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Donor-recipient age difference – an independent risk factor in cyclosporin-treated renal transplant recipients

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Abstract. Whilst HLA matching is routine in renal transplantation the possible benefits of matching donor to recipient age have not been previously explored. The simultaneous effect on graft survival of donor and recipient age was therefore investigated for 274 consecutive first cadaver transplant recipients treated by cyclosporin immunosuppression in two centres. The overall graft survival was 77%, and was not significantly different between the two centres. Individually there was no significant effect of donor or recipient age but taken together, the *difference in age* significantly affected graft survival ($P < 0.01$) regardless of the mode of failure. The 1-year graft survival for all failures was 66.2% when the donor was 5 or more years older, 84.5% when the donor was 5 or more years younger and 71.7% when the donor was within 5 years of the recipient's age. Multivariate analysis, taking into account other variables (HLA matching, dialysis time and type, donor/recipient sex, local/imported kidneys, sensitivity, operation time, total ischaemic time, pre-operative transfusions) indicated that age difference was the single most important variable ($P < 0.01$). The only other important covariate risk factor in improving graft survival was HLA-DR matching ($P < 0.05$). Donor-recipient age difference is a potentially important recipient selection criterion in cyclosporin-treated renal transplant patients.

Key words: Age difference, donor-recipient – Donor-recipient age difference

In the United Kingdom and throughout Europe transplant waiting lists are rising mainly as a result of the increased acceptance of older patients for dialysis [32]. One possible solution to this increased demand for donor organs would be to use elderly donors. Recent reports suggest that older donors are an important and necessary contribution to the pool of organs available but that their use could lead to inferior results compared to younger donors despite reasonable HLA matching [9, 12, 21, 29, 30].

Previously, efforts to improve the results of kidney graft survival have been based on matching for HLA antigens [13, 16, 27]. Little attention has been directed to the possible influence of donor-recipient age difference. In this study we have used the experience from the transplant units of Leicester and Newcastle to assess the effect of cadaveric donor age upon graft survival whilst allowing for recipient age. To allow comparison of other potential risk factors within a reasonably homogeneous group only first cadaver recipients were considered.

Patients and methods

The study population consisted of 274 first cadaver recipients transplanted between June 1983 and September 1987, with minimum follow-up period of 12 months. The two centres provided roughly equal proportions of the study population, with 141 consecutive transplants from Leicester and 133 consecutive transplants from Newcastle. Immunosuppressive therapy for all patients consisted of 10–17 mg/kg per day cyclosporin in the first post-operative week, tapering rapidly to 6 mg/kg per day by the eighth week [28]. Cyclosporin levels were monitored using serum trough levels. In addition all patients were pre-transfused and receiving dialysis up to operation. Three modes of failure were considered: immunological failure (IF), non-immunological failure (NIF), and death with a functioning graft (DWF). Date of graft loss was defined as the date of return to maintenance dialysis.

In order to assess the effect of the donor-recipient age relationship the data were divided into three groups:

(1) donor older: donor 5 or more years older than recipient

(2) donor ± 5 years: donor within 5 years of recipient

(3) donor younger: donor 5 or more years younger than recipient

Whilst the effect of donor and recipient age was the primary focus of the study, other pretransplant risk factors considered were: HLA-A, -B and -DR mismatches, dialysis time and type (HD or CAPD) pre-operative transfusions, total ischaemic time and operative time, donor and recipient sex, source of kidney (imported or local), and sensitization (defined as the most recent percentage panel reactivity). Details of the patients studied are summarized in Table 1. The

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Table 1. Characteristics of study population. Characteristics 2–7 are expressed as medians (ranges), and 8–13 as frequencies

		Leicester	Newcastle	Pooled
1	Number of recipients	141	133	274
2	Recipient age (years)	46 (10–72)	42 (4–70)	44 (4–72)
3	Donor age (years)	34 (3–79)	35 (2–62)	34 (2–79)
4	Pre-transfusions	7 (1–103)	5 (1–85)	6 (1–103)
5	Total ischaemic time (min)	1124 (266–2760)	1175 (268–4366)	1135 (266–4366)
6	Dialysis time (months)	17.4 (3.1–130.7)	29.2 (0.7–170.4)	20.2 (0.7–170.4)
7	Operative time (min)	32 (15–113)	30 (18–55)	31 (15–113)
8	HLA-A mismatch (0/1/2)	31/85/25	23/67/43	54/152/68
	-B	28/81/32	44/32/57	72/113/89
	-DR	48/73/20	47/56/30	95/129/50
9	Recipient sex (M/F)	92/49	64/69	156/118
10	Donor sex (M/F)	78/63	47/86	125/149
11	Dialysis (HD/CAPD)	83/58	56/77	139/135
12	Source (imported/local)	46/95	37/96	83/191
13	Recent sensitivity (0/>0)	123/18	107/26	230/44

two centres had relatively similar patient characteristics, with the exception of dialysis, where Newcastle tended to have a longer dialysis period with more CAPD patients, whereas Leicester had fewer patients with two mismatches on the B or DR loci. There was no significant difference between the centres in the proportion of donors defined as older, within 5 years or younger when compared to the recipients.

Both univariate and multivariate statistical methods were employed. Univariate methods to assess directly the overall effect of a single covariate included product-limit survival plotting together with log-rank and generalized Wilcoxon score tests [17]. Multivariate methods to allow for all risk factors simultaneously included the Cox proportional hazards model [17] and a Weibull mixed model for heavily censored data [6]. Both of these models were found to fit the data well.

Results

During the follow-up period there were 44 immunological failures, 20 non-immunological failures and 10 patients who died with a functioning graft. One-year graft survival rates were 89.5% for Leicester patients, 80.8% for Newcastle patients, and 85.3% overall, when immunological failures only were studied. Corresponding figures when technical failures were included were 84.1%, 75.0% and 79.7%, respectively, and 82.2%, 72.2% and 77.3%, respectively, when DWF graft failures were also considered. There was no significant difference in graft survival rates between the two centres under any of the three modes of failure. Results are given for the combined data set only. Unless otherwise stated the same pattern is observed in both centres individually. 'Significant' results are confirmed by both univariate and multivariate analysis.

Multivariate analysis of all potential risk factors indicated that only two factors were important in determining graft outcome. Donor-recipient age difference was highly significant ($P < 0.01$) and HLA-DR mismatches were also important ($P < 0.05$).There was no significant centre effect.

Recipient ages varied from 4 to 72 years with one-third being over 50 years old. There was no evidence of recipient age having any effect on graft survival when considered in isolation from donor age. For instance, 1-year graft survival rate for the 91 patients aged over 50 years was 79.1%, not significantly different ($P > 0.2$) from that of 76.5% for the 183 younger recipients.

Donor ages ranged from 2 to 79 years with one-fifth being over 50 years old. For the Leicester population, donors over 50 years of age had an inferior graft survival compared with younger donors ($P < 0.01$) whereas for Newcastle data (which included fewer older donors) this difference was not seen. The combined data therefore reflected a poorer graft survival from donors over 50 years of age, 68.4% at 1 year as compared to 79.7% for donors under 50 years, ($P = 0.08$) though not a statistically significant effect.

Donor-recipient age difference

The difference between donor and recipient age ranged from −50 to +34 years. The former figure corresponded to a 64-year-old recipient given the kidney of a 14-year-old donor (this patient died of myocardial infarction with a functioning graft 2 days after transplant). The latter figure corresponded to a 37-year-old recipient given the kidney of a 61-year-old donor (and whose graft was still functioning successfully at follow-up 18 months after transplant). When graft survival was assessed in relation to the donor age bands defined as older, within 5 years or younger, a clear and significant ($P < 0.01$) trend was apparent over these groups for the combined data or for the two centres individually, regardless of the mode of failure (Table 2).

HLA matching

The relatively small sample size did not allow a full study of interaction between HLA-A, -B and -DR antigen mismatches. Nonetheless, if a 'good' match is defined as no

Table 2. One-year graft survival (%) – donor-recipient age effect. IF, immunological failures; NIF, non-immunological failures; ALL, includes 'death with a functioning graft'; values in parentheses are standard deviations

Failures	Donor younger	Donor ± 5 years	Donor older
IF	91.4 (2.4)	80.5 (5.3)	75.6 (5.5)
IF + NIF	87.7 (2.7)	73.2 (5.7)	67.2 (5.9)
ALL	84.5 (3.0)	71.7 (5.8)	66.2 (5.9)

Table 3. One-year graft survival (%) – HLA-DR matching effect. IF, immunological failures; NIF, non-immunological failures; ALL, includes 'death with a functioning graft'; values in parentheses are standard deviations

Failures	HLA-DR mismatches		
	0 ($n = 95$)	1 ($n = 129$)	2 ($n = 50$)
IF	91.3 (2.9)	83.5 (3.4)	78.8 (6.2)
IF + NIF	88.4 (3.3)	77.2 (3.7)	69.3 (6.6)
ALL	86.3 (3.5)	75.2 (3.8)	65.8 (6.7)

Table 4. Relationship between donor-recipient age difference and HLA-DR mismatching (immunological failures only)

Donor-recipient age difference bands	HLA-DR mismatches	Grafts (n)	1-year graft survival (%)
Donor ± 5 years or younger	0	75	95.8 (SD 2.4)
Donor ± 5 years or younger	>0	134	83.9 (SD 3.3)
Older donor	0	20	74.1 (SD 10)
Older donor	>0	45	76.2 (SD 6.6)

DR mismatches, and at most one on A or B combined, then we found no evidence of any difference between good matches and otherwise: 1-year survival rates being 81.1% ($n = 32$) and 76.8% ($n = 242$), respectively. However, if the loci were considered separately then there was evidence that improved HLA-DR matching was incrementally beneficial to graft survival, ($P < 0.05$) regardless of the mode of failure (Table 3). There was no evidence of any individual benefit from HLA-A or -B matching.

Combined effects

Table 4 gives 1-year graft survival rates at various combinations of matching for HLA antigen and for donor-recipient age difference. The detrimental effect of transplanting kidneys from older donors to younger recipients appeared more important than that of poor DR matching, although both factors were important and excellent results were obtained when both were optimal, i.e. the donor was not older and there were no HLA-DR mismatches. Improved graft survival was found when the donor-recipient age difference was optimal even if there were DR mismatches, but if the donor was more than 5 years older than the recipient then improving the HLA-match did not affect graft survival.

Discussion

The improved quality of life achieved by transplantation has meant that the transplant waiting list has increased and produced an ever-widening gap between the supply and demand for donor organs. This study has confirmed that the age distribution of the two dialysis populations are consistent with the international figures, with more than 25% of patients over 50 years of age [32]. Despite early fears that older recipients may be at increased risk of graft failure, we have been able to confirm recent reports [2, 3, 8, 15] that recipient age per se is not a major contraindication to transplantation. If we are to transplant more older recipients, then an increased use of elderly donors would be a logical solution to the long waiting time [13]. The criteria for donor selection have, until recently, been relatively rigid and few centres were prepared to accept kidneys from donors over 60 years of age. In order to cope with the increased demands the idea of using kidneys from older donors has been an increasingly attractive option [9]. Previous uni- and multivariate analyses have not taken into account age difference, and have found risks associated with donor rather than recipient age [4, 9, 12, 14, 21, 29, 30]. This is the first study to document the benefits of considering the relative ages of donor and recipient, rather than the absolute ages only. When all variables including age difference were taken into account, donor-recipient age and HLA-DR matching were the only two important risk variables. One of the benefits of age matching could be an improved graft outcome when using organs from older donors, provided they were not more than 5 years older than the recipient. This effect is likely to be especially important in meeting the needs of an elderly dialysis population [26].

The explanation of the benefits of age matching in relation to graft loss is unclear, although it may reflect the decreasing functional reserve of kidneys with increasing donor age [1, 11, 22, 31]. In a previous study it was well established that above the age of 30 years the glomerular filtration rate decreases linearly with time at a rate of approximately 13 ml/min per decade [31]. The limited functional reserve of kidneys from older donors would then be further reduced by insults which could include cyclosporin toxicity [28], and chronic rejection [10]. Effectively, the life of the graft would be shortened. Immunological response also decreases with advancing age and so the allograft response to an older donor organ might be expected to be less [19, 25]. This hypothesis is borne out by the long-term results of transplantation in the elderly [24, 33]. The poor results observed in the two centres when transplanting an older organ with limited reserve to a young patient with an aggressive immune response would, therefore, be explained. It is important that the results were valid regardless of the definition of graft failures since reports have argued that there is a non-immunological element to chronic graft failure [7]. Progressive graft deterioration in recipients of renal transplants from older donors may be the inevitable effect of aging [11] compounded by previous rejection episodes [10] and cyclosporin toxicity [5].

The conclusions of this preliminary study are obviously limited by the number of cases available, although it has the advantage of a relatively homogeneous population of grafts which were managed in a similar way. It would, however, be worth exploring the limiting age bands and the relative importance of age match versus HLA matching. Clearly donor-recipient age difference could be an important consideration in determining transplant outcome and may reduce the unnecessary late failures [18, 23]. The clear message is that older donors are a valuable resource, but best used for older recipients.

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