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Urological complications, vesicoureteral reflux, and long-term graft survival rate after pediatric kidney transplantation

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Abstract: To describe a single-center experience with kidney transplantation and then study some donor and recipient features that may impact on graft survival and urological complication rates. We reviewed our database searching for pediatric patients who underwent kidney transplantation from August 1985 through November 2012. Preoperative data and postoperative complications were recorded. Graft survival rates were analyzed and compared based on the type of donor, donor's age from deceased donors, and recipients' ESRD cause. Kaplan–Meier curves with log rank and Wilcoxon tests were used to perform the comparisons. There were 305 pediatric kidney transplants. The mean recipient's age was 11.7 yr. The mean follow-up was 11.0 yr. Arterial and venous thrombosis rates were 1.6% and 2.3%, respectively, while urinary fistula and symptomatic vesicoureteral reflux were diagnosed in 2.9% and 3.6% of cases, respectively. Deceased kidney transplantation had a lower graft survival rate than living kidney transplantation (log rank, $p = 0.005$). Donor's age ($p = 0.420$) and ESRD cause ($p = 0.679$) were not significantly related to graft survival rate. In long-term follow-up, type of donor, but not donor's age, impacts on graft survival rate. ESRD cause has no impact on graft survival rate, showing that well-evaluated recipients may have good outcomes.

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Kidney transplantation has been considered the gold standard treatment for ESRD in pediatric patients (1, 2), improving their quality of life and providing a longer patient survival rate when compared to dialysis (3). However, there is clear imbalance between the number of patients in waiting list and kidneys available for transplantation. Improvements in the surgical transplant technique and better strategies for pre- and postoperative care of these patients have increased the graft survival rate, but it has been not enough.

The paucity of organs has motivated the search for donor and recipient characteristics that could impact negatively on kidney transplantation and anticipate an unfavorable outcome. Herein, we aim to describe our single-center experience with pediatric kidney transplantation, and then study donor and recipient features that could impact on graft survival and urological complication rates.

Abbreviations: ESRD, end-stage renal disease; s.d., standard deviation; VUR, vesicoureteral reflux.

Patients and methods

Study design

After Institutional Review Board approval, we retrospectively reviewed our database searching for pediatric patients (under 18 yr) who underwent kidney transplantation from August 1985 through November 2012. Preoperative data recorded were recipient's age at transplantation, gender, and ESRD cause, as well as type of donor (living donor or deceased donor) and donor's age. Postoperative data included overall graft and patient survival rates, and

surgical complications (arterial and venous thrombosis, arterial stenosis, urinary fistula, and symptomatic vesicoureteral reflux). Transplanted patients were investigated for vesicoureteral reflux with voiding cystourethrography if they presented with recurrent febrile urinary tract infection, hydronephrosis diagnosed by an ultrasound, and/or increase in the serum creatinine level. Voiding cystourethrography was not routinely performed.

Graft survival rates were analyzed and compared based on the type of donor (deceased vs. living kidney donor), donor's age from deceased donors (≤10, 10–17, and ≥18 yr), and recipients' ESRD cause (nephrological vs. urological disease). Patients with and without bladder augmentation were analyzed apart. Further analysis was made to evaluate the impact of dialysis (preemptive vs. non-preemptive kidney transplantation) on graft survival rate.

It was considered a urological cause of ESRD: vesicoureteral reflux, posterior urethral valve, ureteropelvic junction obstruction, neuropathic bladder, bladder exstrophy, persistent urogenital sinus, and Prune belly syndrome.

Preoperative evaluation and surgical technique

All candidates for kidney transplantation were submitted to abdominal ultrasound. Voiding cystourethrography was indicated for children with a history of urinary tract infection, incontinence, and/or previous urological manipulation. Urodynamic study was performed in cases of neurogenic dysraphism, posterior urethral valves, and obstruction, as indicated by cystogram. Children with severe bladder dysfunction had an individualized treatment, and patients with poor bladder compliance or reduced capacity were preferentially treated before kidney transplantation. Bladder augmentations were performed before kidney transplantation. Patients who underwent bladder augmentation (31 cases, 10%) were usually submitted to ileal cystoplasty (18 cases, 58%), although the ureter was our first choice when it was available (11 cases, 35.5%). The remaining two cases underwent bladder augmentation with sigmoid (one case, 3.25%) and bladder autoaugmentation (one case, 3.25%). All children with augmented bladder, neuropathic bladder, or with difficulties in spontaneous drainage were trained in clean intermittent catheterization before transplantation.

Kidney transplantation was performed in the classic manner using extraperitoneal access in all subjects, even for those weighing <20 kg (4). Ureteral reimplantation was performed using a modified Gregoir technique. Ureteral stent was not routinely left, and it was placed just in case of some technical difficulty. A transurethral Foley catheter was left indwelling for 10 days in patients with bladder augmentation and in five days in the remainder of the children.

Several immunosuppressive schedules were administrated during the period of this study. It was based on cyclosporine, corticosteroids, and azathioprine until 1995. Then, mycophenolate mofetil replaced the azathioprine. In 2000, tacrolimus replaced cyclosporine, and thereafter, the children were treated with tacrolimus, mycophenolate, and corticosteroids. Regarding induction agents, thymoglobulin and methylprednisolone were used for high immunological risk renal transplant recipients, while basiliximab and methylprednisolone were used for low immunological risk renal transplant recipients.

Statistical analysis

All data were descriptive and based on frequencies. Graft survival rates were compared with Kaplan–Meier curves and analyzed with log rank and Wilcoxon tests. Student's *t*-test was used to compare continuous variables, whereas Mann–Whitney *U*-test was used to compare categorical variables between living donor and deceased donor transplants. SPSS version 20.0 (SPSS Inc., Chicago, IL, USA) was used to analyze the collected data, and significance was set at $p < 0.05$.

Results

There were 305 pediatric kidney transplants. The mean ± s.d. recipient's age was 11.7 ± 4.0 yr, and most of the patients were male (55.4%). Ninety-six patients had a urological cause of ESRD. The most common cause was vesicoureteral reflux (36 pts; 37.5%), followed by posterior urethral valve (28 pts; 29.1%), and neuropathic bladder (24 pts; 25%). Of those with a urological cause, 31 (32.3%) underwent bladder augmentation, most of them due to neuropathic bladder (myelomeningocele, sacral agenesis) or inadequate bladder compliance (posterior urethral valve, bladder exstrophy). The majority of patients were submitted to living kidney transplantation. Table 1 summarizes the demographic data, while Table 2 shows the comparison between living donor and deceased donor transplants.

The mean follow-up was 11.0 ± 8.9 yr. Overall graft survival rate in one, five, and 10 yr of follow-up was 87.0%, 68.7%, and 58.6%, respectively. Overall patient survival rate in one, five, and 10 yr of follow-up was 95.9%, 91.2%, and 85.7%, respectively. Table 3 shows the urological complication rates. Arterial and venous

Table 1. Overall demographic data

Number of transplants	305
Number of re-transplants	34
Recipient mean (± s.d.) age (yr)	11.7 ± 4.0
Recipient gender (male)	55.4%
ESRD cause (nephrological vs. urological)	68.9% : 31.1%
Donor (living : deceased)	68.2% : 31.8%

Table 2. Demographic data of living donor and deceased donor kidney transplants

	Living donor transplants	Deceased donor transplants	p-Value
Recipient's mean (± s.d.) age	12.2 ± 3.9	11.4 ± 4.0	0.090
Gender (male)	56.7%	54.6%	0.712
Urological cause of ESRD	30.9%	29.9%	0.599

Table 3. Number (%) of urological complications

Arterial thrombosis	5 (1.6)
Venous thrombosis	7 (2.3)
Arterial stenosis	5 (1.6)
Urinary fistula	9 (2.9)
Vesicoureteral reflux	11 (3.6)

thrombosis rates were 1.6% and 2.3%, respectively, while urinary fistula and vesicoureteral reflux were reported in 2.9% and 3.6% of cases, respectively. Three (27.3%) of 11 patients, who had vesicoureteral reflux to the transplanted kidney, also had vesicoureteral reflux to the native kidneys. Four (11.1%) patients with native vesicoureteral reflux had also renal dysplasia. Patients with vascular thrombosis were submitted to transplantectomy. All patients with arterial stenosis (1.6%) were clinically managed, but one patient who required an arterial stent placement. All urinary fistulas were successfully treated with ureteral reimplantation. Symptomatic patients with vesicoureteral reflux (3.6%) were submitted to polymer injection and antibiotic prophylaxis. Transurethral injection therapy was performed with polyacrylate/polyalcohol copolymer (Vantris®, Promedom, Cordoba, Argentina) in three cases, hyaluronic acid/dextranomer (Deflux®, Q-Med AB, Uppsala, Sweden) in one case, and carbon-coated beads (Durasphere®, Carbon Medical Technologies Inc., St. Paul, MN, USA) in one case. There were no postoperative complications. No renal obstructions were seen after injection therapy. In one case, the child had recurrent urinary tract infection after Deflux® therapy and antibiotic prophylaxis was needed. Five cases were managed only with antibiotic prophylaxis. Only one patient underwent ureteral reimplantation because of a high degree of vesicoureteral reflux. Children with VUR were treated 17.5 ± 23.0 (range 4–84) months after kidney transplantation. Six of 11 patients had their treatment performed before one yr. Mean follow-up after treatment was 142.9 ± 94.3 months.

Only the type of donor impacted on graft survival rate (Fig. 1). Deceased kidney transplantation had a lower graft survival rate than living kidney transplantation (log rank, $p = 0.005$). Donor's age ($p = 0.701$), dialysis ($p = 0.942$), and ESRD cause ($p = 0.679$) had no impact on graft survival rate. Overall, mean (range) donor's age was 32.6 (2–60) yr. Mean deceased donor's age was 19.1 (2–60) yr, whereas mean living donor's age was 38.1 (21–60 yr). Usually, it was accepted kidneys from donors with age raging from five to 50 yr, weighing more than 20 kg. However, in some special cases, prioritized recipients received kidneys from older donors.

Overall, the acute rejection rate was 56.8% during the whole follow-up. Based on immunosuppression regimen, the acute rejection rate was 72.2% and 39.8% in the period from 1985 to 2000 and 2000 to 2012, respectively ($p < 0.001$).

Discussion

The shortage of organs for kidney transplantation motivates the search for donor and recipient characteristics that can impact on graft survival and postoperative complication rates. In this study, we presented a large cohort of pediatric patients who underwent kidney transplantation, showing a low rate of postoperative complications. Furthermore, only the type of donor impacted significantly on graft survival rate.

According to the Organ Procurement and Transplantation Network and Scientific Registry

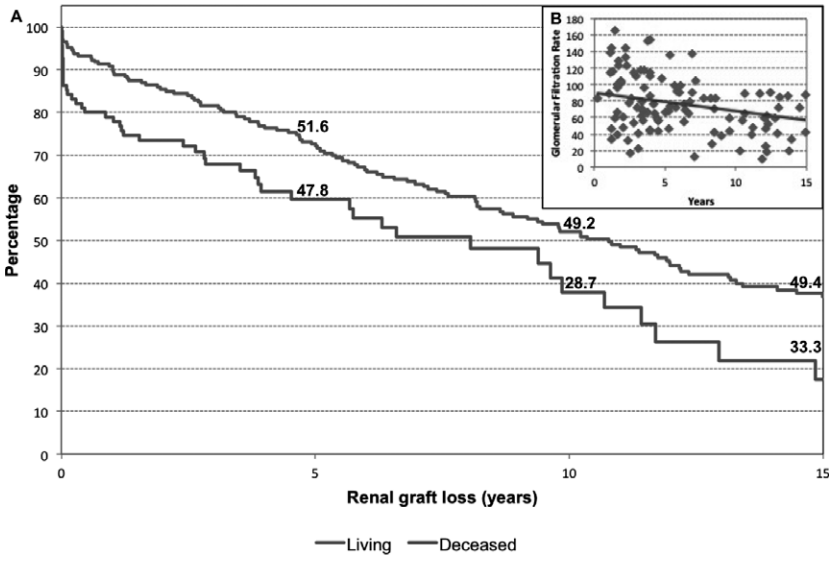

Fig. 1. (a) Graft survival rates according to the type of donor ($p = 0.005$). Average glomerular filtration rate at five, 10, and 15 yr (mL/min/1.73 m^2). (b) Overall glomerular filtration rate.

of Transplant Recipients, the graft survival rate is higher for living kidney donation when compared to deceased donation. Graft survival rate in five-yr follow-up is 81.4% and 68.8% for living and deceased donation, respectively (5). Shapiro and Sarwal (6) also reported a global rate of one-yr kidney graft survival in pediatric transplant recipients of 93% for living donors compared to only 77% for deceased donors. Likewise, in our study, there was a significantly higher graft survival rate for living kidney transplants ($p = 0.005$).

Although the type of donor was an important factor, the donor's age did not impact significantly on graft survival rate. We had different results compared to those described by Bisignano et al. (7) that reported a worst outcome in patients who received organs from older donors (hazard ratio 2.52; 95% CI 1.42–4.47; $p = 0.002$). Regarding dialysis, we did not find a statistically significant difference between patients who had preemptive kidney transplantation and patients who were on dialysis ($p = 0.942$). We speculate that the low number of preemptive kidney transplants (<10% of our sample) may explain the absence of difference between the groups.

In the pediatric population, urological disease as cause of ESRD is relatively common; thus, a detailed evaluation of the recipient before kidney transplantation to avoid graft dysfunction is mandatory. In our study, urological ESRD was not associated with a lower graft survival rate. Individualized management was probably the key for the success of the transplant in this special population. Correction of structural urogenital abnormalities, and optimization of emptying and storage function of the bladder have to be achieved before transplantation (8, 9). Children with ESRD due to nephrological cause only require an ultrasound to evaluate the upper urinary tract system, post-void residual, and bladder morphology. On the other hand, patients with a history of urinary tract infection, incontinence, urological surgery, or urinary diversion have to be completely evaluated before transplantation. Voiding cystourethrography was routinely performed to evaluate reflux, bladder characteristics and capacity, post-void residual, and urethral condition. Cases suspicious for bladder dysfunction were evaluated with urodynamic study as previously described (8, 10). Following these ideas, our outcomes in patients with ESRD due to urological cause were similar to those with nephrological ESRD cause, even for patients with bladder augmentation. Nahas et al. (8) in a study with 211 patients who underwent 216 kidney transplants (136 children with ESRD due to a non-urological cause and 75 children with urological disorder) showed similar graft survival rate in five-yr follow-up in both groups and concluded that children with lower urinary tract dysfunction may undergo kidney transplantation with a safe and adequate outcome. Other studies have also confirmed that children with reconstructed bladder may undergo kidney transplantation with the same outcome (graft survival and function) as those with normal bladders (11, 12).

Regarding the urological complication rate, we had similar or better outcomes than those previously reported in the literature (13, 14). Our vascular complication and urinary fistula rates were lower than 3%, and our symptomatic vesicoureteral reflux rate did not achieve 5%. Furthermore, all patients with arterial stenosis and urinary complications were successfully managed. Tanabe et al. described their experience with 107 pediatric kidney transplants reporting only seven (6.5%) surgical complications: one ureteral stricture, one ureteral necrosis, one renal artery stenosis, one lymphocele, one subcapsular hematoma, one bladder leakage, and one significant vesicoureteral reflux to the graft. Three patients required a new surgical intervention, and only one patient lost the graft (15).

This study has some limitations that are inherent to its retrospective design. The immunosuppressive therapy changed during the years, and it was not considered when studying the postoperative complication and graft survival rates. Moreover, the low rate of postoperative complications also prevented us of performing a more detailed evaluation regarding factors related to their occurrence.

We presented a large cohort of pediatric population who underwent kidney transplantation with a low urological complication rate, showing that well-evaluated pediatric patients may present reasonable long-term outcomes. Graft survival rate was related to the type of donor, but not to recipients' characteristics.

Conclusion

In long-term follow-up, type of donor, but not donor's age, impacts on graft survival rate. ESRD cause has no impact on graft survival rate, showing that well-evaluated recipients may have reasonable outcomes with a low urological complication rate.

Authors' contributions

Fabio C. M. Torricelli: Participated in drafting article and data analysis/interpretation; Andreia Watanabe:

Participated in concept and design; Affonso C. Piovesan and Ioannis M. Antonopoulos: Participated in data collection; Elias David-Neto: Participated in critical revision of article; William C. Nahas: Participated in critical revision of article and supervision.

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