Kidney transplantation in children: impact of young recipient age on graft survival

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Abstract

Background. It has been suggested that recipient age may have an effect on renal graft survival due to its potential influence on the competence of the immune system. A comparison of graft survival between children and elderly adults, however, has never been performed.

Methods. Forty patients ≤18 years old were included in the study group and compared with a control group of patients ≥65 years using a case–control analysis. Apart from age, matching criteria were the number of HLA mismatches and the date of transplantation.

Results. The mean age differed by 57 years between study and control group (10 ± 5 vs 67 ± 2, P < 0.001). There was no difference in the number of initially non-functioning grafts, sex distribution, immunosuppression, number of HLA mismatches on the HLA-DR, -B and -A locus, cold ischaemia time and the number of patients with panel-reactive antibodies. The only difference was a lower donor age in the study group (17 ± 14 vs 35 ± 16, P < 0.001) compared with the control group. During the follow-up of 109 ± 54 and 79 ± 49 months, respectively, acute rejections were more frequent in the study group (25 vs 12, P < 0.01). There was no significant difference in graft survival between both groups when death with functioning graft was excluded.

Conclusions. This study which compares two groups of patients with a mean age difference of 57 years could not demonstrate an effect of young recipient age on graft survival, though the incidence of acute rejections appeared to be significantly higher in the paediatric population. Thus paediatric renal transplanted patients do not seem to have a disadvantage regarding graft survival due to their young recipient age.

Keywords: acute rejection; cold ischaemia time; graft survival; HLA matching; kidney transplantation; recipient age

Introduction

The effect of a young age (<18 years) on renal transplant recipients on the incidence of rejections and long-term graft survival has not yet been investigated in a controlled trial. On the other hand, several publications have suggested that older age of renal graft recipients is associated with a lower immunological activity with regard to graft rejection: older patients appeared to have a better long-term graft survival than younger patients when patient’s death with functioning graft is excluded. This observation has been explained by a reduced number of rejection episodes [1,2]. We recently showed, however, that censored graft survival—which excludes death with functioning graft—and the incidence of rejection episodes was equal in three adult groups of renal transplanted patients of different age [3]. Thus, an effect of age on graft survival in adult renal graft recipients could not be demonstrated.

However, it is not clear whether this is also the case in paediatric patients who could have a highly competent immunological system. In order to investigate the effect of young recipient age on renal graft outcome and the incidence of rejection episodes, we compared a group of paediatric renal transplanted patients with a control group of elderly renal graft recipients. The incidence of

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acute rejection episodes and chronic rejection as a cause of graft loss as well as patient and graft survival was investigated by the method of a retrospective case-control study.

**Patients and methods**

**Patients**

The study group (SG) consisted of patients of ≤18 years, and the control group of case-matched patients >65 years. Renal transplantsations were performed at the Medizinische Hochschule Hannover between April 1983 and October 1995. Data recorded up to June 2002 were included.

The study protocol is described elsewhere [3]. In brief, all patients included received grafts that were blood group compatible, HLA matched and allocated by Eurotransplant. Tissue typing was performed using standard serological methods (complement-dependent cytotoxicity cross-match test); DNA methods have been applied alternatively in donors and recipients since 1995. Matching was achieved according to the following criteria with decreasing priority: number of mismatches at the HLA-DR locus, the HLA-B locus, the HLA-A locus (up to a total difference of three) and the date of transplantation (up to a difference of 3 months). Patient data were obtained from the transplant centre’s database without reference to their clinical outcome. Exclusion criteria were retransplants and grafts from living donors. Additional clinical parameters evaluated were the cold ischaemia time, donor age, and initial non-function as defined as more than one haemodialysis session after transplantation. All acute rejections were histologically proven according to criteria described elsewhere [4], and received specific treatment. Acute rejections and graft losses were classified as either early or late, depending on whether they occurred within or beyond a period of 2 months after transplantation, respectively. Chronic rejection was diagnosed, after the clinical diagnosis had been made (slow rise of creatinine, proteinuria, hypertension), by histological means as defined elsewhere [4].

Three cyclosporin A-based standard immunosuppressive protocols were administered to the patients as follows. (i) **Protocol I (initially functioning graft).** Cyclosporin A (trough level 200 ng/ml initially, afterwards 100–150 ng/ml; monoclonal-specific radioimmunoassay, Sandoz, Basel, Switzerland) plus prednisolone (1 mg/kg/day p.o. tapered over ~3 months to a maintenance dose of 7.5 mg/day). (ii) **Protocol II (initially non-functioning graft).** Cyclosporin A (trough level 120–150 ng/ml initially, afterwards 50–100 ng/ml) plus azathioprine (2 mg/kg/day) plus prednisolone (as above). In patients with high immunological risk (presence of cytotoxic antibodies), protocol II was complemented by antithymocyte globulin (ATG, Fresenius, Bad Homburg, Germany, 5 mg/kg/day for 7 days) for induction therapy. The management of acute graft rejection consisted of 500 mg of methylprednisolone i.v. for 3–5 days depending on the response to therapy; in cases of steroid resistance, OKT3 (5 mg/day for 5–10 days) was administered. (iii) **Protocol III (paediatric transplantation).** Cyclosporin A (trough level 200–250 ng/ml initially, afterwards 100–150 ng/ml) plus prednisolone (300 mg/m² i.v. during transplantation followed by 60 mg/m²/day p.o. in the first week, tapered over 6 weeks to a maintenance dose of 4 mg/m²/day p.o.). Acute graft rejection episodes were treated for 6 days with prednisolone 300 mg/m² i.v. In cases of steroid resistance, cyclosporin was switched to tacrolimus, instead of OKT3, which was administered as described in the adult protocol until 1992.

The trough levels of cyclosporin A were controlled thrice weekly while patients were in hospital, and every 4–6 weeks after discharge (dose adjustments were made immediately in order to remain within the therapeutic range). All patients were followed-up at least twice a year in the out-patient clinic.

Graft survival was determined by two methods. Total graft survival included all graft losses independent of the cause. Censored graft survival excluded graft losses due to patient death with a functioning graft, but included graft loss in patients who died with a functioning graft and whose death was related to immunosuppressive therapy, such as infectious complications or lymphoma [5].

**Data collection**

All data concerning the donor, graft allocation and the clinical course were obtained from the transplant centre’s database and the hospital’s medical records.

**Statistical analysis**

Analysis of patient survival, total graft survival and censored graft survival was performed using a Kaplan–Meier estimate. Significance was determined by the log-rank test. Otherwise the Student’s t-test, Wilcoxon test, Fisher’s exact test or McNemar’s test for paired observations with Yate’s continuity correction were employed, as appropriate. Statistical significance was given for a P-value of ≤0.05.

The influence of recipient age, cold ischaemia time, donor age and initial graft function on censored graft survival was investigated by performing a multivariate analysis employing the Cox proportional hazards model using a backward selection procedure.

**Results**

Forty patients were included in the study group. All cases were matched to a control according to the

<table>
<thead>
<tr>
<th>Table 1. Data characterizing the study group and the control group</th>
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<tr>
<td>Study group</td>
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<td>---------------------------------</td>
</tr>
<tr>
<td>Number</td>
</tr>
<tr>
<td>Gender (M/F)</td>
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<tr>
<td>Recipient age (years)</td>
</tr>
<tr>
<td>HLA mismatch</td>
</tr>
<tr>
<td>HLA-A</td>
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<td>HLA-B</td>
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<tr>
<td>HLA-DR</td>
</tr>
<tr>
<td>PRA (n)</td>
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<tr>
<td>CIT (h)</td>
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<tr>
<td>Donor age (years)</td>
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<tr>
<td>Follow-up (months)</td>
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<td>INF</td>
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NS, not significant; PRA, panel-reactive antibodies > 50% at time of transplantation; CIT, cold ischaemia time; INF, initially non-functioning graft.
matching criteria. The data characterizing the study population and control group are listed in Table 1. In the study group, 18 patients were 7–12 years old, 10 were younger, 12 were older. The difference in the mean age of 57 years was highly significant (10 vs 67 years, \( P < 0.001 \)). The mean difference between dates of transplantation was 51 ± 61 days. Apart from donor age, which was lower in the study group (17 vs 34 years, \( P < 0.001 \)), all other clinical parameters relevant for graft survival such as the cold ischaemia time, the number of HLA mismatches, the number of patients with panel-reactive antibodies, the sex distribution and the number of initially non-functioning grafts were statistically not significantly different. None of the patients was lost to follow-up. Two cases in each group of graft loss due to patient death were included in the analysis of censored graft loss as the deaths were due to infection considered to be due to immunosuppression.

Patient survival and total (=uncensored) graft survival was significantly higher in the study group (see Figures 1 and 2): patient survival after 1, 5 and 10 years was 93, 93 and 89% in the study group compared with 95, 65 and 28% in the control group, respectively. Uncensored graft survival was 90, 88 and 67% in the study group compared with 90, 63 and 25% in the control group, respectively. However, there was no statistically significant difference regarding censored graft survival between the study and control group (see Figure 3): 93, 90 and 71% compared with 90, 87 and 73%, respectively. As determined by multivariate analysis, recipient age was the only parameter that proved to have a significant influence on patient \( (P < 0.05) \) and uncensored graft survival \( (P < 0.05) \). For censored graft survival, the total number and the number of multiple rejections was the dominant independent risk factor \( (P < 0.01) \). Old recipient age had no significant negative impact on censored graft survival. None of the remaining parameters had a significant influence on censored graft survival.

The clinical course of the study group compared with the control group is listed in Table 2: there was a significantly higher number of patients with acute rejections in the study group. With respect to the number and the time of occurrence, there were significantly more early (20 vs 9, \( P < 0.01 \)) and multiple (8 vs 1, \( P < 0.05 \)) acute rejections in the study group. The number of patients with late rejections was not significantly different (5 vs 3) between the study population and the control group. Chronic rejection was diagnosed in seven out of eight cases of late censored graft loss in the study group compared with three out of eight cases in the control group. Three cases in the study group were biopsy proven and four patients had multiple and/or late acute rejections suggesting chronic rejection; one patient had recurrent glomerulonephritis. In the control group, two cases of chronic rejection were diagnosed by histology and one clinically. The remaining five cases of late censored graft loss in the control group were due to recurrent glomerulonephritis (\( n = 1 \)), abscessing pyelonephritis (\( n = 1 \)), surgical complications (\( n = 1 \)) and death following infectious complications related to immunosuppression (\( n = 2 \)).

Early graft losses were due to acute rejections (\( n = 2 \) control group) or death following infectious complications related to immunosuppression (\( n = 2 \), study group).

![Patient Survival](image_url)

**Fig. 1.** Patient survival of renal graft recipients ≤18 years (study group, SG) and ≥65 years (control group, CG; \( P < 0.0001 \)). Numbers of patients at risk are listed below. There were four deaths in the study group and 28 in the control group.
Discussion

This investigation evaluates the effect of young recipient age on renal graft survival. The data have been collected from a homogenous group of patients: retransplants and grafts from living donors were excluded, since these factors are relevant for graft survival [1,6,7]. Retransplants and grafts from living donors are more frequent in paediatric compared with adult patients with end-stage renal failure. Thus, these exclusion criteria prevented the inclusion of a larger number of case patients. All remaining paediatric patients transplanted in the observation period were included.
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Table 2. Clinical course in the study group compared with the control group

<table>
<thead>
<tr>
<th>Number of patients with acute rejections</th>
<th>Study group</th>
<th>Control group</th>
<th>P</th>
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<tbody>
<tr>
<td>Total</td>
<td>25</td>
<td>12</td>
<td>0.01</td>
</tr>
<tr>
<td>Single</td>
<td>17</td>
<td>11</td>
<td>NS</td>
</tr>
<tr>
<td>Multiple</td>
<td>8</td>
<td>1</td>
<td>0.05</td>
</tr>
<tr>
<td>Early</td>
<td>20</td>
<td>9</td>
<td>0.01</td>
</tr>
<tr>
<td>Late</td>
<td>5</td>
<td>3</td>
<td>NS</td>
</tr>
<tr>
<td>Associated with INF</td>
<td>5</td>
<td>3</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS, not significant; INF, initially non-functioning graft.

Both groups are highly comparable with respect to most of the factors relevant for graft survival [6,8–11]: the total number of HLA mismatches and the number of mismatches on the HLA-A, -B and -DR locus were equal between the two groups because they were matching criteria for the case–control analysis. Other parameters were equal, most probably due to the single-centre design (cold ischaemia time, immunosuppression, number of initially non-functioning grafts) and the exclusion of retransplants (number of patients with panel-reactive antibodies). The follow-up was significantly shorter in the control group secondary to the higher mortality in this group. The only factor that showed a highly significant difference was donor age. This is caused by the practice of age matching between donor and recipient. Increasing donor age has a negative effect on graft survival [7,8,12]. However, the impact of donor age on graft survival follows a J-shaped curve. The effect is minimal at 20–30 years and increases with higher and younger donor age [8,13,14]. Thus, with a mean donor age of 17 and 35 years in the study and control group, respectively, there is no evidence that its effect on both groups was different with respect to graft survival. In addition, multivariate analysis showed that none of these factors had a dominant effect on graft survival in our study population. Therefore, recipient age remains the only relevant characteristic that is of highly significant difference between both groups.

There is no study that compares two groups of renal transplant recipients with this wide age gap of nearly 60 years in a case–control manner. Therefore, this study provides important information regarding the impact of recipient age on graft survival and on the activity of the immune system.

In the present study, patient and uncensored graft survival of the control patients was significantly decreased. This is simply explained by their shorter life expectancy. In accordance with that, recipient age was the predominant confounding factor. We previously showed that there is no difference in graft survival censored for death in adult patient groups of different age [3]. Now, we have been able to demonstrate that this is also the case in paediatric patients compared with a control group of 65 years and older. Five-year patient and censored graft survival in our study of 66 and 87% in the control group is similar to previously published data of 65–69% and 81–89%, respectively, in patients 55–70 years of age [2,13,15]. However, regarding the study group, the uncensored 5-year graft survival of 88% is markedly better compared with registry data showing 57–64% in patients 3–21 years of age [16]. The same applies to 3-year censored graft survival of 90% in our study group compared with 72% of a registry population 6–18 years of age [17].

So far, the question of the impact of recipient age has been evaluated using large populations in retrospective, non-controlled studies with differing results. Some studies show a survival benefit with increasing age if graft survival is censored for death [2,13,15]. One single-centre study did not show a difference in censored graft survival between two different age groups [18]. The difference between our results and most of these data are caused by the study design of a single-centre case–control analysis. Factors relevant for graft survival in both groups are as close as possible, and treatment modalities such as immunosuppressive therapy are standardized. However, most importantly, the graft survival of the paediatric group is superior compared with registry data as a consequence of the single-centre study design.

The total number and multiple rejections were the only risk factors as shown by the multivariate analysis. In accordance with our results, previously published data demonstrate a higher incidence of acute rejection episodes in children compared with adults. This suggests a more vigorous immune response in children leading to a higher incidence of graft failures secondary to immunological reasons [19]. On the other hand, it has also been shown recently that increasing recipient age is an independent risk factor for allograft failure censored for death and acute rejection, indicating that graft loss due to non-immunological reasons increases with age [20]. Now even by employing two study groups of renal graft recipients whose mean age differs by almost 60 years, we still could not demonstrate an effect of recipient age on censored graft survival. This can be explained by the fact that a more potent immunological competence in children is counterbalanced by an increasing incidence of non-immunological causes for allograft failure when patients get older. This conclusion is confirmed by the higher number of graft losses due to chronic rejection in the paediatric group. However, the study population is too small to show significant differences.

In summary, our data provide strong evidence that paediatric renal graft recipients do not have a disadvantage regarding graft survival censored for death because of their young age, although they develop a significantly higher number of rejection episodes. Since the paediatric immunosuppressive protocol was comparable with the adult one with regard to its immunosuppressive effect, one might postulate that a more powerful immunosuppression in children may lead to fewer rejections in children with the possible consequence of an additional benefit on graft survival.
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Conflict of interest statement. None declared.

References


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