Better long-term functional adaptation to the child’s size with pediatric compared to adult kidney donors

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Better long-term functional adaptation to the child’s size with pediatric compared to adult kidney donors.

Background. Pros and cons for pediatric kidney donors have been debated, especially with respect to survival rates. However, the effect of donor age on kidney function remains conflicting. The aim of this study was to compare short and long-term renal function according to the age of the donor, in grafts from adult living related (LRD), adult cadaveric and pediatric cadaveric donors (PedCD) following pediatric transplantation (Tx).

Methods. One hundred and thirty-four children were repeatedly followed for four years, and 44 were followed for eight years. Absolute and relative glomerular filtration rate (GFR; inulin clearance, mL/min and mL/min/1.73 m², respectively) were determined within 6 months, and yearly thereafter.

Results. Absolute GFR increased along with body growth in the PedCD group (P < 0.001) during the 4 years following Tx, leading to stable relative GFR, whereas absolute GFR of the LRD group did not change, with a progressive decrease of relative GFR (P < 0.001). Relative GFR did not differ between PedCD and LRD recipients by the sixth month but became higher in PedCD 4 years post-Tx (70 ± 25 vs 52 ± 19 mL/min/1.73 m², P < 0.001). Among those followed for 8 years, relative GFR showed a slow decrease in both recipient groups from 6 years post-Tx. At 8 years post-Tx, relative GFR was still significantly higher in PedCD than in LRD (57 ± 19 vs. 45 ± 19; P < 0.05).

Conclusions. Adult-sized grafts may adapt to pediatric recipients during the first months post-Tx, but graft function cannot improve thereafter along with the increase in body size of the recipient. Interestingly, the absolute GFR of children receiving pediatric grafts increased along with body growth, leading to a stable relative GFR up to 6 years post-Tx.

Renal transplantation (Tx) is the treatment of choice in children with end-stage renal disease. Although survival rate in transplant children is improving, it is important to ensure optimal renal function over decades in order to optimize growth and development. Most major factors influencing long-term renal transplant survival have been identified through large multicenter analyses [1–3]. The pathogenesis of graft dysfunction cannot be explained only by immunologic phenomena but several antigen-independent risk factors have been demonstrated [4]. Any kind of donor kidney mass reduction may be one of these factors, and could result in failure to meet the metabolic demand of the recipient, subsequently leading to long-term graft loss. In multicenter series, both graft survival and kidney function were reduced when organs were taken from either very young (<10 years of age) or very old donors (>70 years of age) compared with young or middle-aged ones [5]. The best one-year graft survival rates were obtained from donors aged 15 to 40 years [5] and the optimal donor age was defined as 20 to 25 years by the North American Pediatric Renal Transplant Cooperative Study [6]. However, recent studies have shown that pediatric donors (<10 years of age) provided the best long-term graft survival and the lowest late graft loss rate (abstract; Hardy et al, Pediatr Transplant 4:105, 2000) [5]. Such good results may be due to a greater number of functioning nephrons compared to aging kidneys, in which a physiological nephron loss may occur. Despite a lower graft survival rate at one year, possibly due to the high risk of vascular thrombosis, the long-term results were superior, as pediatric transplanted kidneys may grow in the recipient (abstract; ibid). Thus, it seems that both initial mass of the transplanted kidney and its capacity to adapt to an increasing demand during body growth are important factors for long-term renal function in pediatric Tx.

As a complement to two large European and North
American series that focused on the evaluation of survival rates and outcome predictive factors, the present study was conducted in all children with a functioning graft in two centers to investigate adaptation capacities of the grafted kidney to the recipient, independent of patient and graft survival rates. The aim of our study was to compare short- and long-term renal graft function of pediatric recipients in relation to donor age, that is, adult living related donors (LRD) and adult cadaveric donors (AdCD) versus pediatric cadaveric donors (PedCD) independent of any other known factor, such as HLA-matching, cold ischemia time, number of acute rejection episodes, etc.

METHODS

Patients

Between January 1982 and December 1999, 261 children and adolescents (108 girls), 104 from Huddinge University Hospital (Stockholm, Sweden) and 157 from Edouard-Herriot University Hospital (Lyon, France), received 294 renal transplants. Their mean age was 9.3 ± 5.1 (range 0.4 to 18.0) years at Tx. One hundred and seventy-eight transplants were performed with cadaver donors (CD), 36 using AdCD (>18 years), 138 using PedCD (=18 years) and 4 whose donor age was unknown, while 116 received a graft from LRD (108 parents, 5 grandparents, 2 aunts, and 1 adult brother). The glomerular filtration rate (GFR) assessment was not available in 55 patients, because of graft loss within the first 6 months post-Tx. All patients with a functioning graft were routinely investigated by renal function tests performed within 6 months post-Tx and yearly thereafter. No patient was excluded for medical reasons. One hundred and thirty four patients were repeatedly followed for at least four years (Table 1).

Among the 134 patients, 96 had congenital disorders: 55 malformative uropathies and/or renal hypo/dysplasia, 41 hereditary diseases (nephronophthisis, autosomal recessive polycystic kidney disease, Finnish-type congenital nephrotic syndrome, Alport syndrome, cystinosis, Drash syndrome, etc). The remainders suffered from acquired diseases such as chronic glomerulonephritis (N = 19), focal segmental glomerulosclerosis (N = 8), neonatal renal vein thrombosis (N = 3), hemolytic uremic syndrome (N = 7) and miscellaneous disorders (N = 1).

Immunosuppression

All patients received a standard regimen including prednisone, azathioprine and cyclosporine. In the Stockholm’s group, cyclosporine was started immediately after Tx and, in Lyon, induction treatment (rabbit anti-thymocyte globulins) was given and cyclosporine was started when the serum creatinine value was below 100 μmol/L. In Stockholm, cyclosporine dose was adjusted, aiming at a trough blood level of 300 ng/mL (monoclonal RIA) during the first month, 200 ng/mL during the second month and 100 ng/mL after three months; the Lyon’s

<table>
<thead>
<tr>
<th>Patients from Stockholm</th>
<th>Number of patients</th>
<th>Number of transplants</th>
<th>Type and number of donor</th>
<th>Age of the recipient mean ± SD (range)</th>
<th>Age of the donor mean ± SD (range)</th>
<th>Number of acute rejection episodes during the 1st year post-Tx (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>61 (30 F)</td>
<td>1st: 55</td>
<td>All: 61</td>
<td>CD = 15</td>
<td>10.1 ± 4.2 (1.8–15.9)</td>
<td>34.0 ± 13.5 (18.6–62.6)</td>
<td>0.9 ± 0.8 (0–2)</td>
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<tr>
<td></td>
<td>2nd: 6</td>
<td>AdCD = 9</td>
<td>5.9 ± 5.2 (0.4–14.6)</td>
<td>8.1 ± 3.6 (3.2–11.8)</td>
<td>2.2 ± 0.8 (1–3)</td>
<td>0.8 ± 0.8 (0–3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PedCD = 6</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>LRD = 55</td>
<td>7.6 ± 5.1 (1.1–17.8)</td>
<td>37.2 ± 7.2 (24.5–55.3)</td>
<td>0.8 ± 0.8 (0–3)</td>
<td></td>
</tr>
<tr>
<td>Patients from Lyon</td>
<td>73 (30 F)</td>
<td>1st: 67</td>
<td>CD = 77</td>
<td>12.9 ± 3.9 (7.7–17.2)</td>
<td>36.0 ± 7.8 (26.8–45.0)</td>
<td>1.3 ± 1.3 (0–3)</td>
</tr>
<tr>
<td></td>
<td>2nd: 3</td>
<td>AdCD = 57</td>
<td>9.2 ± 4.7 (0.7–15.9)</td>
<td>7.1 ± 4.3 (1.1–16.2)</td>
<td>1.2 ± 1.1 (0–4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3rd: 3</td>
<td>PedCD = 53</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>LRD = 46</td>
<td>9.9 ± 3.8 (3.2–15.5)</td>
<td>38.0 ± 4.6 (31.3–49.0)</td>
<td>0.9 ± 1.0 (0–3)</td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>134 (60 F)</td>
<td>1st: 122</td>
<td>CD = 72</td>
<td>11.0 ± 4.2 (1.8–17.2)</td>
<td>34.6 ± 11.7 (18.6–62.6)</td>
<td>1.0 ± 0.9 (0–3)</td>
</tr>
<tr>
<td></td>
<td>2nd: 9</td>
<td>AdCD = 13</td>
<td>8.8 ± 4.8 (0.4–15.9)</td>
<td>7.2 ± 4.2 (1.1–16.2)</td>
<td>1.3 ± 1.1 (0–4)</td>
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<td></td>
<td>3rd: 3</td>
<td>PedCD = 59</td>
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<tr>
<td></td>
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<td>8.2 ± 4.9 (1.1–17.8)</td>
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<td>0.8 ± 0.9 (0–3)</td>
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</table>

F is female.

Table 1. Characteristics of patients followed four years post-transplantation (Tx)
Dubourg et al: Renal function after pediatric transplantation

of 0.9% sodium chloride (about 2 mL/kg for 10 min followed by a continuous infusion of 0.5 or 1 mL/min depending on the BW). This enabled patients to void by spontaneous micturition every 30 minutes. Three to four urine samples were collected and a blood sample was drawn midway through each collection period. Clearance values were obtained from the average results of the three to four periods. Measurements of plasma and urine polyfructosan were performed using a standard colorimetric method on an autoanalyzer (AAI; Technicon, Tarrytown, NY, USA). No significant differences were found when comparing data of different donor groups between the two centers. The studies were approved by the Ethical Committee in both centers.

Statistics

Results are expressed as mean ± SD. According to the parameters, the Student t test and analysis of variance (ANOVA) for repeated measurements followed by Scheffé’s test were used for statistical analysis. The probability of graft and patient survival according to the type of donor and center was assessed by the Kaplan-Meier method followed by a Log rank test. Probabilities of less than 0.05 were considered to be significant.

RESULTS

The overall five-year patient and graft survival rates for all 294 Tx were 93 and 78%, respectively. Graft and patient survival data according to the type of donor are given in Figure 1. No difference was found between the overall graft and patient survival between the two centers. Only the graft survival rate was significantly higher in the adult LRD group compared with both AdCD and PedCD (* P < 0.01).

Independent of donor source, relative GFR at one and five years post-Tx was 66 ± 22 (N = 236) and 58 ± 23 (N = 118) mL/min/1.73 m², respectively. The relative GFR within six months post-Tx was not significantly different between LRD (71 ± 25 mL/min/1.73 m², N = 104) and PedCD (65 ± 23 mL/min/1.73 m², N = 108), nor between PedCD and AdCD (55 ± 27 mL/min/1.73 m², N = 34). The relative GFR of AdCD was significantly lower than that of LRD within six months post-Tx, but did not differ thereafter.

These results were confirmed by sequential assessment of 134 patients (59 PedCD, 62 LRD and 13 AdCD) who were repeatedly tracked over four years post-Tx (Fig. 2A). In PedCD, absolute GFR and body surface area (BSA) increased concomitantly between the sixth month and the fourth year of follow-up, while the relative GFR did not change significantly. On the other hand, absolute GFR of LRD did not increase along with the child’s growth and relative GFR decreased. Relative GFR of the PedCD was significantly higher than those groups aimed at a trough cyclosporine blood level of 150 to 200 ng/mL during the first six months and 100 to 150 ng/mL thereafter.

Methods

Three groups of patients were studied: 134 patients (59 PedCD, 13 AdCD, 62 LRD), 72 patients (31 PedCD, 41 LRD) and 44 patients (17 PedCD, 27 LRD) were tracked over four, six and eight years, respectively. Renal function was assessed by GFR measurement based on polyfructosan clearance (Inutest, 25%; Laevosan-Gesellschaft, Wien, Austria). A standard technique was used with a continuous infusion after a priming dose of polyfructosan 30 mg/kg body weight (BW). Water diuresis was induced by oral water intake of 5 mL/kg BW during the first hour followed by 5 mL/kg every 30 minutes in the Stockholm group; in the Lyon group, an oral water intake of 5 mL/kg BW was given followed by 3 mL/kg every 30 minutes combined with an intravenous infusion

Fig. 1. Patient and graft survival rates with adult cadaveric donors (AdCD; - - -), adult living related donors (LRD; -·-·) and pediatric cadaveric donors (PedCD; -). The graft survival rate with LRD is significantly higher than with both AdCD and PedCD (* P < 0.01).
Fig. 2. Absolute (ml/min; ○) and relative (ml/min/1.73 m²; △) GFR and body surface area (BSA m²; ▼) of the children who received a graft from a pediatric cadaveric, a living related or an adult cadaveric donor. Data are mean ± SD. The patients were investigated exhaustively over the 4 (A), 6 (B) and 8 (C) years post-transplantation. The absolute GFR improved significantly in the pediatric group ($P < 0.0001$) during the 4 and 6 years post-transplantation. However, the absolute GFR of living related donor group remained unchanged despite growth, so that relative GFR decreased ($P < 0.0001$). Note that BSA increased significantly in the 2 groups ($P < 0.0001$). Stars show intervals that are significantly different from the first assessment (Scheffe’s test, $P < 0.05$).
of both AdCD and LRD from the first to the fourth years. Similar changes were noted in recipients of 31 PedCD and 41 LRD followed over six years (Fig. 2B). In addition, the relative GFR of PedCD was significantly higher than that of LRD from the second to the sixth year after Tx.

The sequential assessment of 17 PedCD and 27 LRD over eight years showed two different profiles along with time (Fig. 2C): (1) an improvement of absolute GFR of PedCD and a stability of relative GFR during the first four-year period, and (2) a decrease in relative GFR of donor source (PedCD or LRD) during a second period of time, due to the lack of change in absolute GFR despite body growth. After eight years, the relative GFR of PedCD was still higher than that of LRD (57 ± 19 vs. 45 ± 19 mL/min/1.73 m², P < 0.05).

**DISCUSSION**

In large European and North American series, the one- and five-year graft survival rates of children after renal Tx have dramatically improved up to 80 and 65%, respectively [7–9], with the best rates being observed after living-related donation [10]. Our current study found that the overall one- and five-year graft and patient survival rates are comparable to other series, and the graft survival rate is significantly better with LRD than with CD.

The aim of renal replacement therapy during childhood is to restore their potential for normal growth and development, in order to reach optimal final height. A graft therefore must provide good renal function over a long period of time to allow adequate growth [11, 12].

The outcome of pediatric renal Tx is influenced by numerous factors. The role of the donor source on the long-term renal function outcome has not been extensively studied and remains controversial. The number of grafts from PedCD, LRD or AdCD depends more on local convenience and cultural background than on rationale from clinical trials. We therefore collected data from the departments of pediatrics in Huddinge University Hospital (71% LRD, 13% PedCD and 16% AdCD) and in Lyon University Hospital (18% LRD, 70% PedCD and 10% AdCD), two centers using comparable immunosuppression protocols and prospective renal function monitoring. The aim of the study was to compare renal function of transplanted kidneys with respect to the type and age of the donor (that is, PedCD, AdCD and LRD), independent of any other known factors. Both centers have previously reported part of their results in a limited number of patients [13, 14]. Other known factors—such as HLA-matching, cold ischemia time, number of acute rejection episodes—are comparable between the two groups, and suggest LRD as a favored donor source.

Independent of the duration of follow-up, the overall GFR approximated 60 mL/min/1.73 m² during the first five years post-Tx, which is comparable with other experiences [15–18]. As shown by Gellert et al, relative GFR in adult donor groups (AdCD and LRD) was not different from the PedCD group at six months post-Tx, probably as a result of an adaptation of the graft function to the recipient requirements [15]. Conversely, the relative GFR of LRD is higher than GFR of AdCD only at six months post-Tx. This was previously shown by Sekaly et al, who concluded that GFR was higher in allotransplants from LRD compared to CD kidneys only in the first 12 months following Tx, but the age of the donors was unknown [19].

The capacity of the kidney graft to adapt could be evaluated by sequential assessment of GFR of patients exhaustively analyzed during four, six or eight years. The absolute GFR of pediatric graft recipients improved significantly during the first six years post-Tx. As shown in Figure 2 A and B, sequential absolute GFR measurements correlated positively with BSA, which increased as the children grew. An increase in absolute GFR on follow-up suggests that there is a significant reserve capacity for growth and/or compensatory hypertrophy in the transplanted kidney from a pediatric donor. Provoost et al demonstrated both in rats and humans receiving grafts from donors of unequal body size that the function of the transplanted kidney adapted to the body size of the recipient [20]. Offner et al speculated that such an adaptation is limited with a nadir kidney function six weeks after Tx when the donor was less than 10 years old [21].

When evaluating kidney function in the child recipient and the adult living donor simultaneously within five to six months after Tx, Bohlin and Berg [22] and Berg, Bohlin and Tydén [23] showed that while the absolute GFR of the recipient was significantly lower than that of the donor, the relative GFR did not differ. They concluded that the absolute GFR of the recipient was directly related to the size (BSA) of the recipient with a functional adaptation of the adult graft to the small size of the recipient. In the present study, sequential determination of GFR started three to six months post-Tx and absolute GFR of patients receiving LRD grafts did not change over the six and eight years post-Tx despite the child’s growth. As a result the relative GFR decreased significantly, as previously noticed by Qvist et al, who found a slow decrease in relative GFR in both LRD and CD donors, with an age of approximately 28 years in CD donors [24]. These results suggest that, following an initial adaptation of the adult-sized kidney to the small size of the recipient [22, 23], the graft cannot experience a long-term adaptation to the increasing requirement of the growing child. Such a functional adaptation may be due to reduced renal blood flow in the graft because of a low cardiac output of the pediatric recipient leading...
to ischemic damage to the kidney and subsequent limitation in absolute GFR increase. On this basis, Sarwal et al recommended an aggressive assisted fluid support during the first 6 to 12 months post-Tx in infants in order to allow optimal perfusion of the size-discrepant adult sized kidneys (abstract: Pediatr Transplant 4:105, 2000).

In children who were traced for eight years after Tx, GFR showed a slow decrease independent of the donor source, LRD or PedCD. Sorrof et al showed that the decrease in estimated GFR (Schwartz formula) occurred at the same rate for both CD and LRD grafts [17], suggesting that the drop in graft function was due to early and gradual loss as opposed to accurate onset of irreversible rejection episodes. However, in our study, the relative GFR in the PedCD group did not change significantly until six years post-Tx, whereas GFRs at seven and eight years were significantly different from the GFR at two years post-Tx. Conversely, absolute GFR of LRD did not change over the eight-year follow-up, with a progressive decrease in relative GFR. The kidney from PedCD therefore might lose its adaptation capacity to increase with the child’s body size after about six years post-Tx. The lack of adaptation ability of the graft kidney, early after Tx with LRD and later after Tx with PedCD, could be due to the reduced number of functioning nephrons with additional progressive renal scarring due to either chronic rejection and/or to progressive focal segmental glomerulosclerosis secondary to reduced renal mass [25]. However, the capacity of functional adaptation of the renal graft to the increasing requirement of the growing child might not be approached by the response to protein load. Indeed, Englund et al studied the renal reserve capacity in transplanted children and found that these patients still had a capacity to increase their function following an oral protein load [26, 27].

Recently, the importance of donor age with respect to the so-called senescence of the kidney graft has been pointed out by Halloran, Melk and Barth [28] and, in another study, the donor age was reported as having the greatest impact on long-term renal function [29], both studies supporting our results.

Conclusion

Our study favors the use of young cadaveric donors in pediatric kidney Tx, as graft function adapts to the body size increase of the child over time. However, grafts from adult donors (AdCD or LRD) probably adapt to the body size of the child in the first months post-transplantation, but are unable to parallel the growth thereafter. On the other hand, the absolute GFR of children with pediatric kidney grafts does increase along with growing body size of the child, leading to long-lasting, stable relative GFR. In the long term, the initial reserve capacity of the pediatric kidney seems to be inadequate, and a slow decrease in relative GFR occurred at the same rate as adult donor recipients. Many studies have claimed that renal mass of the graft is essential in the long-term renal function outcome. We still have to question the significance of renal mass: is renal weight or functioning nephron number the main determinant? Does the pediatric graft have the capacity to respond to growth factors that are lacking in an adult kidney graft?

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APPENDIX

Abbreviations used in this article are: AdCD, adult cadaveric donors; BSA, body surface area; GFR, glomerular filtration rate; LRD, living related donors; PedCD, pediatric cadaveric donors; Tx, transplantation.