes mellitus (yes *vs* no)	0.06	1.82	0.97–3.39
Immunosuppression (MP+AZA *vs* MP+CsA)	0.001	3.33	2.50–4.35

RR, relative risk; CI, confidence interval; PRA, panel reactive antibodies; MP, methylprednisolone; AZA, azathioprine; CsA, cyclosporin A.

provided equivalent results. Compared to young recipients, who had received kidneys from young donors (yd/yr), graft survival was significantly reduced in the following two groups: od/yr (RR, 1.86; 95% CI, 1.18–2.91; $P=0.007$) and old donor/medium recipient (RR, 2.11; 95% CI, 1.35–3.30; $P=0.001$).

The reasons for graft failure were influenced by both, donor age and recipient age (Table 3). Concerning donor age, the incidence of graft loss due to acute rejection episodes and arterial occlusion was higher in kidneys from old donors as compared to kidneys from young donors. Concerning recipient age, the incidence of graft loss due to acute and chronic rejection was higher in young recipients, whereas the incidence of graft loss due to arterial occlusion and death with functioning graft was higher in old recipients. In young recipients who had received kidneys from old donors (group 3), the incidence of graft loss due to acute and chronic rejection was highest as compared to all other groups.

Table 3. Reasons for graft failure according to the age match (%)

Patients	YD/YR ($n=498/926$)	YD/OR ($n=78/167$)	OD/YR ($n=104/132$)	OD/OR ($n=19/44$)
Acute.rejection	29.9	10.3	33.7	15.8
Chronic rejection	14.1	11.5	24.0	10.5
Cyclosporin toxicity	0.4	0	1.0	0
Never-functioning kidney	0.4	1.3	1.0	5.3
Arterial occlusion	4.8	9.0	6.7	15.8
Venous thrombosis	2.8	3.9	0	0
Bleeding/rupture	2.0	3.9	1.9	5.3
Infection	0.2	0	1.0	0
Glomerulonephritis	2.4	2.6	3.9	0
Interstitial Nephritis	0.2	0	0	5.3
Death with functioning graft	11.2	26.9	1.9	26.2
Unknown	31.6	30.6	24.9	15.8

Discussion

The influence of donor age [2–9] and recipient age [2,8,10,11] on renal allograft survival is well described. However, the question whether their influence on renal allograft survival is dependent on each other, is still not sufficiently answered. The results of the few studies in which this question was addressed are controversial [3,12–16]. In 1990, Donnelly *et al.* observed that the detrimental effect of using organs from donors >50 years old can be offset by ensuring the recipient is not more than 5 years younger than the donor [12]. Unfortunately, this study was limited by the small number of cases included ($n=141$). In four following studies such a dependency could not be confirmed [3,14–16]. Investigating 397 consecutive first cadaver renal transplants in adult patients, Newstead and Dyer [14] found that 1-, and 3-year graft survival of donor kidneys within 5 years of the recipient's age was not different from those with an age difference of more than 5 years. Pirsch *et al.* [15] described similar 1- and 3-year graft survival rates when donors were >30 years younger, 6–29 years younger, within 5 years of age, and >5 years older than recipients. Similarly, Morales *et al.* [16] could not detect a difference in 2-year graft survival between donors more than 5 years younger than recipients and donors more than 5 years older, nor was there a difference when the age disparity was 10 or 15 years. Investigating more than 30 000 cadaveric kidney transplants, Alexander *et al.* [3] confirmed that the impact of both donor age and recipient age on the risk of graft failure were independent of one another up to 2 years after transplantation. In 1995, Cecka and Terasaki [13] reported that functional graft survival of kidneys from old donors (>60 years) was better in old recipients (>60 years), as compared to all other age groups. This result was especially surprising, as both, Cecka and Terasaki [13] and Alexander *et al.* [3] referred to data from the UNOS Registry database. In part, this discrepancy may be because Cecka and Terasaki analysed functional graft survival, whereas Alexander *et al.* analysed actual graft survival. However, the failure to detect such a dependency may also be due to too short an observation period ($\leqslant 3$ years) [3,14–16] and due to the fact that the absolute donor age was not taken into account [14–16].

It was the aim of our study to address this important question, using a sufficiently long observation period (8 years) and a sufficiently large patient population ($n=1269$). In order to fulfill these prerequisites, we included patients transplanted between 1979 and 1989. Depending on the date of transplantation, these patients received two different types of immunosuppression: MP plus AZA (1979–1984) or MP plus CsA (1984–1989). By applying multivariate, stepwise Cox proportional hazards regression analysis, we took these two different immunosuppressive protocols into account. By subdivision of the relatively long transplant interval into two 5-year intervals, we also ruled out a potential era effect. In contrast to most previous investigations [14–16], our analysis was not based on the age difference, but on the absolute age of donors and recipients. Therefore we divided donors and recipients into two different age groups by an arbitrary division. According to the current literature on the separate influence of donor age and recipient age on renal allograft survival [17], the relevant age limit for both donors and recipients ranges between 50 and 60 years. Therefore we defined 55 years of age as the limit between 'old' and 'young'. In our view, this approach is more promising than dividing patients according to the age difference between donor and recipient alone, as the latter may provide false negative results due to age differences within the same age group.

Extending the results of Donnelly *et al.* [12] and Cecka *et al.* [13], our results indicate that functional and even actual long-term graft survival of kidneys from old donors is significantly reduced in young recipients as compared to all other age combinations. Stepwise multivariate regression analysis underlined that the effect was independent from other relevant patient characteristics, including the type of immunosuppression. The relative risk of graft loss was approximately 2-fold higher in this group of patients as compared to all other patient groups. Graft loss in these patients was mainly caused by an elevated incidence of acute and chronic rejection. A cumulative effect, consisting of the reduced capacity of kidneys from older donors to respond to physiological and pathological stresses [18] and the more reactive immune system of young recipients [19–22], may be a logical explanation for this phenomenon. This may also reflect some kind of 'nephron underdosing', which is known to be a major cause of renal allograft failure [23–25].

In summary, our results provide evidence that kidneys from old donors do not well in young recipients. In contrast, actual graft survival of these kidneys is significantly better in old recipients. Therefore, kidneys from old donors should be matched with old recipients. Such an allocation policy may help to increase especially long-term allograft survival in future. Taking into account the interdependence of donor age and cause of death variables [26], the use of pretransplant routine biopsies [27,28], as well as dual transplantation with both donor kidneys [29,30] may be additional tools, in order to further improve graft survival of kidneys from old donors.

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