



ORIGINAL ARTICLE

Small donors for small recipients – excellent growth and long-term function of single kidney grafts

Metin Cetiner¹, Andreas Paul², Juergen W. Treckmann², Susanne Dittmann², Rainer Büscher¹, Peter F. Hoyer¹ & Anja K. Büscher¹

1 Paediatric Nephrology, University Children's Hospital, University Duisburg-Essen, Essen, Germany
2 General, Visceral and Transplantation Surgery, University Hospital Essen, Essen, Germany

Correspondence

Anja K. Büscher, University Children's Hospital, University Duisburg-Essen, Hufelandstr. 55, 45122 Essen, Germany.
Tel.: 0049-201-723-2565;
fax: 0049-201-723-5947;
e-mail: anja.buescher@uk-essen.de

SUMMARY

Small-donor kidneys (≤ 20 kg donor weight, SDK) are preferably transplanted en bloc in adults. Concerns about thrombotic complications or hyperfiltration hinder their use in children, particularly as single grafts. Low centre experience and donor-to-recipient size are rated critical regarding outcomes. We evaluated SDK transplantation (SDTx) in paediatric recipients at a specialized transplant centre. Between 2008 and 2018, SDTx was performed in 40 children (mean age 5.4 ± 1.4 years, single grafts $n = 38$, donor weight ≤ 10 kg: $n = 10$). Perioperative complications were rare ($n = 3$), mainly thromboses despite immediate heparinization and resulted in graft loss in one patient. Overall, early and long-term GFR were excellent (76 ± 21 and 100 ± 11 ml/min/1.73 m², first month and year 5, respectively). Three patients presented with delayed graft function. Graft volume increased significantly (69 ± 38 vs. 111 ± 33 ml within 5 years; $P < 0.0001$). Patients showed catch-up growth to normal range (SDS for height -2.06 ± 1.6 to -1.60 ± 1.5). Stratification by recipient age and donor weight revealed superior results in young recipients (≤ 3 years) and ≤ 10 kg donors, respectively. Outcome of single SDK grafts was excellent. Gain of GFR and graft volume was even higher in patients with very small donor or recipient size, regardless of a reduced donor-to-recipient weight ratio. Therefore, SDTx should be considered favouring small paediatric recipients.

Transplant International 2021; 34: 2735–2745

Key words

graft function, graft thrombosis, graft volume, kidney transplantation, paediatric recipients, small donor grafts

Received: 21 April 2021; Revision requested: 23 August 2021; Accepted: 10 September 2021;
Published online: 3 November 2021

Introduction

Renal transplantation (RTx) is the best treatment option in patients with end-stage renal disease (ESRD). This accounts in particular for paediatric patients as fundamental development processes are of high importance at that stage of life. Therefore, early transplantation should be pursued to minimize time on dialysis. Contrarily,

increasing prevalence of ESRD together with a decline of living kidney donations led to expanding waiting lists with deleterious effects on lifetime and quality [1–3]. Kidneys from donors < 20 kg (SDK) are a still underutilized organ source and to date preferably transplanted en bloc in adults [4–6]. Recent studies demonstrated favourable SDK outcome for this setting [4,5]. Superior graft survival was associated with donor weight

>10–15 kg, higher donor/recipient weight ratio (D/R), en bloc versus single grafts, and a high level of experience at the transplant centre [4–8]. In contrast, lower donor-to-recipient size was shown to result in higher graft loss [9] possibly related to hyperfiltration-induced kidney injury [10]. Moreover, recent registry data reported the highest risk of graft failure for young recipients of grafts from young donors (<5 years of age) [11]. Together with reports about early complications as graft thrombosis, these concerns currently discourage the use of SDK as single grafts and in paediatric recipients [5–7,11,12]. However, their small size qualifies them as ideal organs for children preventing difficulties of size-mismatched RTx as renal allograft compartment syndrome and/or hypoperfusion [13,14]. Their use as single grafts could expand the donor pool-diminishing waiting time. Therefore, detailed long-term data on young recipients receiving single grafts are highly requested [15,16].

We present encouraging experience of SDK transplantation (SDTx) in young children performed at a specialized organ-transplant centre. The retrospective analysis included 40 paediatric recipients (mean age 5.4 ± 1.4 years) receiving SDKs (95% single grafts) and focused on perioperative complications, early and long-term graft function, organ growth, and hyperfiltration injury.

Patients and methods

Collection and processing of clinical data

We retrospectively analyzed clinical data of paediatric patients (age 0–18 years) following RTx from a deceased small donor (donor weight ≤ 20 kg). Conditions regarded critical, such as donor weight ≤ 10 kg or young recipient age, were subject of further subanalyses. RTx was performed at the University Hospital of Essen between 01/2008 and 12/2018. Procurements were conducted by standards defined by Eurotransplant. All donors were brain-dead heart-beating donors, and the kidneys of donors ≤ 5 years were procured en bloc. If organs were used as single grafts, the paired kidney was not discarded but reallocated by eurotransplant. Transplantations and postoperative treatment were conducted by a transplant team with long-standing experience with paediatric solid-organ transplantation, including a 24/7 paediatric ultrasound facility (Toshiba SSA-790A, PVT 375BT; Toshiba Medical Systems Europe B.V., Zoetermeer, Netherlands). Biopsies of the transplanted organs were conducted ultrasound-guided with a small needle

(18 gauche) and under sedation with ketamine/midazolam. After hospital discharge, patients were followed up at the University Children's Hospital, Department of Paediatric Nephrology, in at least monthly intervals until adulthood or change of transplant centre. Glomerular filtration rate (GFR) was calculated according to the Schwartz formula [17]. Anthropometric parameters were converted into standard deviation score (SDS) according to the data published by Kromeyer-Hauschild *et al.* [18]. The local ethics committee approved the study (21-9816-BO).

Clinical data

Donor characteristics

Age, weight, height, body mass index (BMI), gender, cause of death, and GFR.

Recipient characteristics

Age, weight, height, BMI, gender, underlying kidney disease, dialysis (preemptive transplantation, hemodialysis, peritoneal dialysis), cold and warm ischemia time (CIT, WIT), human leukocyte antigen (HLA) mismatch, waiting time, D/R, and immunosuppression.

Outcome parameters

Graft and patient survival, GFR, delayed graft function (DGF, dialysis within the first week after RTx), graft volume (ml) in patients without dilation of the urinary tract [19] and graft perfusion, perioperative complications (e.g., bleeding, urinary leakage, arterial/venous thrombosis), donor-specific antibodies (DSA, Luminex multiplex assay), graft histology (Banff classification) [20], biopsy-proven rejection episodes, proteinuria, and post-transplant lymphoproliferative disease (PTLD). Data on graft survival, function, and growth were raised for the following time points: 1 week, 1 month, 1-, 3-, and 5-year(s) post-transplant.

Statistics

Data are given as mean value \pm standard deviation (SD). Comparison of continuous variables was performed with Students' *t*-test and one-way ANOVA. The level of statistical significance was predefined as $P < 0.05$ (two-tailed). Correlations were performed by linear regression analysis. Survival data were analyzed by Kaplan-Meier test. Statistical analysis was performed

using GraphPad Prism© (version 5.01 for Windows; GraphPad Software, San Diego, CA, USA).

Results

Patients

During the study period (01/2008–12/2018), 122 paediatric patients (0–18 years) received an RTx at the University Hospital of Essen, and 40/122 (33%) from a deceased donor with a body weight ≤ 20 kg (small donor). In 10/40 (25%) of these patients, donor weight was ≤ 10 kg. 2/40 patients underwent combined liver/kidney transplantation, and another 3/40 patients had received a liver transplant previously (0.3, 0.8, and 3.6 years before RTx). The mean observation time was 6.4 ± 3.7 years.

Donor characteristics

Anthropometric donor data are provided in Table 1. The cause of brain death was hypoxia in 13/40 patients (33%), trauma in 11/40 (28%), and cerebral bleeding in 6/40 (15%). 2/40 (5%) donors died from brain tumors and 1/40 (3%) from meningitis; 7/40 (18%) were classified as other causes of respiratory failure.

Recipient characteristics

The anthropometric data of recipients are given in Table 1. Underlying renal diagnosis was congenital anomalies of the urinary tract in 17/40 patients (43%), nephrotic syndrome in 8/40 (20%), cystic kidney disease in 6/40 (15%), metabolic disease, atypical hemolytic uremic syndrome, or renal failure owing to perioperative or postpartum complications in 3/40 (8%) patients, each. Before RTx, 27/40 (68%) patients were treated with peritoneal dialysis, 2/27 (7%) changed to

hemodialysis owing to recurrent peritonitis. 6/40 (15%) received hemodialysis and another 2/40 (5%) combined hemodialysis/peritoneal dialysis owing to hyperoxaluria. 5/40 patients (13%) underwent preemptive RTx. Mean waiting time since initiation of dialysis (or time on the Eurotransplant waiting list in case of preemptive transplantation) was 2.0 ± 1.6 years (range 0–7).

Transplantation

38/40 (95%) patients received a single graft; 2/40 were transplanted en bloc. Transplantations were carried out after careful ex vivo backtable kidney preparation with reconstruction of injured vessels, if applicable. Accessory arteries were either ligated (small upper-pole vessels) or implanted end-to-side in the main renal artery. An extraperitoneal approach using a modified Gibson incision (single grafts and en bloc) was applied. After preparation of pelvic vessels and ligation of lymphatic vessels to prevent lymphoceles, renal artery was anastomosed end-to-side to the common iliac artery in 70% of cases (27% aorta/bifurcation, 3% external iliac artery). Venous anastomoses were performed end-to-side to either the common iliac vein or the V. cava, preferably on the right side, avoiding any kinking or contortion (Fig. 1). Site of anastomosis was chosen at the discretion of the surgeon depending on vessel diameter. Microsurgical technique using surgical loupes, 6/0 or 7/0 monofilament sutures, elongated incision after using satinsky clamp, and single stitch technique preventing stitch stenosis have been applied in all anastomoses. Ureteral drainage was established after retrograde filling of the bladder with age adapted volumes. 36/40 (90%) patients received an antireflux ureteroneocystostomy according to Lich-Gregoir (another 2/40 (5%) ureterocutaneostomy or uretero-ureterostomy, each) with temporary insertion of a ureter stent in 33/40 (83%) cases. In 7/40 patients, no ureter stent was inserted due to technical or anatomical reasons. However, none of these patients experienced urine leakage or ureter obstruction. In 8/40 (20%) patients, simultaneous nephrectomy was performed: owing to simultaneous liver transplantation (2/40), enlarged kidneys in case of cystic kidney disease (1/40), or high-grade vesicoureteral reflux (3/40) and bilateral nephrectomy in patients with *WT1* mutations and increased risk of nephroblastoma (2/40). Data on CIT, WIT, HLA mismatch, and D/R are given in Table 2. Immunosuppression consisted of tacrolimus, prednisone, and mycophenolate mofetil in 25/40 patients (63%), tacrolimus with prednisone in 6/40 (15%), or

Table 1. Anthropometric data of recipients and donors.

	Recipient	Donor
Age (months)	65.4 \pm 52.1	23.4 \pm 17.2
Gender, male (n/%)	20/50%	28/70%
Weight (kg)	18.0 \pm 10.9	13.8 \pm 3.6
Weight (SDS)	-1.3 \pm 1.6	0.3 \pm 1.0
Height (cm)	100.7 \pm 24.9	93.0 \pm 13.1
Height (SDS)	-2.06 \pm 1.61	0.84 \pm 1.22
BMI (kg/m ²)	16.7 \pm 2.2	15.8 \pm 2.0
BMI (SDS)	0.07 \pm 1.43	-0.3 \pm 1.5

BMI, body mass index; SDS, standard deviation score.

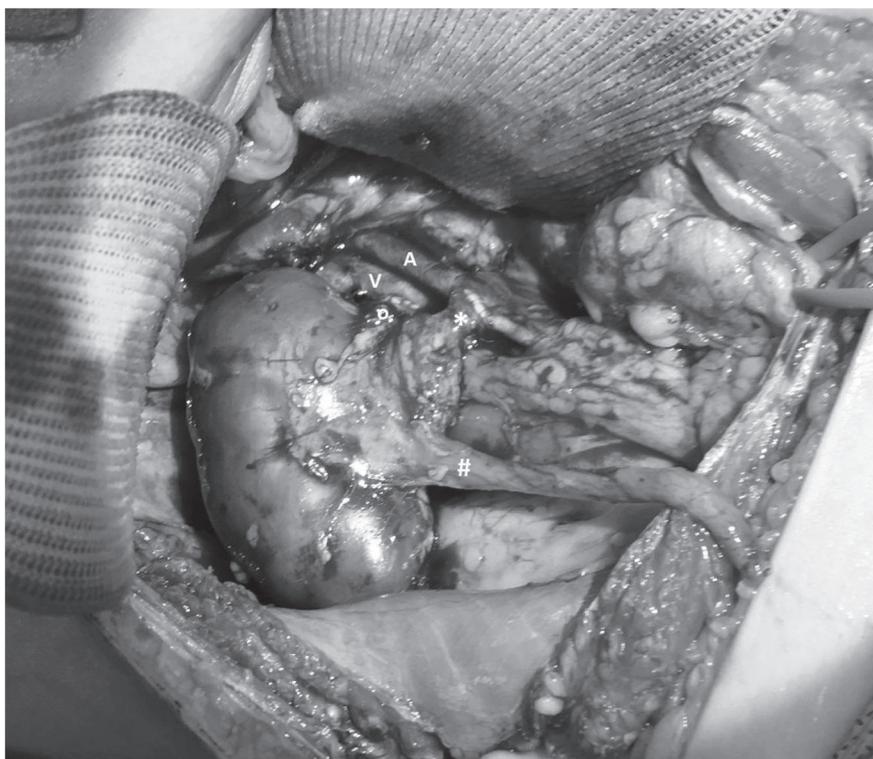


Figure 1 A common iliac artery, V common iliac vein, * arterial anastomosis: renal artery to common iliac artery (end-side), ° venous anastomosis: renal vein to common iliac vein (end-side), # ureter of the transplant kidney before implantation in the bladder

Figure 1 Abdominal situs of a 2-year-old recipient (10.6 kg body weight, 74 cm longitudinal height). Kidney transplant from a small donor (1 month, 4 kg body weight, 54 cm longitudinal height); anastomosis of renal artery end-site to the common iliac artery and renal vein end to side to the common iliac vein.

Table 2. Transplant data.

D/R	0.95 ± 0.45*
WIT (min)	26.0 ± 7.7
CIT (h)	14.0 ± 4.5
HLA A mismatch (n)	0.9 ± 0.6
HLA B mismatch (n)	1.4 ± 0.6
HLA DR mismatch (n)	1.0 ± 0.6
Proteinuria (mg/g crea)	324 ± 222 (241 ± 148)
1 (5) year(s)	
Height (SDS) at RTx (5 years)	-2.06 ± 1.61 (-1.60 ± 1.45)

BMI, body mass index; CIT, cold ischemia time; crea, creatinine; D/R, donor/recipient weight ratio; HLA, human leucocyte antigen; RTx, renal transplantation; SDS, standard deviation score; WIT, warm ischemia time.

*Recipients ≤3 years 1.24 ± 0.42, recipients >3 years 0.74 ± 0.33, donor ≤10 kg 0.73 ± 0.3, donor >10 kg 1.03 ± 0.46.

cyclosporine A together with prednisone (9/40, 2/9 with additional basiliximab, 6/9 with mycophenolatemofetil). Anticoagulation included i.v.-unfractionated heparin

(200 IE/kg/day) for two weeks, starting four hours post-transplant followed by oral acetylsalicylic acid. In case of thrombophilia, i.v.-heparin was started already during transplantation, and doses were adjusted to achieve 1.5-fold prolongation of partial thromboplastin time. After two weeks, subcutaneous low-molecular-weight heparin (enoxaparin) was administered for another 6 weeks (target anti-Xa activity 0.2–0.4) and thereafter oral acetylsalicylic acid [21].

Outcome

Patient and graft survival

3/40 (8%) patients died 2, 10, and 93 months after transplantation, all with functioning grafts. All of them had underlying syndromic disease with multiple comorbidities and severe developmental delay. Cause of death was unrelated to RTx [aspiration ($n = 2$), septicemia after orthopedic surgery ($n = 1$)]. Overall graft survival was 98% (39/40), and one graft was lost because of thrombosis of the renal vein two weeks after RTx. 3/40

patients (7%) presented with delayed graft function, two of them after combined liver/kidney transplantation (hemodialysis for 3 and 5 days, respectively) and another patient because of undiscovered peritonitis at RTx (peritoneal dialysis for 7 days). Comparison of paediatric recipients receiving a graft from a donor >20 kg body weight at our centre within the same time interval ($n = 82$) revealed inferior graft survival in the latter (10-year-graft survival 71/82 (87%) Fig. 2). 2/82 patients of this cohort died with functioning grafts after 0.5 and 5 years, respectively.

Graft function

Overall, mean GFR increased significantly over time from 80 ± 23 ml/min/1.73 m² at RTx to 100 ± 11 ml/min/1.73 m² 5 years later ($P = 0.0003$, Table 3a). After an initial decline of $\Delta - 4.3 \pm 24.4$ ml/min/1.73 m² within

the first month, GFR rose continuously until year 3 and remained within the same range until the end of the observation period ($\Delta - 0.6 \pm 14.8$ ml/min/1.73 m²). Stratification according to recipient age revealed that total gain of GFR was highest in adolescents ($\Delta + 33.8 \pm 12.0$ ml/min/1.73 m² up to 3 years post RTx); however, GFR declined during further follow-up (-9.7 ± 14.9 ml/min/1.73 m² to year 5). In contrast, young recipients (0–3 years) presented with a steady rise of GFR over the whole observation period (Table 3a, Fig. 3a). Analysis concerning donor weight (\leq and >10 kg) demonstrated a significant gain of GFR in both groups (≤ 10 kg: $\Delta + 24.3 \pm 26.7$ ml/min/1.73 m² ($P = 0.03$) and >10 kg: $\Delta + 18.8 \pm 10.5$ ml/min/1.73 m² ($P = 0.04$), respectively, Table 3a). Donor weight ≤ 10 kg was associated with a higher gain of GFR compared with recipients of grafts of >10 kg donors and a steady rise of GFR until the end of the observation

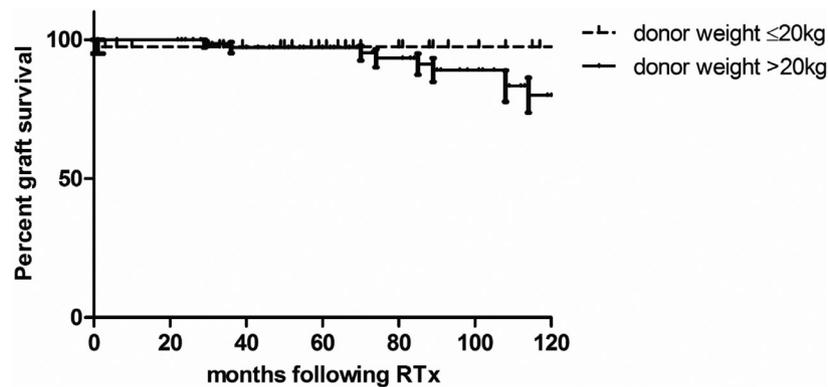


Figure 2 Graft survival of small-donor (≤ 20 kg body weight) kidney grafts ($n = 40$) and of grafts from donors with higher weight ($n = 93$) transplanted at our transplant centre between 2008 and 2018. Graft survival of small-donor kidneys tends to be better compared with higher donor weight.

Table 3. (a) Calculated GFR post-transplant (ml/min/1.73 m²) and (b) increase of graft volume (ml) in relation to the graft volume at one week post RTx.

	All	Recipient age ≤ 3 years	Recipient age > 3 years	Donor weight ≤ 10 kg	Donor weight > 10 kg
(a)					
1 week	80 ± 23	85 ± 22	76 ± 23	81 ± 19	80 ± 24
1 month	76 ± 21	77 ± 24	75 ± 18	81 ± 15	74 ± 22
1 year	88 ± 25	78 ± 31	94 ± 18	96 ± 27	86 ± 24
3 years	101 ± 16	102 ± 19	100 ± 14	103 ± 14	100 ± 17
5 years	100 ± 11	106 ± 12	96 ± 10	105 ± 12	97 ± 10
(b)					
Δ to 1 month	12 ± 17	11 ± 13	14 ± 20	12 ± 12	12 ± 19
Δ to 1 year	39 ± 38	29 ± 28	43 ± 41	26 ± 6	42 ± 42
Δ to 3 years	42 ± 62	30 ± 15	47 ± 73	40 ± 2	43 ± 74
Δ to 5 years	48 ± 38	45 ± 32	51 ± 45	80 ± 25	16 ± 14

GFR, glomerular filtration rate; RTx, renal transplantation.

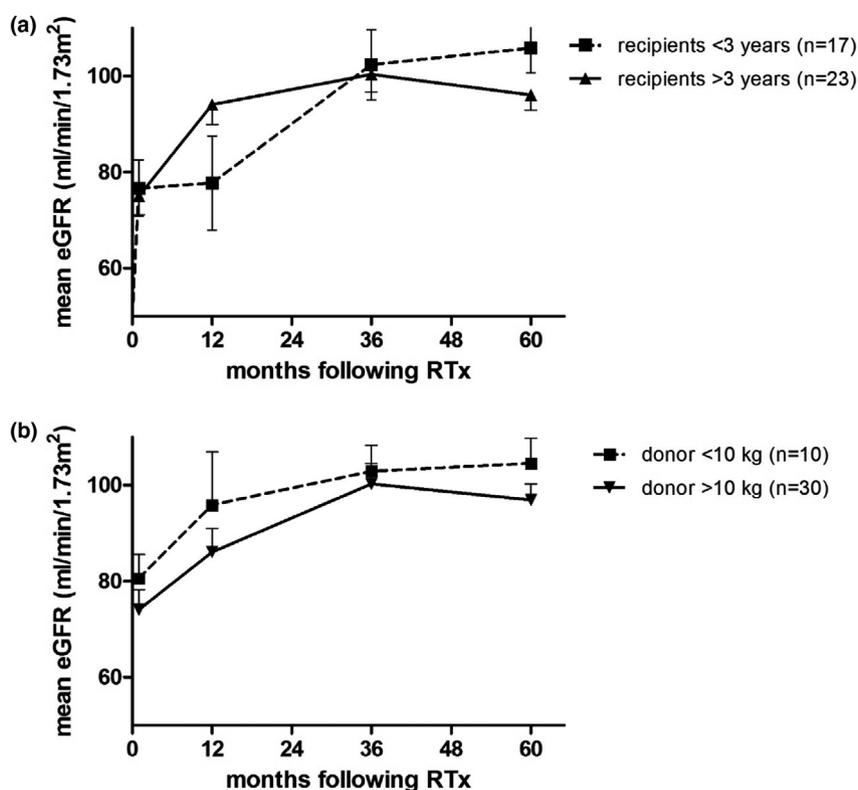


Figure 3 Mean calculated GFR over time (a) in recipients \leq and >3 years of age and (b) in donor age \leq or >10 kg. Increase of GFR is more pronounced in infant recipients (≤ 3 years, $n = 17$) and donor weight ≤ 10 kg ($n = 10$).

period. Patients with higher donor weight (>10 kg) reached their maximum of GFR after 3 years post-transplantation and stagnated thereafter (Fig. 3b).

Graft volume

Graft volume increased significantly in all patients (69 ± 38 ml (week 1) to 111 ± 33 ml (year 5), $P < 0.0001$, Table 3b). In patients with a follow-up >5 years ($n = 12$, mean 7.7 years), a further increase ($\Delta + 28$ ml) was noted. Graft volume one week post-RTx significantly exceeded body weight-related normal range of a single kidney of healthy children (i.e., 30–40 ml; $P < 0.01$), which may be owing to procedure-related swelling. With further organ growth, graft volume reached the normal range of body weight-related total kidney volume (Fig. 4b). Graft volume rose continuously in younger patients aged 0–3 years ($\Delta + 45 \pm 32$ ml until year 5, $P < 0.01$). Older patients (3–16 years) had a lesser total increase ($\Delta + 28 \pm 66$ ml until year 5 ($P < 0.05$), Fig. 4a). Stratification according to donor weight revealed a higher growth potential of kidneys of smaller donors ≤ 10 kg ($\Delta + 80 \pm 25$ within 5 years compared with $\Delta + 16 \pm 14$ ml in donors >10 kg, $P = 0.0005$; Table 3b, Fig. 4b).

Graft perfusion assessed by Doppler ultrasound revealed mean resistance indices between 0.69 ± 0.08 and 0.76 ± 0.08 and, therefore, within the normal range at all time-points of the study.

Complications

The rate of perioperative surgical complications (within 30 days after transplantation) was low ($n = 3$, 7.5%) and mainly caused by thromboses. Urinary leakage followed by presumed renal vein thrombosis led to necrosis of the graft and removal three weeks after transplantation in one patient. This patient received a single graft from an 18-kg donor. Anticoagulation with heparin was started early during transplantation anticipating 1.5-fold prolongation of partial thromboplastin time because of a homozygous methyltetrahydrofolate-reductase gene mutation. Two others, who received grafts of donors with a body weight of 10 kg, experienced thrombosis of the renal vein (within 3 h post-transplant) and the external iliac artery (during transplantation), respectively, with full recovery of graft function after immediate surgical revision. Both patients had thrombophilic conditions suffering from congenital nephrotic syndrome. In addition, in the first case, the

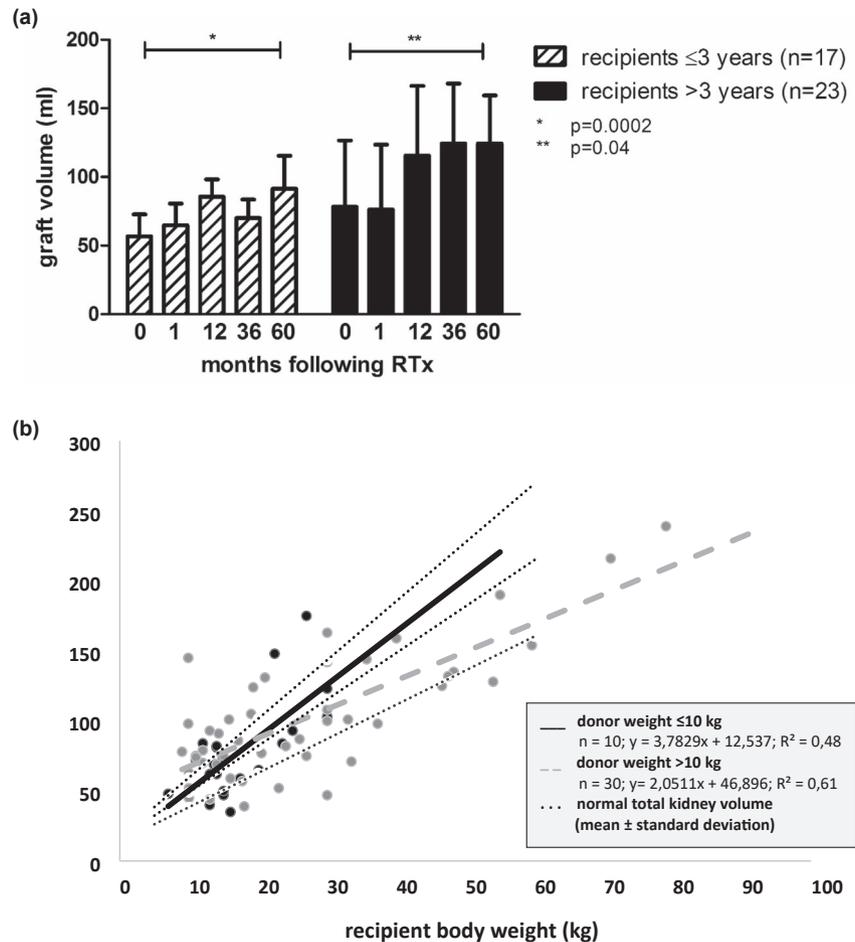


Figure 4 Graft volume stratified according to (a) recipient age (\leq and >3 years) and (b) donor weight (\leq and >10 kg). Increase of graft volume is superior in young recipients (0–3 years, $n = 17$) and rises continuously. (a) >3 -year-old recipients ($n = 23$) show a maximum graft volume after 3 years with a certain decline thereafter. (b) Donor weight ≤ 10 kg ($n = 10$) is associated with a steady and superior rise of graft volume compared with >10 kg donors ($n = 30$). Graft volume is within the upper normal range of total body-weight-related kidney volume.

renal vein of the donor organ was injured during organ procurement (lateral incision reconstructed with a V. cava patch); in the second case, the patient – receiving an en bloc transplant – experienced a prolonged spasm of the external iliac artery during transplantation with subsequent recurrent thrombosis of this vessel. Finally, a goretex patch was inserted, and the patient received heparinization for 3 months. Thrombosis re-occurred at the same site after 2 years despite ongoing aspirin therapy and was excised without impairment of transplant function.

Three patients developed an acute cellular rejection within the first month after RTx [Banff 1b ($n = 2$) and Banff 1a ($n = 1$)]. Graft function normalized after steroid pulse therapy in all patients as well as histology in control biopsies 1–5 months later. One patient presented with an acute humoral rejection within three weeks after RTx. Graft function normalized after

therapy with steroids, intravenous immunoglobulins, and rituximab as in another two patients with late biopsy-proven humoral rejections, 60 and 103 months post-transplantation. DSA without clinical and/or histological signs of rejection were detected in another five patients 0.1, 2.3, 5.2, 6.8, and 7.6 years after transplantation, respectively (mean fluorescence intensity max. 7900–14 000). One patient developed monoclonal EBV-positive PTLD six months after RTx and 16 months after prior liver transplantation with full recovery after rituximab and change of baseline immunosuppression.

Proteinuria was of low to a moderate extent in all patients and declined over time (mean 324 ± 222 , 288 ± 167 , 267 ± 162 , and 241 ± 148 mg/g creatinine 1 month, 1, 3, and 5 years post-transplant, respectively, Table 2). Incidence of proteinuria >200 mg/g creatinine decreased likewise (74%, 57%, 46%, and 41% of patients 1 month, 1, 3, and 5 years after transplantation).

Histology

Protocol biopsies were performed in 29 patients within 6–12 months after transplantation and revealed normal histology in 87%. Biopsies were not associated with major problems (bleeding, loss of transplant kidney, or injury of adjacent organs). In two patients, interstitial fibrosis of 10% and 25% was detected. No patient showed Alport-like irregularities of the glomerular basement membrane (GBM).

Height development

At RTx, mean longitudinal height of study patients was -2.1 ± 1.6 SDS (Table 2). Impaired growth was more pronounced in adolescents (10–16 years) with -2.5 ± 1.8 SDS compared with -2.4 ± 1.5 SDS in 3–10 year-old children and -1.5 ± 1.6 SDS in patients ≤ 3 years ($P = 0.001$). After RTx, longitudinal height improved in all age groups (Table 2), especially in young recipients (≤ 3 years) with $\Delta + 0.5$ SDS (mean height -1.0 ± 0.8 SDS at 5 years). 3–16-year-old patients ($\Delta + 0.4$ SDS) showed enhanced growth rates; however, longitudinal height did not reach the normal range (-2.0 ± 1.6 SDS at 5 years).

Other correlations

Linear regression analysis revealed a significant correlation of CIT and GFR at 1 and 3 years post-RTx ($P < 0.01$ and $P < 0.01$, respectively), but not early post-transplant and at 5 years. No significant impact was demonstrated for waiting time, mode of dialysis, WIT, HLA mismatch, donor and recipient weight or height, D/R ($</>0.75$, $</>1$, $</>0.5$), or recipient BMI, respectively.

Discussion

In this study, we report an excellent outcome of SDTx in children and adolescents. Overall graft survival was even higher compared with grafts from donors >20 kg body weight (98% vs. 87%) transplanted within the same time interval. Moreover, conditions considered particular critical within SDTx as single grafts as very young recipients (0–3 years) or very low donor weight (≤ 10 kg), achieved equal or even better results, supporting a call for a preferable use of SDK in paediatric recipients.

Efforts to alleviate increasing organ shortage put SDK into the focus. As these organs are primarily

transplanted en bloc in adults, data are mainly raised for this setting, whereas experience in infants and single grafts is scarce and controversial. Superior graft survival was associated with donor weight >10 – 15 kg, adolescent or adult recipients, and en bloc transplants [4–8,11,13,22–27]. Likewise, a recent registry-based study reported worse graft outcomes from young donors in young recipients (<5 years), even suggesting prioritized allocation of donors >5 years for infant recipients [11].

Our study focused on SDK paediatric recipients, analyzing graft function and growth over a 5-year observational period. The cohort consisted of predominantly young recipients (mean age 5.4 years) receiving single grafts in the majority of cases. The paired kidneys were re-allocated (in five cases to another patient of this study) and not discarded contributing to an expansion of the donor pool. Mean donor age and weight was 2.2 years and 14 kg, in 25% donor weight was below 10 kg. Overall graft function was excellent with 98% graft survival and a mean GFR of 100 ± 11 ml/min/ 1.73 m² after 5 years. Other studies evaluating SDTx in children differed significantly regarding study design. Therefore, comparability is limited. Sui *et al.* [13] included primarily school-aged recipients (mean age 10 years), providing a considerable increase in vessel diameter; however, 10% lost their grafts early because of vascular thrombosis. Pape *et al.* [23] described the superiority of paediatric compared with adult donors in infant recipients, but most donors were significantly older than in our cohort. Zhao *et al.* [24] reported a case series of four patients receiving grafts from donors of 2.5–5 kg with a high rate of complications (3 of 4 patients), leading to graft loss in 25%. Other studies were restricted to en bloc transplants with adolescent recipients and provided only a short observation time [27]. Compared with all the above-mentioned studies, general outcome in our cohort concerning graft survival and GFR was at least comparable but most often better.

Besides donor/recipient characteristics, centre experience was rated as one major parameter regarding SDTx outcome, with low centre volume being critical, especially in low donor weight [7]. Our data were raised at a transplant centre with a long-standing experience in paediatric solid-organ transplantation. Recently, Hoyer *et al.* [28] published the outcome of paediatric donor RTx with superior long-term graft function of <13 kg compared with juvenile (13–0 kg) and standard criteria donors (5-year GFR 98.9 ± 5.5 vs. 74.1 ± 6.2 and 81.6 ± 6.9 ml/min/ 1.73 m², respectively). Earlier Gallinat *et al.* [29] demonstrated favourable outcome and noninferiority of single grafts compared with en bloc

transplants of donors ≤ 5 years. Surgical experience may also be indicated by the short warm ischemia time of 26 min, which was considerably shorter than in other studies with similar donor and recipients' characteristics [13,24], as well as the low percentage of DGF. Of note, the high number of simultaneous unilateral or bilateral nephrectomies (20% of patients) or simultaneous liver transplantations in our study did not increase the complication rate.

Perioperative complications are regarded as responsible for impaired early graft function in SDTx. Despite the small size of grafts and recipients' situs, our study's perioperative complication rate was low (7.5%). The main cause was thrombosis, which was presumed to have led to graft loss in one child after a previous revision of a urinary leakage. In two other patients, immediate thrombectomy was successful. All thrombotic events occurred despite prophylactic heparin therapy; however, all patients had thrombophilic conditions. Occurrence of thrombotic events was neither correlated with very low donor weight nor with single grafts. Vascular thrombosis was the leading cause for graft loss in most studies except for the study of Pape *et al.* [23], which may be related to the larger dimension of vessels owing to higher donor age and weight. Urological complications, such as ureteral stenosis or leakage, were of minor importance in our study as well in recently published larger cohorts [30,31].

Donor–recipient size mismatch is controversially discussed regarding its predictive value for graft function in children and adults. Cardiovascular complications, abdominal compartment [14], or downregulation of filtration without the ability to adapt function later in case of large-for-size organs contrast concerns regarding hyperfiltration injury or graft thrombosis reported for small donor-size [6,10,24]. Although a significant proportion of patients in our study had a mismatch of D/R ($<0.75/>1.25$), multivariate analysis revealed no significant impact of this parameter on graft survival. Excellent outcome was demonstrated for young recipients (D/R > 1.25) but also for very small donors (D/R < 0.75). Likewise, analysis of SDTx in adults revealed no differences concerning BMI or body weight [32]. Studies not focusing on SDK indicate inferiority of lower donor weight in case of pronounced weight difference (>30 kg). However, mortality was lower in case of a donor to recipient weight ratio $<75\%$ [9,33]. In adolescent recipients, Dick *et al.* [34] concluded a significant association of graft loss and low donor/recipient body surface ratio.

Hyperfiltration-induced kidney injury is one major concern in small donor-to-recipient size and, therefore,

in SDTx. Jiang *et al.* [10] reported adult SDK-recipients presenting with proteinuria and Alport-like splitting and lamination of the glomerular basement membrane (GBM). Histological findings were detected within 4–18 months after transplantation. In our study size mismatch was present in 40% of patients (D/R < 0.75). The majority of patients (70%) received a protocol biopsy within 6–12 months after transplantation, and another 15% were biopsied on indication later. However, none of our patients showed similar GBM irregularities. Furthermore, proteinuria was only of low to a medium extent with a maximum of 324 ± 222 mg/g creatinine one month after RTx and 57% of patients being above the normal range at that timepoint. Prevalence and extent of proteinuria decreased over time and did not exceed data from other studies evaluating proteinuria in paediatric RTx not restricted to small donors [35].

Kidney volume is regarded as the most precise indicator of kidney size, especially in growing individuals. However, most studies rely on kidney length as volume measurement is more laborious. We observed a significant increase in graft volume in all patients of our study. As graft volume exceeded single kidney volume normalized for donor weight at the time of RTx, an initial swelling of the graft and, therefore, even greater growth has to be assumed. This inherent growth potential of paediatric grafts, which allows adaptation to the growing organism, was already described by Pape *et al.* [23] and others and is one of the major advantages of paediatric donor organs. Müller-Deile *et al.* [36] demonstrated upregulation of podocyte proliferation markers leading to adaptation of kidney grafts to recipient size in case low D/R. Interestingly, in our cohort, increase in GFR and graft diameter was more pronounced in young recipients compared with juvenile patients or adolescents. Strikingly, though comparable donor age, both parameters improved in all patients up to 3 years post-transplant, but then stabilized in adolescent recipients while continued to rise in small infants. Furthermore, grafts with a donor weight of less than 10kg revealed better results compared with a higher donor weight. Graft volume showed an association with recipients' weight and even reached the weight-related normal range of total kidney volume.

Growth retardation is a major problem in ESRD and even post-transplant despite nutritional improvements and growth hormone therapy [37]. In our study, patients' longitudinal height was severely impaired with -2.1 SD at the time of transplantation. In part, this is explained by a high proportion of patients with

syndromic diseases, including the clinical symptom of short stature additional to uremia-related growth retardation. However, all patients showed significant catch-up growth with 80% being within the normal range at the end of the study (mean $-1.6SD$). This is even a higher proportion than recently reported by the ESPN/ERA-EDTA registry analyzing 3492 paediatric transplant recipients' data irrespective of donor size [37]. In our study, catch-up growth started delayed after the first-year post-transplant despite normalization of kidney function in 98% of patients within one month. In contrast, Liu *et al.* [38] – also analyzing children after SDTx – reported a pronounced growth rate during the first year. However, in this study, patients with syndromic diseases affecting growth were excluded and children received a corticosteroid-free immunosuppressive regimen (withdrawal after 1 week). Overall, in our study, SDTx was associated with excellent growth even flattening potential adverse effects of steroid maintenance or short stature-associated diseases.

This study is subject to several limitations as retrospective data collection and small patient cohort resulting in limited statistical power. However, the single-centre design allowed careful and accurate collection and analysis of clinical data, which is a major advantage compared with multi-centre studies or registry data. Furthermore, the long-standing expertise of the transplant team ensured tight clinical identification of complications as well as precise comparability and value of raised data.

In light of increasing organ shortage, the usability of SDK is of high interest. However, most studies concentrate on SDK in adults, whereas data regarding paediatric recipients are scarce. Our study revealed excellent outcome of SDTx in children and did not support generalized concerns regarding high perioperative complication rates, a consecutive decrease of early graft function,

or single grafts. Of note, very young recipient age (0–3 years) and low donor weight (≤ 10 kg) were associated with a continuous rise of GFR and graft volume until the end of the observation period, whereas gain of function and growth stagnated in adolescents and higher donor weight after 3 years post-transplantation. Therefore, although experience has to be extended in further studies, our data support the notion that SDTx should be pursued in specialized transplant centres and preferably allocated as single grafts to small paediatric recipients.

Authorship

MC: research design, data collection and analysis. AP and JW: Treckmann: research design and data analysis. SD: data analysis. RB: research design and data analysis. PFH: research design, data analysis, writing of the manuscript. AKB: data collection and analysis, research design and writing of the manuscript.

Funding

Open Access funding enabled and organized by Projekt DEAL. WOA Institution: UNIVERSITATSKLINIKUM ESSEN.

Conflicts of interest

All authors declare no conflicts of interest.

Acknowledgement

We thank Dr. R. Hirtz for his professional statistical support.

REFERENCES

1. NAPRTCS 2014 annual report of the North American paediatric renal trials and collaborative studies.
2. UNOS Organ Procurement and Transplantation Network (OPTN), 2017.
3. Meier-Kriesche H-U, Port FK, Ojo AO, *et al.* Deleterious effect of waiting time on renal transplant outcome. *Transplant Proc* 2001; **33**: 1204.
4. Suneja M, Kuppachi S, Katz D, Hunsicker L. Small split paediatric kidneys to expand the donor pool: an analysis of scientific registry of transplant recipients (SRTR) data. *Transplantation* 2019; **103**: 2549.
5. Bhayana S, Kuo YF, Madan P, *et al.* Paediatric en bloc kidney transplantation to adult recipients: more than suboptimal? *Transplantation* 2010; **90**: 248.
6. Pelletier SJ, Guidinger MK, Merion RM, *et al.* Recovery and utilization of deceased donor kidneys from small paediatric donors. *Am J Transplant* 2006; **6**: 1646.
7. Maluf DG, Carrico RJ, Rosendale JD, Perez RV, Feng S. Optimizing recovery, utilization and transplantation outcomes for kidneys from small, ≤ 20 kg, paediatric donors. *Am J Transplant* 2013; **13**: 2703.
8. Kayler LK, Magliocca J, Kim RD, Howard R, Schold JD. Single kidney transplantation from young paediatric donors in the United States. *Am J Transplant* 2009; **9**: 2745.
9. Miller AJ, Kiberd BA, Alwayn IP, Odutayo A, Tennankore KK. Donor-recipient weight and sex mismatch and the risk of graft loss in renal

- transplantation. *Clin J Am Soc Nephrol* 2017; **12**: 669.
10. Jiang Z, Liang Y, Zhong T, *et al*. Paediatric donor glomerulopathy is a possible cause of abnormal urinalysis in adults receiving small paediatric donor kidneys. *Transplantation* 2020; **104**: 1695.
 11. Chesnaye NC, van Stralen KJ, Bonthuis M, *et al*. The association of donor and recipient age with graft survival in paediatric renal transplant recipients in a European Society for Paediatric Nephrology/European Renal Association-European Dialysis and Transplantation Association Registry study. *Nephrol Dial Transplant* 2017; **32**: 1949.
 12. Sureshkumar KK, Reddy CS, Nghiem DD, Sandroni SE, Carpenter BJ. Superiority of paediatric en bloc renal allografts over living donor kidneys: a long-term functional study. *Transplantation* 2006; **82**: 348.
 13. Sui M, Zhao W, Chen Y, *et al*. Optimizing the utilization of kidneys from small paediatric deceased donors under 15 kg by choosing paediatric recipients. *Pediatr Transplant* 2016; **20**: 3.
 14. Ortiz J, Parsikia A, Horrow MM, Khanmoradi K, Campos S, Zaki R. Risk factors for renal allograft compartment syndrome. *Int Surg* 2014; **99**: 851.
 15. Foster BJ. The promise of single kidney transplants from small paediatric donors. *Transplantation* 2019; **103**: 2225.
 16. Damji S, Callaghan CJ, Loukopoulos I, *et al*. Utilisation of small paediatric donor kidneys for transplantation. *Pediatr Nephrol* 2019; **34**: 1717.
 17. Schwartz GJ, Work DF. Measurement and estimation of GFR in children and adolescents. *Clin J Am Soc Nephrol* 2009; **4**: 1832.
 18. Kromeyer-Hauschild K, Wabitsch M, Kunze D, *et al*. Perzentile für den Body-mass-Index für das Kindes- und Jugendalter unter Heranziehung verschiedener deutscher Stichproben. *Monatsschrift Kinderheilkunde* 2001; **149**: 807.
 19. Dinkel E, Ertel M, Dittrich M, Peters H, Berres M, Schulte-Wissermann H. Kidney size in childhood. Sonographical growth charts for kidney length and volume. *Pediatr Radiol* 1985; **15**: 38.
 20. Roufosse C, Simmonds N, Clahsen-van Groningen M, *et al*. A 2018 reference guide to the Banff classification of renal allograft pathology. *Transplantation* 2018; **102**: 1795.
 21. Kranz B, Vester U, Nadalin S, Paul A, Broelsch CE, Hoyer PF. Outcome after kidney transplantation in children with thrombotic risk factors. *Pediatr Transplant* 2006; **10**: 788.
 22. Zhu L, Fu C, Chen S, *et al*. Successful single-kidney transplantation in adult recipients using paediatric donors aged 8 to 36 months: comparable outcomes with those using paediatric donors aged >3 years. *Transplantation* 2019; **103**: 2388.
 23. Pape L, Offner G, Ehrlich JH, de Boer J, Persijn GG. Renal allograft function in matched paediatric and adult recipient pairs of the same donor. *Transplantation* 2004; **77**: 1191.
 24. Zhao WY, Zhang L, Zhu YH, *et al*. En bloc kidneys transplanted from infant donors less than 5 kg into paediatric recipients. *Transplantation* 2014; **97**: 555.
 25. Yaffe HC, Friedmann P, Kayler LK. Very small pediatric donor kidney transplantation in pediatric recipients. *Pediatr Transplant* 2017; **21**: e12924.
 26. Winnicki E, Dharmar M, Tancredi D, Butani L. Comparable survival of en bloc versus standard donor kidney transplants in children. *J Pediatr* 2016; **173**: 169.
 27. Butani L, Troppmann C, Perez RV. Outcomes of children receiving en bloc renal transplants from small paediatric donors. *Pediatr Transplant* 2013; **17**: 55.
 28. Hoyer DP, Dittmann S, Büscher A, *et al*. Kidney transplantation with allografts from infant donors-small organs, big value. *Pediatr Transplant* 2020; **24**: e13794.
 29. Gallinat A, Sotiropoulos GC, Witzke O, *et al*. Kidney grafts from donors ≤5 yr of age: single kidney transplantation for paediatric recipients or en bloc transplantation for adults? *Pediatr Transplant* 2013; **17**: 179.
 30. Fananapazir G, Tse G, Di Geronimo R, *et al*. Urologic complications after transplantation of 225 en bloc kidneys from small paediatric donors ≤20 kg: incidence, management, and impact on graft survival. *Am J Transplant* 2020; **20**: 2126.
 31. Gander R, Asensio M, Molino JA, *et al*. Is donor age 6 years or less related to increased risk of surgical complications in paediatric kidney transplantation? *J Pediatr Urol* 2018; **14**: 442.e1–8.
 32. Kayler LK, Zendejas I, Gregg A, Wen X. Kidney transplantation from small paediatric donors: does recipient body mass index matter? *Transplantation* 2012; **93**: 430.
 33. Arshad A, Hodson J, Chappelou I, Nath J, Sharif A. The influence of donor to recipient size matching on kidney transplant outcomes. *Transplant Direct* 2018; **4**: e391.
 34. Dick AA, Mercer LD, Smith JM, McDonald RA, Young B, Healey PJ. Donor and recipient size mismatch in adolescents undergoing living-donor renal transplantation affect long-term graft survival. *Transplantation* 2013; **96**: 555.
 35. Seeman T, Šimková E, Kreisinger J, *et al*. Proteinuria in children after renal transplantation. *Transplant Proc* 2005; **37**: 4282.
 36. Müller-Deile J, Bräsen JH, Pollheimer M, *et al*. Graft growth and podocyte dedifferentiation in donor-recipient size mismatch kidney transplants. *Transplant Direct* 2017; **3**: e210.
 37. Bonthuis M, Groothoff JW, Ariceta G, *et al*. Growth patterns after kidney transplantation in European children over the past 25 years: an ESPN/ERA-EDTA registry study. *Transplantation* 2020; **104**: 137.
 38. Liu Z, Zhao WY, Zhang L, Zhu YH, Zeng L. Growth of paediatric recipients after renal transplantation from small paediatric deceased donors weighing less than 15 kg. *Pediatr Transplant* 2019; **23**: e13306.