Effect of donor/recipient body weight ratio, donor weight, recipient weight and donor age on kidney graft function in children

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Abstract

Background. We hypothesized that supplementing a higher mass of renal parenchyma from adult donors, and their younger age, would improve graft function in paediatric recipients.

Methods. We calculated estimated glomerular filtration rate (eGFR; Schwartz formula) and absolute glomerular filtration rate (absGFR) in 57 renal-grafted children (1995–2007) aged 3.1–17.9 years, weighing 12.9–85.0 kg, on discharge from the hospital after transplantation (TPL), 1 year after TPL and at the last follow-up (1.5–11.7 years after TPL). We correlated their eGFR with the individual ratio between the donor and recipient body weight at the time of TPL (donor/recipient body weight ratio; D/R BWR), and we evaluated the effect of the donor and the actual recipient body weight on the eGFR and absGFR.

Results. The D/R BWR varied from 0.65 to 5.23. We found a significant positive correlation between D/R BWR and eGFR at discharge from the hospital (P < 0.001), 1-year post-TPL (P < 0.001) and at the last follow-up (P < 0.05). Using multiple linear regression analyses, we found that both eGFR and absGFR values were much more determined by the actual recipient weight than by the donor weight (27.6% and 43.4% at discharge, by 24.4% and 57.0% 1 year after TPL, and 0.0% and 20.0% at the end of the follow-up). A tendency for lower eGFR with increasing age of donors was apparent at discharge and 1 year after TPL, but it reached statistical significance only at the last follow-up (r = 0.4254, P < 0.01).

Conclusion. In paediatric renal transplants, the value of D/R BWR directly correlated with eGFR in the early and late posttransplant periods. However, this correlation was mainly influenced by the recipient weight, while the donor weight played only a minor or negligible role.

Introduction

In 1988, Brenner hypothesized that a low inborn nephron number may be, at least partially, responsible for subsequent development of hypertension and renal disease [1]. Later, he also suggested that the kidney graft survival might be influenced by the nephron supply to a recipient [2]. In 1994, Mackenzie et al. [3] found that nephron supply might be a major determinant of long-term allograft outcome in rats. In 1995, analysis of the effect of some nonimmunologic factors on cadaveric renal allograft survival in 31 000 kidney recipients from the United Network for Organ Sharing revealed that the donor age, large body size of the recipient, female gender and African-American race were all important factors that accelerated the graft loss [4,5]. It is well established that the kidneys of small children, when transplanted into adult recipients, increase their size and function with time after transplantation (TPL) [6,7]. On the other hand, the functional adaptation of a large kidney from an adult donor, transplanted to a child, is not completely understood. We hypothesized that supplementing a high mass of renal parenchyma from adult donors would increase glomerular filtration rate and slow the speed of progressive injury affecting the renal allograft in paediatric recipients. To test this hypothesis, we analysed the effect of a donor body weight, i.e. renal mass supplementation, in relationship with recipient body weight and the effect of a donor age on the level of estimated glomerular filtration rate (eGFR; Schwartz equation) [8] and absolute glomerular filtration rate (absGFR) at different time periods after TPL in paediatric recipients.

Patients and methods

We performed a retrospective chart review of kidney graft function with respect to the individual ratio between the donor and the recipient body weight at the time of TPL (donor/recipient body weight ratio; D/R BWR). We also analysed the effect of age of our donors on graft function.

All 101 patients transplanted from January 1995 to December 2007 at the University Hospital Motol, Prague, Czech Republic, were screened for eligibility in this retrospective study. The inclusion criteria were a

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functioning graft at the end of this time period for at least 1 year, uncomplicated post-TPL course and continuous long-term follow-up in our paediatric TPL centre. Patients with major surgical, severe immunologic (more than two biopsy-proved acute rejection episodes) or other serious complications (severe hypertension, pyelonephritis) with a possible long-lasting effect on the graft function were excluded from the study. Since 1995, a standard surgical technique has been used. Immunosuppression consisted of the administration of cyclosporine A or tacrolimus (since 1996), azathioprine or mycophenolate mofetil (since 2005) and prednisone. The induction therapy with antithymocyte globulin or anti-IL2 antibodies was received by 8 and 21 patients, respectively. Acute rejections were treated by either intravenous methylprednisolone or antithymocyte globulin.

Nine children were taking ACE inhibitors; no patient used angiotensin receptor blockers.

Altogether, 57 kidney grafts in 57 children were included in the study. The cohort consisted of 32 males and 25 females, aged 3.1–17.9 years (12.3 ± 4.1 years, mean ± SD), with weight from 12.9 to 85.0 kg (37.1 ± 15.4). The primary renal diseases were nephropathies in 11, autosomal recessive polycystic kidney disease in 7, tubulointerstitial nephritis in 7, congenital nephrotic syndrome in 5, obstructive uropathy in 4, vesicoureteral reflux in 3, focal and segmental glomerulosclerosis in 4, glomerulonephritis in 3, congenital hydropsplasia in 6, vasculitis in 2 and unknown in 5. Duration of follow-up after TPL was 1.5–11.7 years (5.42 ± 2.42). Twenty and 28 patients were compatible in 2 and 3 HLA antigens, respectively, while only 3, 5 and 1 patients were compatible in 1, 4 and 5 HLA antigens, respectively. Panel reactive antibodies varied from 0 to 88% and were negative in 44 patients (77%). Cold ischaemia time was 17.9 ± 2.1 h. All TPLs were from cadaver donors between the ages of 11 and 52 years (mean 19 years) with body weight from 35 to 90 kg (69.9 ± 12.4). Other donor acceptance criteria were as follows: serum creatinine levels at donation not >30% over the limit for a given age, satisfactory urine volume, previously healthy donor, anatomically normal kidney, cold ischaemia time up to 24 h and warm ischaemia time up to 2 min.

Serum creatinine levels were determined in the Department of Biochemistry and Pathobiochemistry of the University Hospital Motol, Prague, by a standard method (Jaffe reaction without deproteinization, Siemens Comp. Kit). eGFR was calculated according to the Schwartz formula [8], and absGFR was calculated on the basis of eGFR using body surface area (BSA) of the child. The data were evaluated at discharge from the hospital after TPL (3–6 weeks after surgery), 1 year after TPL and at the last follow-up.

For statistical evaluation, Pearson correlation coefficient was used. To describe the relationship between dependent (eGFR and absGFR) and a set of independent variables (donor weight, recipient weight, recipient BSA), multiple linear regression model was applied. For comparison of means, unpaired t-test was used. All tests were two sided, and the P < 0.05 value was considered as statistically significant.

Results

Effect of the D/R BWR on eGFR after TPL

The D/R BWR varied from 0.65 to 5.23 (2.29 ± 1.08). We found a significant positive correlation between D/R BWR and eGFR at discharge of patients from the hospital after surgery (r = 0.6064, P < 0.001), 1 year after TPL (r = 0.5599, P < 0.001) and at the end of follow-up (r = 0.3048, P < 0.05) (Figure 1A, B and C). The correlation was strongest in the early posttransplant period but was still significant at the end of follow-up. Using multiple linear regression model, we found that recipient versus donor weights determined eGFR by 27 versus 6% at discharge from the hospital and by 24 versus 4% 1 year after TPL, respectively. At the end of follow-up, the contributions of neither the recipient weight nor the donor weight were recognizable.

Effect of the D/R BWR on absGFR after TPL

The D/R BWR nor the donor weight correlated with the absGFR. At the three evaluated post-TPL periods, the absGFR correlated with the recipient BSA (r = 0.6665, 0.7300 and 0.4389, at discharge, 1 year after TPL and at the end of follow-up, respectively, P < 0.001 for all), with the recipient weight (r = 0.6501 and 0.7393 for the first two periods, P < 0.001 for both and r = 0.4174, P < 0.01 at the end of follow-up) and with the recipient age (r = 0.2997, P < 0.05 at discharge and r = 0.3633, P < 0.01 1 year after TPL; at the end of follow-up, the correlation was not found). Using multiple linear regression model, we found that the recipient weight determined the value of absGFR by 43%, while the donor weight only by 4% at discharge from the hospital. One year after TPL and at the end of follow-up, the contribution of the recipient actual weight was 57 and 20%, respectively, while no contribution of the donor weight was documented.

Effect of the donor age on eGFR after TPL

There was no significant correlation between the donor age and eGFR at patient discharge after surgery and 1-year post-TPL. However, a significant negative correlation between the donor age and eGFR was found at the last follow-up (r = 0.4254, P < 0.01) (Figure 2).

Effect of the donor sex on D/R BWR and eGFR

There was no difference between male and female donors for D/R BWR (2.11 ± 0.83 for males and 2.44 ± 1.21 for females) or for graft eGFR in the evaluated post-TPL time intervals.

Discussion

In autologous kidneys, the glomeruli and the kidney parenchyma in general undergo hypertrophy during body growth and increase their function appropriately to the organism demand [9–11]. Similarly, paediatric grafts transplanted to children increased their size and function as a response to the body growth [12, 13]. In general, a quantity of the kidney parenchyma and its functional capacity correlate with anthropometric data of the body. It was also clearly established that both the number and size of the glomeruli show a significant positive correlation to the kidney weight and a negative correlation to the age [14]. The ‘dose’ of transplanted renal parenchyma, which is influenced by many factors, such as the birth weight of a donor, the body habitus at donation, age, gender and race [14, 15] appear to be important determinants of the renal allograft performance in addition to antigen-dependent processes. Moreover, a lower incidence of acute rejection episodes with higher grafted kidney volume has been also described [16, 17].

Few studies longitudinally correlated graft function with descriptive models of the donor body habitus. In the group of 123 graft recipients from living donors, the donor kidney weight correlated with the donor’s body mass index and, after TPL, with creatinine clearance at 12-month post-TPL [18]. The predonation kidney volume or a transplant kidney volume/recipient body weight ratio (the kidney volume was measured either by sonography or by MRI),
correlated positively with GFR at 6 months, 1 and 2 years after TPL [16,19]. The concept of dual kidney TPL also stems from a presumption that the utilization of double kidney transplant from extremely young or old donors can compensate for marginal allograft function of such single kidney [20–22].

Therefore, we hypothesized that the body weight of the donor and thereby the mass of the kidney parenchyma in relation to the recipient body weight may influence graft function in transplanted children.

We found a significant positive correlation between D/R BWR and eGFR at all post-TPL time intervals evaluated. This correlation was strongest shortly after TPL and at 1-year post-TPL (Figure 1A and B), but the slope of the regression line remained ascending and statistically significant even at the last follow-up, nearly 5.5 years after TPL (Figure 1C). It is
apparent from Figure 1C that the variation of eGFR values was broad in comparison with the two earlier periods (Figure 1A and B), and we presume that various immunological and nonimmunological processes partially overlapped the original effect of D/R BWR on eGFR. Other investigators did not find significant differences in both graft function and absolute graft volume at the end of follow-up (38 months) in the three groups of children transplanted from paediatric cadaveric donors with a different ratio between the graft volume and the BSA of the recipient [23]. It is apparent from Figure 1 that the most prominent effect of a kidney parenchyma dosage on eGFR was in the range of very high values of D/R BWR (between 4 and 5), but we found that the decisive factor for both graft eGFR and absGFR was the weight or BSA of the recipient, while transplanted renal mass played only a minor role. Therefore, a recipient metabolic demand is the more important determinant of the graft function than the transplanted donor kidney mass.

It has been known for a long time that the BSA is a basis for the comparison of renal function and the nephron number in infants and adults [24]. In our retrospective study, we used the donor body weight as a measure of the kidney mass, because we did not know the height of most of our cadaveric donors. Our approach is justified by the facts that a body mass also correlates closely with the kidney volume and kidney length, measured by sonography [25], X-ray, CT scanning [26] or with kidney dimensions and volume measured directly after donor nephrectomy [27, 28] or in normal individuals who died suddenly [29].

The donor age was repeatedly identified as an important risk factor for elevated serum creatinine and long-term graft failure [6, 12, 30], especially if donors were >60 years of age [31]. The effect of middle-aged donors on the graft function is less documented. We aim to have organs from younger donors, mostly <50 years; the oldest donor was only 52 years old.

The negative influence of the donor age on eGFR reached statistical significance only at the last follow-up. However, at all evaluated post-TPL time periods, a decreasing slope of the linear regression line between these two variables was apparent. The reasons for accelerated post-TPL time-dependent decrease in eGFR with increasing age of a donor are multiple. The ‘zero hour’ natural nonspecific changes of the graft from older donors (i.e. kidney regressive changes in the body of a donor), like glomerulosclerosis, arteriolosclerosis and interstitial sclerosis [32], may cause the graft to be more sensitive to a progression of the regressive changes of immune and nonimmune mechanisms in the body of a recipient. Moreover, grafts from older donors adapt less appropriately to the growth of a child than grafts from pediatric donors [12, 13].

Conclusion

Our results documented a long-lasting positive effect of D/R BWR and a negative influence of adult middle-aged donors age on eGFR. The D/R BWR was not shown to be a useful parameter to predict posttransplant renal function because both eGFR and absGFR were mainly determined by the recipient body weight. A body mass of the donor (and hence the transplanted kidney mass) influenced graft function only marginally.

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References


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