

## Original Research Article

# Vesicoureteral reflux in the transplanted kidney – risk and prognostic factors: A single-center experience.

### ABSTRACT

**Aims:** To evaluate the impact of vesicoureteral reflux in transplanted kidneys, identify its possible risk factors and define its clinical consequences in a public transplant center.

**Study design:** Retrospective study.

**Place and duration of the study:** Division of Urology, Department of Surgery; Radiology Department and Medical Clinical Department, Campinas State University, between September 2019 and October 2020.

**Methodology:** We analyzed data from patients who underwent kidney transplantation and progressed to kidney failure requiring dialysis due to graft failure. Preoperative evaluation for the new transplant included voiding cystourethrography and ultrasonography of the urinary tract. Twenty-six patients were selected between 2008 and 2018, in whom the preoperative voiding cystourethrography identified vesicoureteral reflux to the previously transplanted kidney. The patients were divided into 2 groups, low-grade and high-grade reflux. The Fisher and Mann-Whitney tests were used for statistical analysis, with a significance level set at 5%.

**Results:** Twenty-six patients were included, with a mean age of 47.8 years, of whom 73.1% were male. The graft had a similar survival, regardless of the degree of vesicoureteral reflux that the transplant presented. The longer the duration of ischemia, the greater the chance of developing high-grade reflux. A correlation was also found between weight gain and high grades of reflux. No relationship was found between the surgical transplant technique and the prevalence of vesicoureteral reflux, or the presence of bacteriuria, the etiology of renal failure, the duration of pre-transplantation dialysis and the age of the patient.

**Conclusions:** The presence of vesicoureteral reflux has no negative impact on renal graft function. There are indications that higher patient weight and prolonged organ ischemia can lead to the occurrence of higher-grade reflux.

*Keywords: Ischemia, Kidney Transplantation, Organ Transplants, Renal Insufficiency, Vesicoureteral Reflux.*

## 1. INTRODUCTION

About 95% of kidney transplants in Brazil are performed by the Unified Health System. The country has possibly the largest public transplant center in the world, called the National Transplant System. According to the Brazilian Transplants Registry, the number of kidney transplants performed increased from 920 in 1988 to 5929 in 2017. The waiting list for kidney transplant in 2017 comprised 21,059 patients [1,2].

There has been a parallel increase in life expectancy and the prevalence of chronic kidney diseases, resulting in an increasing number of candidates for kidney transplantation. The main etiological factors of end-stage kidney disease are: diabetes (28%), different types of glomerulonephritis (25%), hypertension with nephrosclerosis (23%), cystic kidney diseases (9%) and pyelonephritis (5%) [2].

End-stage kidney disease is treated with renal replacement therapy, represented by hemodialysis and peritoneal dialysis or renal transplantation, which is a preferred method as it is associated with a greater survival rate and better quality of life for the patients [3].

Urological surgical complications are relatively infrequent in renal transplants, occurring in 5% – 13% of patients [4]. These include vesicoureteral reflux (VUR), characterized by abnormal urine flow, which occurs from the bladder to the ureter or renal pelvis of the transplanted kidney. There is no consensus on the actual incidence of VUR, with studies reporting values ranging from 2% to 50% [4,5].

The classification of VUR proposed by the International Reflux Group is accepted worldwide. Grade I reflux does not reach the renal pelvis, and there is no dilation of the ureter; in grade II, reflux reaches the renal pelvis and calyx, but there is no dilation of the collecting duct system; in grade III, there is mild to moderate dilation of the ureter and renal pelvis, with slight blunting of the papillary impressions; in grade IV there is more marked dilation of the renal pelvis and calyces, with moderate tortuosity of the ureter, and in grade V there is gross dilation of the ureter and renal pelvis, with loss of papillary impressions [6].

Voiding cystourethrography (VCUG) is the main imaging method for the evaluation of VUR, but it is not routinely performed in kidney transplantation, because it is invasive, requiring urethral catheterization. Moreover, it is associated with morbidities including urinary infections due to urethral manipulation [7,8,9].

The evaluation of the incidence of VUR in the transplanted kidney by VCUG exposes the immunosuppressed patient to the risk of infectious complications of VCUG, which, although small, is not negligible. Thus, the non-performance of VCUG routinely translates into the unavailability of data regarding the incidence of VUR in patients with transplanted kidneys.

The link between the presence of reflux and the increased occurrence of urinary tract infections in transplantation patients is not fully understood. Thus, there is no evidence in the literature that reflux after transplantation alters graft function and survival of patients [7,8,9,10].

Therefore, the idea behind this study was to summarize the current understanding of factors affecting the presence of VUR in the transplanted kidney and its clinical and surgical consequences, as well as to compare the results collected in the literature with the data of transplantations performed in the period from 2008 to 2018.

The objective of the study was to evaluate the impact of vesicoureteral reflux in transplanted kidneys, identify its possible risk factors and define its clinical outcomes.

## **2. METHODOLOGY**

This retrospective study analyzed the data of patients who had previously undergone kidney transplantation but had relapsed to dialysis due to renal graft failure and who, for this reason, were again under routine evaluation before kidney transplantation, that is, were waiting for a new transplant.

The preoperative clinical pre-surgical evaluation included cystourethrography and ultrasound of the urinary tract, with the intention of identifying urinary tract alterations that needed to be corrected prior to renal transplantation. From 2008 to 2018, 26 patients in whom the preoperative VCUG identified VUR in the previously transplanted kidney were selected. These patients experienced graft failure exclusively due to chronic dysfunction of the transplanted kidney, without any surgical complications.

Patients without VCUG, less than 18 years of age, and with surgical graft loss were excluded.

To simplify the statistical analysis, reflux was divided into two categories: low-grade (grades I and II) and high-grade (grades III and IV).

The Fisher and Mann-Whitney tests were used to compare data, with a statistical significance set at 5%.

### 3. RESULTS

Data from 26 patients with a mean age of 47.8 years were collected. No statistically significant difference was observed between the grade of reflux and age. The mean age was 44.3 years in the low-grade group and 49.6 years in the high-grade group ( $P = .33$ ). The prevalence was higher in men (73.1%,  $P = .02$ ). Regarding the donor type, 22 cases received kidneys from deceased donors and 4 cases from living donors. Regarding the kidney used in the transplant, the right kidney was used in 12 cases and the left in the remaining 14 cases.

The most common underlying disease that led to end-stage kidney failure was arterial hypertension in 23% of patients and the cause of the most common graft function loss was chronic rejection in 65% of cases. There was no statistically significant difference between the underlying disease that led to renal failure and the grade of reflux ( $P = .40$ ).

In our study, it was not possible to ascertain the prevalence of VUR, because VUR was one of the inclusion criteria. A predominance of grade III VUR (42.3%) was found in our cohort, corresponding to 11 patients, while 6 patients had grade IV VUR (23.1%), 6 patients grade II VUR (23.1%) and 3 patients had grade I reflux (11.5%). Hence, reflux was divided into two groups: low-grade (grades I and II, with 09 patients) and high-grade (grades III and IV, with 17 patients). No patient was identified with grade V reflux.

The correlation between the surgical reimplantation technique used and the prevalence of VUR could not be determined as all cases were operated using the Lich-Gregoir technique. However, this standardization excluded the bias of different techniques.

Regardless of the grade of reflux in the transplant, in our study the graft had the average survival of 6.2 years in low-grade reflux and 6.1 years in high-grade ( $P = .68$ ), with no statistically significant difference.

No relationship was found between the presence of bacteriuria and VUR or alteration in the evolution of the transplant; 55.3% of the patients had positive urine cultures, while 44.7% did not present positive urine cultures in the preceding six months ( $P = .23$ ). The duration of graft survival was 5.94 years in patients with bacteriuria and 6.5 years in patients without bacteriuria ( $P = .53$ ).

Patients with low-grade reflux (nine patients) did not use antibiotics for prophylaxis of urinary infections, while six patients with high-grade reflux used prophylaxis ( $P = .06$ ), but this did not alter the graft survival.

In our assessment, there was no relationship with the grade of reflux, regardless of the duration of dialysis ( $P = .93$ ). The mean duration of dialysis was 59,21 months in the low-grade reflux group and 61,04 months in the high-grade reflux group.

The longer the duration of ischemia, the greater the chance of developing grades III and IV reflux, as patients with grade I and II had a mean duration of ischemia of  $766.7 \pm 433.5$  min and patients with grade III and IV had a mean duration of ischemia of  $1022.9 \pm 383.2$  min (a difference of approximately 4.2 h). However, probably due to the small number of patients, there was no statistically significant difference between the groups ( $P = .28$ ).

Of the patients with a body mass index (BMI)  $< 25$  (10 patients), five had reflux grade I and II and five had reflux grade III and IV. Of the patients with a BMI between 25 and 30 (12 patients, 46.2%), four had reflux grade I and II and eight patients had reflux grade III and IV. Four obese patients with a BMI  $> 30$  had reflux grade III and IV, without any cases in low grades. We note there is a possible correlation between large weight and the highest reflux grades, although not statistically significant ( $P = .29$ ) due to the low number of the patients studied.

### 4. DISCUSSION

The initial objective of this study was to analyze our institution database and review the medical records of transplanted patients to obtain information on the impact of VUR in the transplanted kidney, as well as its degrees and related clinical outcomes.

During the literature review, a large variability of information and very discrepant results were found, which influenced the format of the present study. We aggregated data from the literature with those collected in our facility, to formulate the basis of future studies on distinct patient groups.

In the literature, very heterogeneous values have been reported regarding the presence of VUR in the transplanted kidney, ranging from 2% to 50% [9,10,11].

Regarding the age, there was no difference between the groups concerning the presence of VUR in our patients. Studies by Engestein et al. [4], Favi et al. [5], and Jung et al. [11] have reported similar results.

In the literature, as for gender, men and women have the same likelihood of developing reflux. In our data, there was a higher prevalence of reflux in men (73.1%); however, it is described that gender did not alter the evolution and duration of the transplant.

A higher prevalence of reflux has been reported in patients who underwent transplantation from a deceased donor (87%) [4], which is like our results (84.6% of the cases had a deceased donor). It is important to highlight that the transplantation from deceased donors is the most common procedure in our institution and worldwide, which makes it challenging to establish the influence of this factor on the occurrence of reflux.

Regarding the type of vesicoureteral reimplantation, all selected patients underwent the Lich-Gregoir procedure, as this is the technique adopted at our institution. Thus, there was no technique-related bias. However, a study by Molenaar et al. [12] showed a difference in VUR rates according to the implantation technique. The incidence of reflux with the Lich-Gregoir technique was 12%, while with the Politano-Leadbetter technique the incidence was 5% ( $P < 0.01$ ). However, the study by Favi et al. [5] and Kayler et al. [13] compared the same two surgical techniques and reported no correlation between the specific procedure and the presence of VUR in the graft.

Whether the presence of reflux of lower or higher degrees altered the evolution of a transplant was also evaluated. In our study, regardless of the degree of reflux, the graft had the approximately the same average survival. The average survival was 6.2 years in grades I and II reflux, and 6.1 years in grades III and IV reflux ( $P = .68$ ). This was also demonstrated by Jung et al. [11], who divided their series into a group without reflux or reflux present at low grades (I and II) and another group with high grades of reflux (III, IV). They concluded that the presence of reflux, even in high grades, has no impact on renal graft function and duration.

Another interesting fact was observed by Favi et al. [5], who divided the patients into two groups based on the presence or absence of VUR. They evaluated renal function by measuring serum creatinine and did not find significant changes in the mean values at one, three or five years after renal transplantation. The mean creatinine values were 1.5 mg/dL  $\pm$  0.6 in the group with VUR, and 1.8 mg/dL  $\pm$  1.1 in the group without VUR, and there was therefore no statistically significant difference between the groups.

In our study, the prevalence of bacteriuria (symptomatic or not) was 55.3%, while 44.7% of the patients did not present positive urine cultures ( $P = .23$ ) in the preceding six months. Since all patients in this study had reflux, no relationship was found between the presence of bacteriuria and VUR or alteration in the evolution of the transplant.

Molenaar et al. [12] were the only group to evaluate the presence of bacteriuria, which may be both symptomatic and asymptomatic. The authors did not find a statistical relationship between the presence of VUR and bacteriuria. There was an average of 17% patients with bacteriuria in the group with VUR and 17.4% patients with bacteriuria in the group without VUR, ( $P = .91$ ); therefore, no statistically significant difference was found.

Inoue et al. [14] found a relationship between the pre-transplant dialysis period and the subsequent occurrence of reflux. The incidence of reflux was 47.6% in patients submitted to 120 months dialysis ( $P = .05$ ) and 44.7% in patients who underwent up to 60 months of dialysis ( $P = .01$ ).

Our data revealed that patients with lower-grade or higher-grade reflux had a mean pre-transplant duration of dialysis similar, around 60 months ( $P = .93$ ), and it was not possible to affirm that the duration of pre-transplant dialysis may increase the occurrence or degree of reflux in the graft. In the low-grade group, the graft survival was 6.2 years and in the

high-grade group it was 6.1 years ( $P=.68$ ), demonstrating that the presence of reflux and its severity did not alter graft survival.

One factor that should be considered was identified: the duration of organ ischemia prior to implantation. In our series, patients with reflux grades I and II had a duration of ischemia of  $766.7 \pm 433.5$  min, and patients with reflux grades III and IV had a duration of ischemia of  $1022.9 \pm 383.2$  min, with a difference of 4.2 h ( $P = .28$ ). However, a larger number of patients is necessary to confirm these findings.

Another factor evaluated was the relationship between the reflux grade and patient's BMI. Although the results did not show a statistically significant difference ( $P = .29$ ), higher grades were observed with a higher BMI. The most common BMI was 25–30 (overweight) in 12 patients (46.2%). Of the patients with a BMI < 25 (10 patients), five had grades I or II reflux and five had grades III and IV reflux. Of the patients with a BMI of 25–30 (12 patients), four had grades I and II reflux and eight patients had grades III and IV reflux. In patients considered obese with a BMI > 30 (four patients), none presented reflux grade I and II; all had reflux grade III and IV.

The prevalence of VUR worldwide varies significantly. The existing data are scarce, since VCUG would be required for the diagnosis of VUR, which is not routinely performed in the postoperative period at most transplant centers.

One issue discussed in all the articles analyzed was the possibility of VUR altering the long-term renal graft survival. All analyses found no association between the presence of VUR and its grading with worsening renal function, and the presence of VUR was not shown to lead to a higher incidence of bacteriuria or urinary infection.

Given the study design and the low number of patients, no definite conclusions have been drawn, but the patient's weight and duration of organ ischemia should be considered as factors that can lead to the occurrence of higher-grade reflux. However, as discussed above, the presence of reflux, its severity and bacteriuria (asymptomatic or symptomatic) did not alter the survival of the graft and its evolution.

#### **4. CONCLUSION**

The presence of VUR had no negative impact on renal graft function in the long term and was not associated with a higher incidence of urinary infection. There are indications that the patient's large weight and prolonged organ ischemia can lead to the occurrence of higher-grade reflux.

#### **CONSENT (WHERE EVER APPLICABLE)**

All authors declare that written informed consent was waived by the institutional ethics committee.

#### **ETHICAL APPROVAL (WHERE EVER APPLICABLE)**

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee (approval number **CAAE**: 97378818.2.0000.5404) and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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