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CLINICAL INVESTIGATION

Renal functional adaptation of the adult kidney following transplantation to the child

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Renal functional adaptation of the adult kidney following transplantation to the child. Nineteen child renal transplant recipients, aged 1.3 to 19.2 years at transplantation, and their adult living-related kidney donors, 27 to 60 years of age at nephrectomy, were investigated simultaneously with regard to renal function. At a median time of three months after transplantation clearances of inulin (GFR) and para-aminohippuric acid (ERPF) were measured, and serum urea and creatinine concentrations were determined. The absolute values for GFR (72 ± 13 ml/min) and ERPF (369 ± 76 ml/min) in the donors were significantly higher than those of the recipients (37 ± 22 and 196 ± 72 ml/min, respectively). The absolute values of GFR and ERPF were significantly correlated with the body surface areas of the recipients. Thus, in relation to body surface area, the GFR, 68 ± 11 ml/min/1.73 m^2, and ERPF, 348 ± 65 ml/min/1.73 m^2, of the donors did not differ from those of the recipients, 68 ± 20 and 375 ± 90 ml/min/1.73 m^2, respectively. Because of the greater body mass, the serum creatinine concentrations of the donors were significantly higher than those of the recipients, whereas the serum urea concentrations were significantly higher in the recipients. The results suggest that transplantation of an adult kidney to a child results in a functional adaptation to the smaller body size of the recipient, and that this adaptation occurs within three months after transplantation.

There are many factors which influence the function of the transplanted kidney. Complications in connection with the operation, for example ischemia, injury to the kidney, ureter or blood vessels and renovascular thrombosis, can impair renal function [1]. Rejection and immunosuppressive therapy are additional factors that can lead to decreased renal function [1]. On the other hand, one might expect the single transplanted kidney to be stimulated to compensatory hypertrophy with ensuing hyperperfusion and hyperfiltration [2]. The original function of the donor kidney is also of importance, as is the size of the kidney. It has been shown that a pediatric donor kidney can increase its function after transplantation to an adult [3]. The renal functional changes of the adult kidney after transplantation to the child have been studied much less. In experimental studies transplantation of an adult rat kidney to a juvenile isogeneic recipient without immunosuppressive therapy has resulted in a rapid decrease in the absolute GFR [4]. It was postulated that this decrease was the result of a functional adaptation to the smaller body size of the recipient. Whether similar functional changes occur after renal transplantation of an adult kidney to a child is not known. The aim of this investigation was to evaluate renal function in children transplanted with a kidney from an adult living related donor, and to compare it with the function of the remaining kidney of the donor.

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Methods

Nineteen children, 10 boys and 9 girls, aged 1.3 to 19.2 (median 6.4) years at transplantation, and their kidney donors, nine fathers, nine mothers, and one grandmother, 27 to 60 (median 38) years old at nephrectomy, were investigated at the same time 1 to 15 (median 3) months after the transplantation. Further characteristics of the children, their underlying disorders and their treatment at the time of the investigation are given in Table 1. Table 2 shows the characteristics and prenephrectomy values of renal function of the donors.

Renal function was evaluated as the glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) determined as the clearances of inulin (Inutest, 25%, Laevosan-Gesellschaft) and para-aminohippuric acid (aminohippurate sodium, 20%, MSD), respectively. A standard clearance technique was used, employing continuous infusion after a priming dose [5]. Water diuresis was induced by the oral ingestion of 20 ml water/kg body wt during the first hour and then 5 ml/kg body wt every 30 minutes. This enabled the patients to empty their bladders by spontaneous micturition every 30 minutes. Four urine samples were collected and midway through each collection period a blood sample was drawn. The clearance values presented are the means of the four clearance periods. The body surface area (BSA) was calculated according to Haycock, Schwartz and Wisotsky [6]. The serum urea concentration was measured by a standard method on the basis of urease glutamate-dehydrogenase and the serum creatinine concentration was measured by a modified Jaffe technique.

The Wilcoxon rank-sum test was used when comparing serum urea and creatinine concentrations. The paired *t*-test was used for the statistical analyses of GFR, ERPF, and the filtration fraction (FF). The correlation coefficients (r) were calculated and the significance of correlations was evaluated with Student's *t*-test. Values are given as means ± SD. The study was approved by the Committee on Ethics of the Karolinska Institute.

Results

Figure 1 shows the GFR in paired donors and recipients in absolute values and related to BSA. The absolute GFR of the donors (72 ± 13 ml/min) was significantly higher ($P < 0.001$)

Table 1. Age, sex, and underlying disorder of the 19 child recipients

Pat. No.	Sex	Age at tx, yr	Intra-abdominal graft	Underlying disorder	Time after tx, months	Medical treatment at the time of investigation *mg/kg/day*						CsA conc. *ng/ml*	No. of rej. epis.
						Pred	CsA	Aza	Furose-mide	Propran-olol	Other		
1	M	1.3	yes	Dysplastic kidneys + urethral valvula	15	0.31	12.5	—	—	—	—	50[a]	0
2	F	5.9	yes	Dysplastic kidney + agenesis	4	0.50	12.5	—	1.0	1.0	—	540[a]	0
3	F	9.1	yes	Juvenile nephronophtisis	10	0.27	8.9	—	—	—	—	550[a]	0
4	F	3.1	yes	Glomerulocystic disease	3	0.54	8.7	—	2.2	3.3	Hydr 1.6	450[a]	1
5	M	5.1	yes	Dysplastic kidney + agenesis	1.5	0.88	11.8	0.8	3.5	7.1	Captopril 0.37, Hydr 5.3	260[a]	1
6	M	4.5	yes	Multicystic dysplastic kidneys	4	0.63	16.5	0.8	1.9	7.6	Nif 2.5, Hydr 0.63, Enalapril 0.47	740[b]	2
7	F	7.1	yes	Renal malformations + UTI	1	0.56	13.5	0.9	—	—	Nitrofurantoin 1.1	1850[b]	0
8	M	13.1	no	Chronic GN	4	0.85	15.3	2.1	—	5.1	Nif 1.7	540[b]	0
9	M	11.3	yes	Polycystic kidney disease	4	0.35	7.1	—	2.8	—	Nif 0.35, Spironolactone 1.8	410[b]	1
10	F	6.4	no	IgA nephropathy	3	0.35	11.3	0.9	1.4	1.4	—	390[b]	2
11	M	4.5	yes	Polycystic kidney disease	3	0.57	11.5	1.4	2.3	1.1	—	468[b]	2
12	M	3.7	yes	Cono-renal syndrome	3	0.91	14.5	1.1	1.8	—	Metoprolol 4.5	320[b]	0
13	F	11.9	no	Anti-GBM GN	4	0.28	5.6	1.4	1.1	0.8	Nif 0.56	94[c]	0
14	F	5.9	yes	Multicystic dysplastic kidneys	3	0.50	6.0	1.0	2.0	—	Nif 1.0	72[c]	1
15	F	12.4	no	Unknown	3	0.18	2.9	0.9	1.0	—	Nif 0.7	83[c]	1
16	M	4.2	yes	Prune-Belly syndrome	3	0.39	9.3	1.0	2.0	2.0	—	127[c]	2
17	M	19.2	no	Dysplastic kidneys	4	0.18	8.2	0.9	—	—	—	390[c]	0
18	M	7.9	yes	Dysplastic kidneys + urethral valvula	3	0.52	10.5	1.1	0.5	—	Norfloxacin 10.5	164[c]	0
19	F	14.8	no	Juvenile nephronophtisis	2	0.21	6.3	1.0	0.6	—	Metoprolol 2.1	141[c]	0

Their medical treatment, cyclosporine trough blood levels and number of experienced rejection episodes at the time of the investigation are given.

Abbreviations are: UTI, urinary tract infection; GN, glomerulonephritis; GBM, glomerular basement membrane; Pred, prednisolone; CsA, cyclosporin A; Aza, azathioprine; Nif, nifedipine; Hydr, hydralazine.

[a] Plasma and [b] whole blood levels, polyclonal RIA method

[c] Whole blood, specific monoclonal RIA method

than that of the recipients (37 ± 22 ml/min). When related to BSA, however, the GFR of the donors (68 ± 11 ml/min/1.73 m^2) did not differ from that of the recipients, (68 ± 20 ml/min/1.73 m^2). When GFR was expressed as the percentage of the donors' prenephrectomy GFR values, the donors had postnephrectomy GFRs of 65 ± 9%. The corresponding value for the recipients was 64 ± 19%.

In Figure 2 the ERPF is illustrated with absolute and relative values. The absolute ERPF value for the donors (369 ± 76 ml/min) was significantly higher ($P < 0.001$) than for the recipients (196 ± 72 ml/min). Related to BSA, the ERPF of the donors (348 ± 65 ml/min/1.73 m^2) was not significantly different from that of the recipients (375 ± 90 ml/min/1.73 m^2). There was no significant difference between the FF of the donors, 20.3 ± 2.6%, and the FF of the recipients, 18.4 ± 5.2%.

In Figure 3 the recipients' absolute values for GFR and ERPF have been related to their BSAs. Significant ($P < 0.001$) correlations of 0.79 and 0.81, respectively, were found.

Figure 4A shows the absolute GFR values of the donors and recipients expressed as percentages of the prenephrectomy donor single kidney GFRs. The calculations are based on the assumption that the donor's prenephrectomy single kidney GFR was 50% of the total GFR. The mean percentage GFR of the donors was 131% of the prenephrectomy single kidney donor GFR. The corresponding GFR value for the recipients was 67%. In Figure 4B the absolute GFRs of the recipients expressed as percentages of the donors' absolute, prenephrectomy single-kidney GFR are related to the BSAs of the recipients. A highly significant correlation was found with a coefficient of 0.86 ($P < 0.001$).

No correlations were found between renal functional parameters and the number of rejection episodes or cyclosporine blood trough levels.

The mean serum urea concentration in the donors was 5.1 ± 0.7 mmol/liter, significantly lower ($P < 0.01$) than that of the recipients (8.4 ± 3.3 mmol/liter). The serum creatinine concentration in the donors (103 ± 15 μmol/liter) was significantly higher ($P < 0.01$) than that of the recipients (68 ± 27 μmol/liter).

Table 2. Renal function before unilateral nephrectomy (nx) in the 19 adult kidney donors

Donor no.	Sex	Age at nx *years*	GFR *ml/min/1.73 m²*	50% of pre-nx GFR *ml/min*
1	M	36	128[a]	69
2	F	41	105[c]	53
3	M	40	88[c]	44
4	M	41	109	58
5	F	60	107[c]	50
6	M	33	90	48
7	M	42	107	62
8	F	35	104[b]	52
9	F	44	101	45
10	F	44	93	43
11	M	27	100	63
12	M	33	120	64
13	F	39	120	53
14	F	34	96	46
15	F	35	95[b]	58
16	F	35	114	61
17	M	45	99[b]	52
18	M	38	117	69
19	F	33	110[b]	66

GFR is the glomerular filtration rate measured as the clearance of inulin.
[a] Clearance of creatinine
[b] Clearance of ^{51}Cr EDTA
[c] The mean of clearances of ^{51}Cr EDTA and creatinine

Discussion

Investigations of the kidney function of renal donors before and after nephrectomy provide information on the response of healthy individuals to uninephrectomy [7–11]. A nearly immediate functional adaptation and a residual renal function of about 70% of the prenephrectomy GFR and ERPF values have been reported [7, 8]. A comparison of the renal function of the donor with that of the recipient provides a basis for the evaluation of such factors influencing the function of the transplanted kidney as the effects of ischemia time, trauma, and mechanical obstruction. Other factors affecting renal function of the transplanted kidney might be immunosuppression, rejection episodes, the size of the kidney donor and recipient, and the effects of compensatory hypertrophy.

Ogden reported a slight, but not significant, difference between donor and recipient GFR and ERPF in cases where the sizes of the donors and the recipients were, for the most part, similar [12]. They reported GFR to be about 71% of the prenephrectomy value soon after nephrectomy as well as three years later. Thus they state that the ideal homograft function should approach 70% of the preoperative donor function if the graft is capable of increasing its function to the same extent as the donor's remaining kidney. In the present study the recipients' GFR per 1.73 m^2 was of the same magnitude as mentioned by Ogden [12], 64% of the donors' prenephrectomy values, and was not different from that of the donors (65%).

The percentage adaptation reported above is calculated from the GFR values corrected for 1.73 m^2 BSA. However, when the renal function data expressed as absolute values were analyzed, the GFRs of the recipients were significantly decreased in comparison with those of the donors. In fact, the decrease was directly related to the size (BSA) of the recipient (Fig. 3). If the decrease in renal function was caused only by trauma, ischemia, or obstruction, it probably would not be significantly correlated with the BSA.

A possibly damaging effect of the immunosuppressive agent, cyclosporine, could be expected. The nephrotoxicity of cyclosporine has been documented, and Hoyer et al report a significantly lower clearance of inulin in cyclosporine treated children six weeks after transplantation as compared to azathioprine treated historical controls [13]. However, in accordance with our findings, the actual cyclosporine blood trough level did not correlate with the GFR.

Another factor of importance for the function of the transplanted kidney might be rejection. In the present group of children who had received kidneys from living related donors, the number of rejection episodes correlated neither with the absolute GFR nor with the GFR related to BSA. An influence of rejection on long-term renal function cannot be ruled out and has been reported by Hoyer et al [13]. They found a significant correlation between the number of rejection episodes and GFR one year, but not six weeks, after transplantation. Thus neither the number of rejection episodes nor cyclosporine seemed to be major determinants of the renal function of the recipients.

Transplantations of kidneys between individuals of different sizes have been studied previously, mostly with regard to a juvenile donor kidney transplanted to an adult. It has been shown that kidneys from young donors have the capacity to increase their GFR and size following transplantation into adults [3, 14–17]. Less attention has been focused on the opposite situation, the transplantation of an adult kidney into a child. Experimental studies have shown that the transplantation of an adult rat kidney to a juvenile rat recipient results in a rapid decrease in the absolute GFR [4]. When the juvenile rat recipient reached adulthood the GFR did not differ from that of adult recipients of adult kidneys, indicating that the initial decrease in GFR was not caused by surgical or ischemic damage. Neither immunological damage nor a nephrotoxic effect of immunosuppressive agents was encountered since isogeneic transplantations were made. The decrease in GFR was interpreted to be a functional adaptation to the small body size of the recipient. Our results indicate that a similar functional adaptation also occurs after the transplantation of an adult kidney to a child. Thus we found a highly significant correlation between absolute GFR and ERPF and the recipients' BSA (Fig. 3).

If no damage, no functional adaptation, and no compensatory hypertrophy occurred in the transplanted kidney, that is, if the transplanted adult kidney retained its prenephrectomy absolute GFR after transplantation to the child, the GFRs of the small recipients would amount to 150 to 225 ml/min/1.73 m^2.

To further analyze the subject of compensatory hypertrophy, we calculated the absolute GFR values of the donors and recipients as percentages of the donors' prenephrectomy single-kidney GFR (Fig. 4A). The donors had GFR values ranging between 93% and 158% (mean 138%) of the prenephrectomy single-kidney values, indicating compensatory hypertrophy of the remaining kidney. Without damaging effects and functional adaptation of the transplanted kidney, the GFR of the recipients would be 100% of the prenephrectomy single-kidney donor GFR even without compensatory hypertrophy. The percentage GFR of the recipients, however, ranged between 21% and 162%

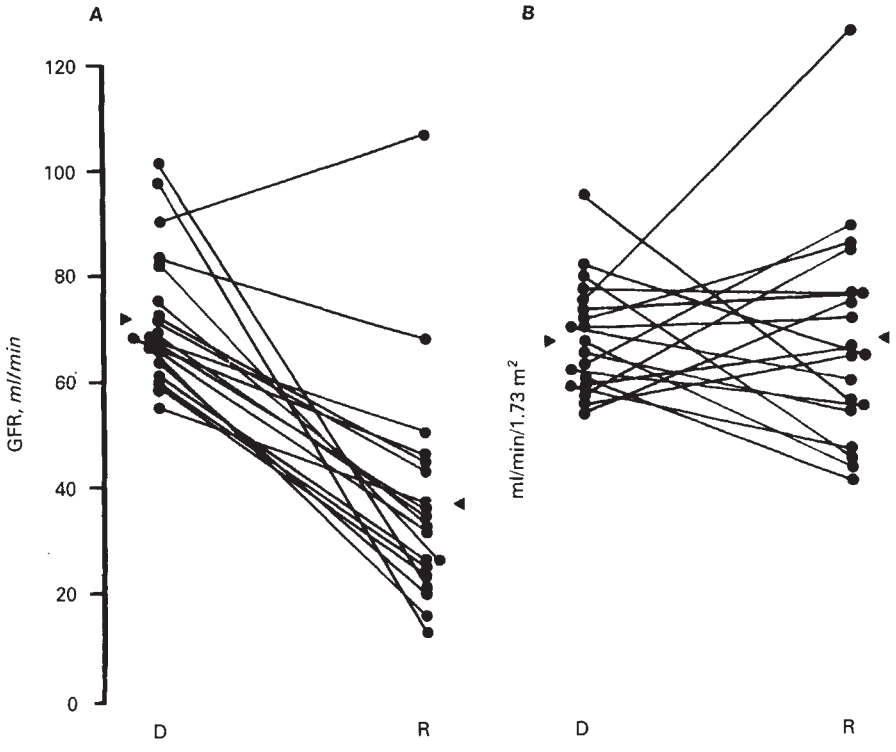

Fig. 1. *Glomerular filtration rates (GFR) of paired adult donors (D) and pediatric recipients (R) expressed in absolute values (A) and related to body surface area (B).* ◀ = mean value.

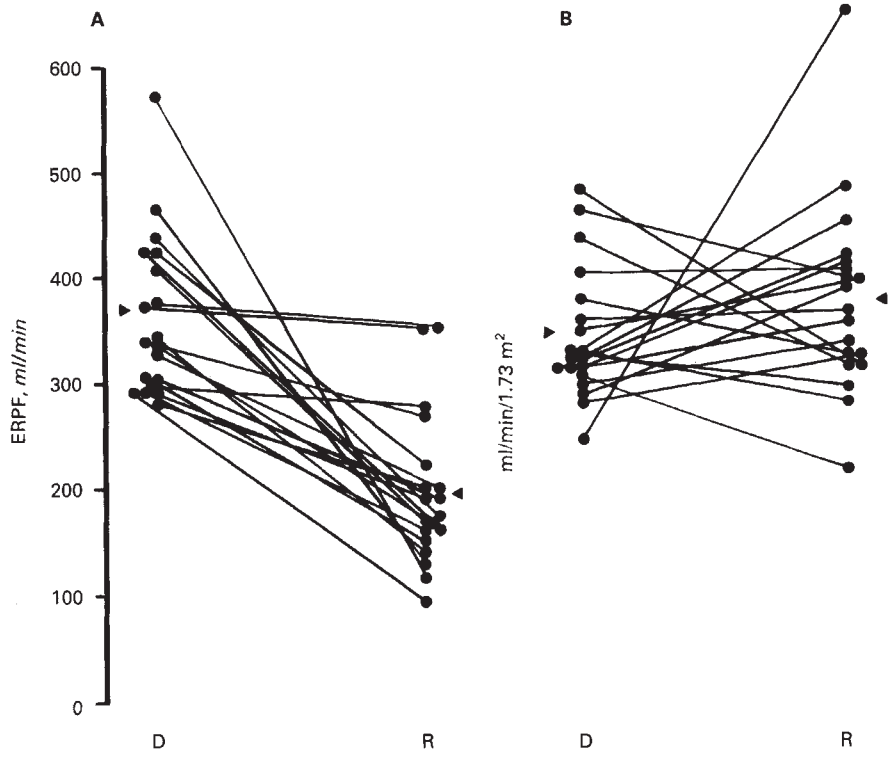

Fig. 2. *Effective renal plasma flows (ERPF) of paired adult donors (D) and pediatric recipients (R) expressed in absolute values (A) and related to body surface area (B).* ◀ = mean value.

(mean 67%) and was highly significantly related to the BSA of the recipient (Fig. 4B). This strongly indicates that functional adaptation of the transplanted kidney to the size of the recipient is an important factor in the decrease in renal function of an adult kidney after transplantation to a child. Previous information on this subject in the literature regarding clinical series is very scanty. In one clinical investigation two groups of child recipients of adult kidneys, under and over 12 years of age,

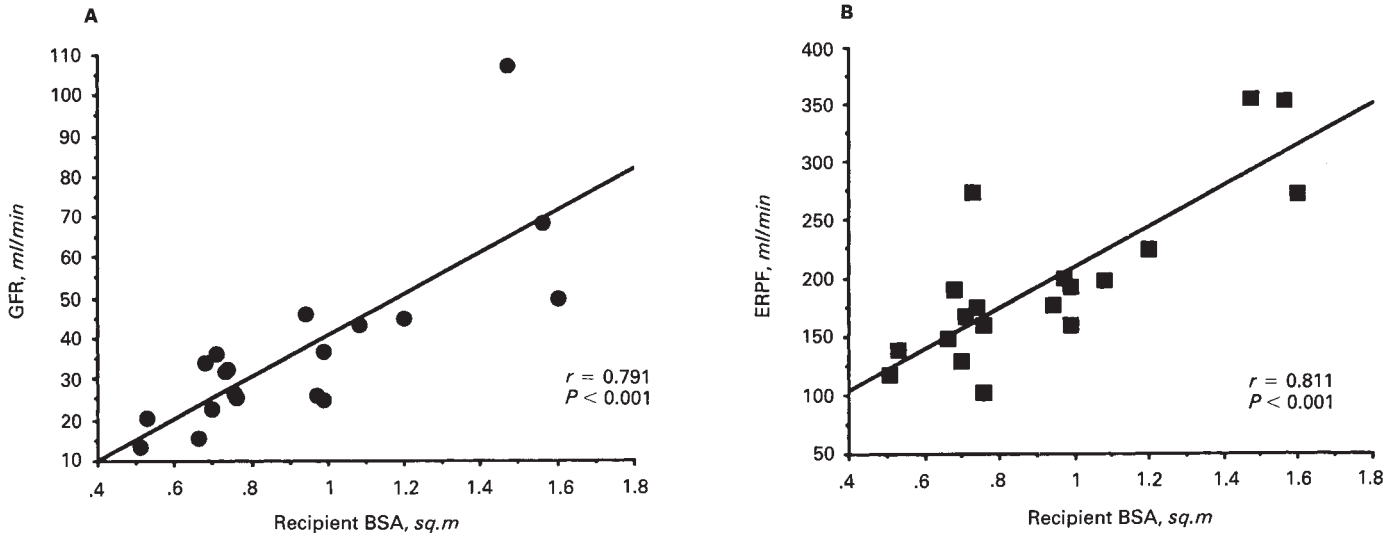

Fig. 3. *The absolute values of glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) in individual patients in relation to the body surface area.*

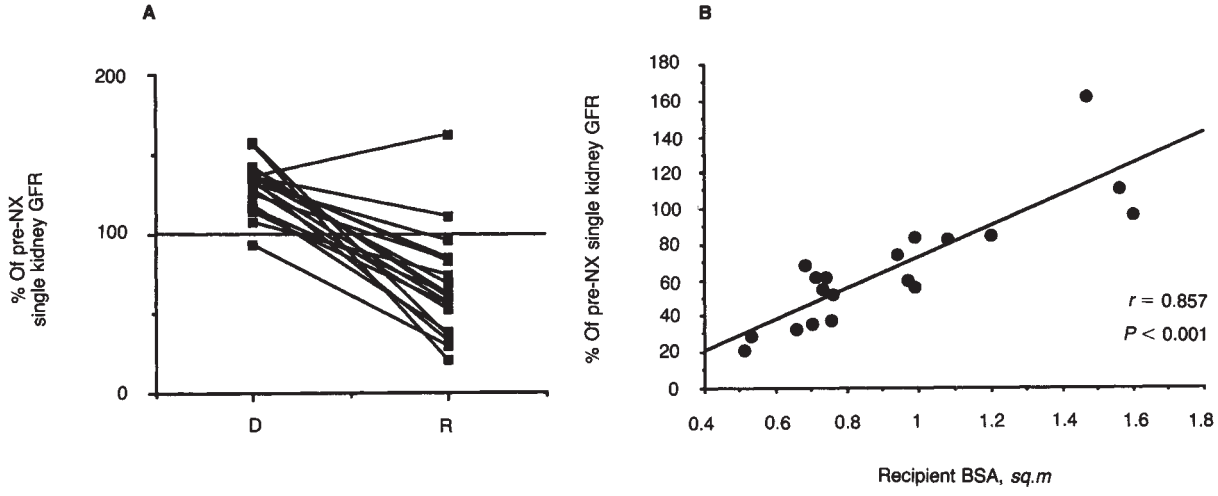

Fig. 4A. *The absolute GFR of donors (D) and recipients (R) in percentages of absolute values of the prenephrectomy (pre-nx) single-kidney GFR of the donors.* The line indicates an unchanged GFR. Values above the line suggest compensatory hypertrophy and values below the line indicate a decrease in the absolute GFR. **4B.** The absolute GFRs of the recipients in percentages of the donors' absolute prenephrectomy single-kidney GFRs (% pre-nx) in relation to the body surface areas (BSA) of the recipients.

respectively [18], were compared retrospectively. Three weeks after transplantation the absolute values for creatinine clearance in the younger recipients were significantly lower than those for the older recipients. However, when related to BSA, the creatinine clearances did not differ between the groups. Silber studied four children during four months after transplantation with adult kidneys and found lower absolute creatinine clearances in the children than in their donors [16]. He also studied kidney length, measured by intravenous pyelography, and found no compensatory hypertrophy in the child recipients, whereas the adult donor's kidneys increased in length during the four month follow-ups. In the present study attempts were made to measure kidney size, but because of the many intra-abdominally placed grafts, there were technical difficulties in measuring kidney size by ultrasound. Bunchman et al measured renal allograft length by ultrasound in recipients less than four years of age after transplantation of an adult kidney [19]. They reported a successive decrease in renal length during two years of follow-up. This lack of compensatory hypertrophy might be a consequence of the renal functional adaptation to a small body size indicated by our results.

The mechanism underlying this functional adaptation is not clear. The lower blood volume of the recipient, resulting in a lower renal perfusion, could be one explanation for the lower GFR. This hypothesis is supported by the fact that there is no difference in FF between the two paired kidneys.

Half of the children were on antihypertensive treatment. Hypertension after renal transplantation is very common in children [20], and there are many possible mechanisms: corticosteroids, cyclosporine, residual renin activity in the native

kidneys, and an increased circulatory burden because of a large graft. A relative arterial stenosis at the anastomosis site is less probable, since posttransplantation hypertension usually decreases with time, and it is often possible to withdraw the antihypertensive therapy within a year or so. This has also been our experience with the children in the present study. Therefore, an arterial stenosis is not a probable cause of a diminished blood flow to the transplanted graft and thus of a decreased ERPF and GFR.

The significantly higher serum creatinine concentrations of the donors compared to those of the recipients could be explained by the great difference in body mass. The relatively increased serum urea concentrations of the recipients might be explained by the nephrotoxic effect of cyclosporine, which is characterized by a disproportionate increase in blood urea nitrogen [21].

In conclusion, the present study shows that after transplantation of an adult kidney to a child there is a decrease in the absolute values of GFR and ERPF, which is proportional to the recipient's size. Thus, related to body surface area, the function of the transplanted kidney in the recipient is equivalent to that of the remaining kidney of the donor. These results indicate a functional adaptation of the adult kidney to the small body size of the child recipient following transplantation.

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