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Mini Review

Pediatric Kidney Transplantation-A Mini-Review about Etiology, Complications and Graft Survival

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ABSTRACT

Kidney transplantation is the standard of care for children in end-stage kidney disease. Despite advances, it is still a challenge. Since this is a relatively infrequent surgery and the complexity to perform studies in children, it is rare to find large clinical trials in this area. The aim of this mini-review is to compile the results of published studies to obtain a global understanding of the current pediatric transplant situation.

Congenital Anomalies of the Kidneys and Urinary Tract (CAKUT) is the main cause of chronic kidney disease in children, and non-CAKUT causes increased frequency with age. Regarding graft loss, surgical complications are still the main cause of which thrombosis is the most common. Another issue is non-adherence to medications, especially within teenagers.

Considering the difficulties of large-scale prospective studies in this area, continued collaboration between reference centers is essential to address ongoing challenges and improve outcomes in this patient population.

Keywords: Pediatric kidney transplant; Kidney transplantation; Surgical complications; Graft survival; Graft thrombosis

INTRODUCTION

Chronic Kidney Disease (CKD) is a complex pathology especially in children and it has a significant negative impact upon their quality of life. Currently, kidney transplantation is the only available treatment that offers long-term benefits to patients. Studies have shown that children who undergo kidney transplantation live, on average, 30 years more than those who remain on dialysis [1]. The transplant allows patients to have a better physical and psychomotor development; and social adjustments, which impacts not only their but also their families quality of life [2]. Therefore, if the severity of the disease is identified as CKD stage 4 or 5 and dialysis, the kidney transplant is considered the treatment of choice.

According to the Organ Procurement and Transplantation Network (OPTN)/ Scientific Registry of Transplant Recipients (SRTR) (OPTN/SRTR) Annual Data Report, the number of children (up to 18 years old) waiting for a pediatric transplant has increased annually, reaching 2782 in 2021, and in the same year 820 transplants were performed, with almost 50% of pediatric candidates waiting for less than 1 year [3].

Despite numerous advances in recent decades, kidney transplantation in pediatric recipients is still a challenge due to several factors, such as the difficulty in organ availability, limited by donor-recipient disproportionality; surgical complications related to caliber of the vessels and ureter; limitations in the use of immunosuppressors and abandonment of immunosuppressive medications, especially by teenagers.

Since this is a relatively infrequent surgery and the complexity to perform studies in children, it is rare to find large clinical trials in this area. However, many groups have published their retrospective analyses, sharing advances and challenges. The aim of this mini-review is to compile the results of these studies to obtain a global understanding of the current pediatric transplant situation.

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LITERATURE REVIEW

Chronic kidney disease etiology

Unlike adults, whose main causes of CKD are diabetes mellitus and hypertension, the child population has several causes; in younger children, Congenital Anomalies of the Kidneys and Urinary Tract (CAKUT) are the main causes, followed by glomerulopathy, which increase in incidence with advancing age [4,5]. According to OPTN/SRTR data, the proportion of candidates with CAKUT as the primary cause of the disease continues to increase, from 27.9% in 2011 to 35.9% in 2021, and the proportions with glomerulonephritis and Focal Segmental Glomerulosclerosis have decreased (FSGS) [3].

Although CAKUT is a commonly used group, it presents a highly heterogeneous population . Lemoine et al., published a study with the most common causes in large registries, including North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS), ItalKid, the European Renal Association (ERA-EDTA) and the Japanese National Registry (JNR) [7-11]. Kidney aplasia/hypoplasia/dysplasia was the most common cause representing 15.8%-57.5% of cases, followed by obstructive uropathy 1.7%-15.3% and reflux nephropathy 5.1%-51.2%. The most common non-CAKUT causes were FSGS 1.8%-19.2% and chronic glomerulonephritis 2.6%-17.4% [6]. A survey carried out by our group also identified CAKUT as the main etiology, with 44.2% of cases, led by aplasia/hypoplasia/dysplasia 13.5%; FSGS represented 14.5% and chronic glomerulonephritis 6.2% [6,12].

After CAKUT, FSGS is the most common cause of CKD in children with the majority of cases being hereditary. Studies have shown a significant risk of disease recurrence after transplant, and response to therapy among patients with idiopathic and genetic FSGS [13-15]. Recurrence occurs in approximately 30% of pediatric kidney transplant recipients, and these numbers are even higher in re-transplantation cases, which leads to lower graft survival rates [16-18].

Surgical complications

Surgical complications remain one of the main causes of graft loss and morbidity in pediatric kidney transplantation [19]. Thrombosis is still the main cause of early graft loss, its reported global incidence after pediatric kidney transplantation is between 2%-10% [20]. Several characteristics have been pointed out in studies as risk factors, for example: Pre-peritoneal transplant dialysis, history of previous transplantation, graft from deceased donor aged less than six years, deceased graft with cold ischemia time higher than 24 hours, and recipient age less than two years [21], donor's BMI, retransplant [12], and donation after death from cardiovascular causes [22]; however, these findings have not been consistently reproduced in other studies. To reduce this risk, measures like systematic screening of patients for thrombophilia and pharmacological thromboprophylaxis in high-risk cases have been proposed [23,24]. However, there is a concern regarding the possibility of bleeding and no consensus have been reached for an ideal anticoagulation protocol.

Urine leak is another early complication, but is uncommon, occurring in 1%-4% of patients [25], its main risk factor are ureteral ischemia and technical errors. A conservative treatment with ureteral stent implantation and bladder decompression is most often sufficient to treat this complication [6].

Other surgical complications may occur later, such as Vesicoureteral Reflux (VUR) and ureteral stenosis. VUR occurs in approximately 2%-13% of cases, probably caused by an insufficient submucosal tunnel at the surgery, and can initially be treated in a minimally invasive way with injection of dextranomer/hyaluronic acid, in case of persistence or recurrence, surgical reimplantation is recommended. Ureteral stenosis can also be initially treated endoscopically, with balloon dilation, but this is not always an effective treatment, and ureteral reimplantation or transposition to a native ureter can be necessary [25].

RESULTS AND DISCUSSION

Immunosuppression

Improvements in immunosuppression regimens have decreased complication rates over the past three decades. It has become increasingly common to use some induction regimen with the aim of reducing the risk of acute rejection in the immediate post-transplant period, when the risk is greater due to decreased T-cell activation. The main induction agents used in pediatric kidney transplantation are therapies with biological antibodies such as basiliximab and thymoglobulin [26]. The improvement of compatibility panels has allowed the early withdrawal of steroids, avoiding complications related to glycemic, lipidic, and bone metabolism. Even so, the latest OPTN/SRTR report that the most common immunosuppression regimen at hospital discharge is the use of tacrolimus plus mycophenolate plus steroids, followed by tacrolimus plus mycophenolate only [3].

Despite advances, in a systematic review Hart et al., found an Antibody-Mediated Rejection (AMR) rate of 3% to 12% and a T-cell mediated rejection rate of greater than 10%, in most of the studies evaluated. Panel-reactive antibodies and donor-specific HLA antibodies were associated with both acute and chronic AMR, as well as HLA and ABOi incompatibility. Patients undergoing retransplantation also had a higher rate of AMR, and usually can be treated with corticosteroids and immunoglobulin infusions [7,27].

Some complications that deserve attention are the incidence of post-transplant lymphoproliferative disease among Epstein-Barr Virus (EBV) negative recipients at 3.5% at 5 years after transplant, compared to 0.9% among EBV-positive receptors [3].

Another challenge is related to adherence, which is known to be a problem, especially in adolescence. Silva et al., found a non-adherence rate of up to 70% in adolescent and pediatric populations. Socioeconomic level, illnesses and psychosocial factors seem to be the main related factors, however, the difficulty in identifying the situation probably makes it underdiagnosed and education actions are necessary to address this complication [28].

Graft failure

The 5-year graft survival rates were 85.2% for deceased-donor recipients and 93.1% for live-donor recipients. The overall incidence of acute rejection in the first year ranged from 7.7% among patients aged 6 to 11 years to 11.3% among patients aged 12 to 17 years [3].

Some studies show that lower weight and height and, consequently, lower body surface area of the recipient are significantly associated with greater graft survival rates [29,30]. Furthermore, Marcou et al., found that donor age and the age difference between donor and recipient can also play a significant role in long-term graft survival rate, especially for donor's ≥ 35 years and an age difference between donor and recipient ≥ 25 years was associated with worse long-term renal graft survival rate. Other studies corroborate the relationship between the age of the donor and recipient and worse outcomes [31-33].

Prolonged time of cold ischemia and HLA incompatibilities are known to worsen graft survival rates [34,35]. The pre-hemodialysis transplant time is also related to a worse outcome, Amaral et al., demonstrated that children on hemodialysis for more than a year had a 52% higher risk of graft failure and those on hemodialysis for more than 18 months had an 89% higher risk when compared to children undergoing preemptive transplantation [36].

CONCLUSION

Despite advances, pediatric kidney transplantation remains a challenge. A comprehensive understanding of the etiology of CKD, improvement of surgical techniques and possibly the creation of an anticoagulation protocol may reduce some of the main complications. The improvement of immunosuppressant's, accompanied by immunological panels is not enough to prevent rejection; non-adherence medications, especially by adolescents, remains a challenge that education programs about the treatment's importance still need to overcome. With the rise in graft survival rates, new problems deserve further attention, such as lymphoproliferative diseases caused by long periods of immunosuppression.

Considering the difficulties of large-scale prospective studies in this area, continued collaboration between reference centers and researchers is essential to address ongoing challenges and improve outcomes in this patient population.

CONFLICT OF INTEREST

The author's declare that there is no conflict of interest.

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