Surgical correction of vesico-ureteric reflux for recurrent febrile urinary tract infections after kidney transplantation

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Objective

- To evaluate the outcome of anti-reflux revision surgery in patients diagnosed with at least a grade 3 reflux at voiding cysto-urethrography in patients with recurrent urinary tract infection (UTI) after renal transplantation.

Patients and Methods

- We identified 60 patients with a diagnosis of recurrent febrile UTI and post-transplantation vesico-ureteric reflux (VUR) who underwent open surgical correction of reflux.
- Patient characteristics, including the aetiology of end-stage renal disease, age, time to VUR correction, type of VUR correction, serum creatinine levels, and number of UTIs before and after correction were documented.

Results

- The median (range) age of the patients was 31.5 (9–65) years. A total of 30 patients underwent uretero-ureterostomy or pyelo-ureterostomy and 30 underwent extravesical or intravesical ureteric reimplantation.
- The median (range) creatinine levels before and after correction were 1.5 (0.8–4.5) mg/dL and 1.3 (0.7–4.5) mg/dL ($P < 0.05$), respectively.
- The median (range) number of UTI episodes reported before the correction surgery was 4 (3–12), whereas number of UTI episodes after the surgery was 1 (0–12), the difference being significant ($P < 0.05$).

Conclusions

- Open surgical correction of post-transplant VUR is an effective and safe method of decreasing UTI episodes and stopping reflux.
- Surgical correction of reflux may prolong the life of the renal graft.

Keywords

kidney transplantation, urinary tract infection, vesico-ureteric reflux, ureteric reimplantation, ureteroureterostomy, pyeloureterostomy

Introduction

Post-transplantation febrile UTI is an important morbidity in the renal transplantation population and post-transplantation VUR is considered to be one of its major causes, leading to renal damage and premature graft loss [1,2]. As most transplant surgeons choose to perform a large and patent but refluxing vesico-ureteric anastomosis to prevent obstruction, VUR is reported in up to 86% of the renal transplant population [3,4]. Febrile recurrent UTI is, however, associated with VUR and is a well-known risk factor for kidney damage, even in patients with normal lower urinary tract function, and this is particularly relevant to the immunosuppressed transplantation population [2].

Although some authors advocate long-term antibiotic prophylaxis to prevent febrile UTI in the post-transplantation population [5], the emergence of resistant micro-organisms and an increase in serum creatinine levels have meant that correction of post-transplantation VUR is required in a substantial number of patients. Endoscopic correction of post-transplantation VUR has been found to be effective in at least 50% of patients [6], but open surgical correction remains the 'gold standard' [1]. Open surgical techniques include pyelo-ureteric or uretero-ureteric anastomosis and redo ureteric reimplantation (RUR) [7–9]. Unfortunately, open surgical correction is not a complication-free procedure and obstruction, leakage or even graft loss resulting from vascular compromise is not uncommon

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[10]. Recently, extravesical RUR (e-RUR) with limited dissection of anastomosis between the graft ureter and bladder has been reported with a reasonable success rate [11].

In the present paper, we report our retrospective experience with 60 patients with recurrent febrile UTI who had undergone renal transplantation and in whom we performed open surgical correction of post-transplant VUR using different surgical techniques.

Patients and Methods

We retrospectively reviewed the charts of all renal transplantation patients who had no lower urinary tract abnormality (any form of BOO or abnormal storage function related to diseases such as neurogenic bladder, posterior urethral valve or diabetic cystopathy) and who underwent primarily surgical correction of post-transplant VUR owing to recurrent febrile UTI (diagnosed as fever >38 °C, documented growth in the urine culture >50 000 col/mL and the presence of costovertebral tenderness) between 2000 and 2008. Patient characteristics were recorded, including the date of transplant, aetiology of end-stage renal disease, sex, age at transplantation, donor classification of transplant, warm and cold ischaemia duration, immunosuppression protocol, number of rejection episodes, method of original ureteric anastomosis, presenting symptoms, grade of VUR using the International Reflux Study Committee Scale, technique of surgical correction of VUR, complications, follow-up imaging results, and number of febrile UTIs before and after correction. The intervals between original transplantation, diagnosis of VUR, surgical correction and the last clinical visit were also recorded. The following serum creatinine values were recorded: the nadir 1 month after transplantation, the level just before surgical correction and the last available level after correction. Transplant renal biopsy results were noted if available. These characteristics were analysed to assess the efficacy of surgical correction of post-transplantation VUR in terms of the number of febrile UTI episodes, serum creatinine level and graft function, and to assess the efficacy and safety of the surgical correction technique.

Study data were analysed using the SPSS 15.0 software program. Continuous variables were expressed as mean (SD) values, ordinal data and continuous variables inconsistent with normal distribution were expressed as median and minimum–maximum values, and frequency data were expressed as percentages. A sign test was used to compare two dependent groups inconsistent with normal distribution and the Mann–Whitney *U*-test was used for two independent groups. Normality analyses were performed using the Kolmogorov–Smirnov test. All hypotheses were designed bi-directionally and the α critical value was considered to be 0.05.

Results

Between 2000 and 2008, 1673 patients underwent renal transplantation at the Organ Transplantation Institute of Akdeniz University. We identified 60 patients (3.58%) who had been diagnosed with post-transplantation VUR and recurrent febrile UTI and who underwent primarily open surgical correction. Patient characteristics are shown in Table 1. All 60 patients presented with recurrent febrile UTI despite antibiotic propyhlaxis. The mean post-transplantation VUR grade was 4.6.

The median (range) follow-up duration after the original transplantation was 6.1 (3–11) years, the median (range) time until the correction of post-transplantation VUR was 21 (4–96) months and there was a median (range) of 40 (15–96) months between the correction and the last clinical visit. The induction therapy and other immunosuppressive treatment protocols used after transplantation are shown in Table 2.

At the pretransplantation urological assessment, all patients underwent a voiding cysto-urethrography (VCUG) and no

Table 1 Patient characteristics ($n = 60$).

Median (min–max) age, years	31.5 (9.0–65.0)
Gender, *n* (%)	
Male	28 (46.7)
Female	32 (53.3)
Graft type, *n* (%)	
Live	52 (86.6)
Cadaveric	8 (13.4)
VUR grade, *n* (%)	
Grade 3	8 (13.3)
Grade 4	40 (66.6)
Grade 5	12 (20)
Primary disease, *n* (%)	
Diabetic nephropathy	1 (1.7)
Familial Mediterranean fever	2 (3.3)
Focal segmental glomerulosclerosis	1 (1.7)
Chronic glomerulonephritis	8 (13.3)
Hypoplastic kidney	2 (3.3)
Hypertension	3 (5.0)
Haemolytic uraemic syndrome	1 (1.7)
Nephrolithiasis	3 (5.0)
Polycystic kidney	2 (3.3)
Pyelonephritis	3 (5.0)
VUR	12 (20.0)
Unknown	22 (36.7)
Median (min–max) no. of HLA mismatches	3 (0–6)
Median (min–max) ischaemia duration	
Live	
Warm ischaemia, s	85 (70–110)
Cold ischaemia, min	40 (25–56)
Cadaver	
Cold ischaemia, h	15 (12–18)

HLA, human leukocyte antigen.

Table 2 Immunosuppression protocols and rejection rates.

Induction therapy			Immunosuppressive treatment protocol			Rejection episodes		
	Patients			Patients		Episode number	Patients	
	n	%		*n*	%		*n*	%
Daclizumab	12	20.0	CSA + MMF	12	45.0	0	22	36.7
ATG	13	21.6	TAC + MMF	27	5.0	1	24	40.0
Basiliksimab	15	25.0	CSA + MNa	3	8.3	2	10	16.7
No induction	20	33.4	TAC + MNa	5	8.3	3	4	6.6
			CSA + SIR + MMF	5	3.4			
			TAC + SIR + MMF	2	10.0			
			CSA + EVE + MMF	6				

ATG, anti-thymocyte globulin; CSA, cyclosporin; TAC, tacrolimus; MMF, micophenolate mofetil; MNa, micophenolate sodium; SIR, sirolimus; EVE, everolimus.

Table 3 Type of open surgical correction of post-transplantation VUR.

Surgery type	*n* (%)
Anastomosis to native ureter	30 (50)
Uretero-ureterostomy	27 (45.0)
Uretero-ureterostomy + bilateral nephrectomy	1 (1.7)
Pyelo-ureterostomy	2 (3.3)
RUR	30 (50)
e-RUR	28 (46.7)
e-RUR alone	19 (31.7)
e-RUR + Bilateral nephrectomy	9 (15.0)
e-RUR and intravesical RUR	2 (3.3)

patient had a bladder capacity, contour or emptying abnormality. No patient reported any voiding abnormality before end-stage renal disease diagnosis. Patients who were diagnosed with VUR to the native kidneys, were subjected to native nephrectomy at the time of renal transplantation if they had severe VUR (Grades IV–V); while distal ureteric ligation was performed in low-to-moderate VUR (Grades I–III).

Original graft ureteric anastomosis was performed over a JJ stent in all patients using the Lich–Gregoir technique, and stents were retrieved by the third week. None of the patients in this study group had any ureteric complication requiring re-operation before the surgical correction of post-transplantation VUR.

All patients were followed up at the renal transplantation clinic with routine clinical visits, and recurrent febrile UTIs were defined as UTI symptoms with three or more episodes within a year, documented with a positive urine culture. VCUG was performed in all patients presenting with recurrent febrile UTI episodes.

The post-transplantation VUR correction surgery types and associated procedures are shown in Table 3. Anastomosis of the graft ureter to the native ureter was the preferred method in 30 patients (50%): end-to-end uretero-ureterostomy was performed in 28 patients and pyelo-ureterostomy in two patients. RUR was preferred in 30 patients (50%): 28 patients underwent e-RUR and two underwent intra- and e-RUR. e-RUR was performed with a complete transection of the graft ureter from the bladder and re-implantation was revised with a much longer extravesical tunnel formation, with specific attention given to avoiding acute angulation of the graft ureter on the bladder. The JJ stent was used for all post-transplantation VUR correction surgeries. Native nephrectomy (owing to VUR and urolithiasis) was performed simultaneously in 10 (16%) of the patients to reduce any possible source of infection. No complication was observed after post-transplantation VUR correction or associated surgeries.

The median (range) number of febrile UTI episodes per year before the post-transplantation VUR correction surgery was 4 (3–12), which decreased to 1 (0–12) after correction ($P < 0.05$). The median (range) serum creatinine level before the correction of VUR was 1.5 (0.8–4.5) mg/dL, which decreased to 1.3 (0.7–4.5) mg/dL after correction ($P < 0.05$). Control VCUG was carried out only in 14 cases with continuation of febrile UTI (eight patients [13.3%]) or increase in serum creatinine values. Persistent VUR was not seen in any patient.

No rejection episode was reported in 22 patients while rejection episodes were observed at least once in 38 patients (Table 2). Graft loss occurred in eight (13.3%) patients. Four (6.6%) patients had recurrent febrile UTI despite resolution of reflux. The mean (SD) number of rejection episodes observed in patients with graft loss was found to be significantly greater than in those without graft loss: 2.2 (0.9) vs 0.7 (0.7) episodes ($P < 0.005$). Kidney biopsy was performed in all patients with graft loss and all were reported to have chronic allograph nephropathy. No graft loss attributable to operative vascular or urological complications was reported in any of the patients who underwent correction surgery.

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Discussion

The incidence of UTI in patients who undergo renal transplantation is high, and is frequently reported at least once after transplantation. The first UTI is observed within a very short period after transplantation, with the incidence reducing as the follow-up period prolongs [12]. A number of different factors have been reported to increase the risk of UTI including female gender, diabetes mellitus, lower urinary tract abnormalities, such as posterior urethral valve and neurogenic bladder, and continuous or intermittent bladder catheterization. Recurrent UTIs associated with those risk factors may be reduced by antibiotic prophylaxis [5]; however VUR is also a well-defined risk factor for recurrent febrile UTI. Coulthard and Keir [12] reported that the same scarring risk applied to kidney transplants subjected to recurrent UTIs and VUR. Although surgical correction of post-transplantation VUR is warranted in a small but significant group of patients who have undergone renal transplantation, surgical methods for correction and their effect on recurrent UTI episodes and graft survival are not well studied. In the present paper, we show that surgical correction of post-transplantation VUR is highly effective in stopping reflux and in decreasing the number of UTI episodes in patients with no lower urinary tract abnormalities.

In renal transplantation the question of whether to perform a refluxing or a non-refluxing anastomosis has not yet been answered. Many transplant surgeons prefer a refluxing anastomosis to prevent inadvertent ureteric obstruction. Moreover, the incidence of VUR in kidney transplant recipients who did undergo non-refluxing ureteric anastomosis is 7–21% [9]; therefore, we routinely perform Lich–Gregoir extravesical ureteric anastomosis during renal transplantations, and make almost no attempt to achieve non-refluxing anastomosis in patients with unknown lower urinary tract abnormalities. In many transplantation series, recurrent UTI with post-transplantation VUR is rare (0–2%). In the present series, out of 1683 renal transplantations between 2000 and 2008, 60 (3.5%) required open surgical correction of post-transplantation VUR for recurrent febrile UTI and 14 (0.08%) underwent endoscopic correction. Although the present series seems comparable with the literature, the recurrent UTI and VUR rate would be much higher if we were to include patients with known lower urinary tract abnormalities. Moreover, a substantial number of cases of post-transplantation VUR might have gone undiscovered since they were not complicated with recurrent febrile UTI; thus, we and many other authors probably underestimate the real incidence of post-transplantation VUR.

Endoscopic correction is a recently emerging option for the surgical management of post-transplantation VUR. Although some discouraging results from centres with limited experience concludes that open surgical correction is the gold standard [9], many authors from more experienced centres have reported VUR resolution rates very close to results obtained in refluxing native kidneys [12]; however, in a recent study, endoscopic correction has been shown to be effective particularly in low-to-moderate grades of VUR and to some degree in severe reflux if an intra-ureteric injection technique is used [6]. Owing to minimal morbidity and acceptable resolution rates, we now prefer two sessions of endoscopic correction in the first place and open surgical correction only in failed ones.

Uretero-ureterostomy and pyelo-ureterostomy have long been used in the management of ureteric complications after renal transplantation. Although there have been some anastomosis problems such as stenosis or urinary leakage in the past [13], recent advances in internal ureteric stents have significantly decreased these complications. We have not observed any complications with uretero-ureterostomy or pyelo-ureterostomy. In two patients we chose to perform pyelo-ureterostomy owing to difficult mobilization of the distal graft ureter. Before surgical exploration, we place a ureteric stent into the native ureter which is planned to be anastomosed to the graft endoscopically and this manoeuvre significantly shortens the surgery time. We performed concomitant nephrectomy in only one patient and we sutured the transected native proximal ureter in the remaining 29 patients. We observed no problems with the native kidney requiring nephrectomy.

Tunnel length at the time of transplantation is also very important. Neuhaus et al. [14] reported that at least 3 cm tunneling resulted in no reflux in their series of extravesical ureteric reimplantation cases during kidney transplants. We therefore perform RUR to increase the tunnel length to >3 cm extravesically. For this purpose, we transect the anastomosis, then open the detrusor caudally for at least 3–4 cm and then perform the anastomosis to the most caudal side of detrusor opening. We always place prolene sutures at the anastomosis side on the detrusor so that we can easily find the anastomosis during RUR. For cases with very dilated graft ureters, we advocate the Politano–Leadbetter method of intra-extravesical reimplantation. We had no cases of leakage or stenosis. Our algorithm is now to perform uretero-ureterostomy in patients with non-refluxing native ureters and to perform ureteric reimplantation in others.

Unfortunately, we did not perform a control VCUG in all cases after post-transplantation VUR correction. Persistent febrile UTI and /or an increase in serum creatinine levels were our indications for a control VCUG. A control VCUG is not recommended after ureteric reimplantations for native kidneys because of the high success rate of the

reimplantation procedure [15]. We believe that a control VCUG is not required for post-transplantation VUR correction unless there is persistent reflux, kidney function deterioration or underlying lower urinary tract abnormality. In the present series, we performed a control VCUG only in 14 cases and only eight had persistent UTI.

It is known from large series of patients with primary VUR that, while repair of reflux will not decrease the future risk of UTI, it decreases febrile UTI frequency significantly compared with antibiotic prophylaxis and observation [16]. Similarly, in the present series, we found that the number of febrile UTI episodes decreased significantly after post-transplantation VUR correction. Only eight patients continued to have recurrent febrile UTIs and four of those ended up with graft loss. It is also noteworthy that although recurrent UTIs were stopped, graft loss occurred in four recipients. We speculate that a median period of 20 months before the correction of post-transplantation VUR is long enough to start the process of chronic graft rejection. This hypothesis is supported by the finding of a higher rate of rejection episodes before VUR correction in cases that resulted in graft loss despite the surgical correction. Although we lack a control group to compare between prophylaxis and surgical correction, we believe that a 40-month follow-up is a very reasonable period to conclude that febrile UTI episodes decrease in the long term as well. Furthermore, serum creatinine levels also decreased after VUR correction, indicating that febrile UTI with VUR damages the renal graft and this damage can be prevented by correction of VUR.

The present study has the limitations inherent in any retrospective series. We did not include patients with recurrent febrile UTI and known lower UTI since we already perform non-refluxing ureteric anastomosis in those patients and even in the presence of a non-refluxing anastomosis the patients continue to have symptomatic UTIs. Sometimes only changing the medical management of lower urinary tract abnormality stops symptomatic UTIs despite persistent reflux. We believed that in order to assess the efficacy and safety of open surgical correction of post-transplant reflux we should choose cases with no associated lower urinary tract abnormalities. Another limitation of the study is the lack of a control VCUG in all cases; however, we strongly believe that if the clinical problem of reflux has stopped there is no need for further invasive studies and surveillance using renal ultrasonography is sufficient.

In conclusion, open surgical correction of post-transplantation VUR can decrease the number of recurrent febrile UTIs and prevent further renal graft damage. Uretero-ureterostomy or pyelo-ureterostomy and RUR methods are safe and effective options for correcting post-transplantation VUR.

Conflict of Interest

None declared.

References

1 **Dupont PJ, Psimenou E, Lord R et al.** Late Recurrent Urinary Tract Infections May Produce Renal Allograft Scarring Even in the Absence of Symptoms or Vesicoureteric Reflux. *Transplantation* 2007; 84: 351–5

2 **Abbott KC, Swanson SJ, Richter ER et al.** Late urinary tract infection after renal transplantation in the United States. *Am J Kidney Dis* 2004; 44: 353–62

3 **Mastrosimone S, Pignata G, Maresca MC et al.** Clinical significance of vesicoureteral reflux after kidney transplantation. *Clin Nephrol* 1993; 40: 38–45

4 **Nie ZL, Zhang KQ, Li QS et al.** Urological complications in 1223 kidney transplantations. *Urol Int* 2009; 83: 337–41

5 **Fox BC, Sollinger HW, Belzer FO et al.** A prospective, randomized, double-blind study of trimethoprim-sulfamethoxazole for prophylaxis of infection in renal transplantation: clinical efficacy, absorption of trimethoprim-sulfamethoxazole,effect on the microflora, and the cost-benefit of prophylaxis. *Am J Med* 1990; 89: 255–74

6 **Yucel S, Akin Y, Celik O et al.** M. Endoscopic vesicoureteral reflux correction in transplanted kidneys: does injection technique matter? *J Endourol* 2011; 24: 1661–4

7 **Salomon L, Saporta F, Amsellem D et al.** Results of pyeloureterostomy after ureterovesical anastomosis complications in renal transplantation. *Urology* 1999; 53: 908–12

8 **Kayler L, Kang D, Mlmenti E, Howard R.** Kidney transplan ureteroneocystostomy techniques and complications: review of the literature. *Trans Proc* 2010; 42: 1413–20

9 **Engelstein D, Dorfman B, Yussim A et al.** A critical appraisal of vesicoureteral reflux in long-term renal transplantation recipients: prospective study. *Transplant Proc* 1997; 29: 136–7

10 **Krishnan A, Swana H, Mathias R, Baskin LS.** Redo Ureteroneocystostmoy using an extravesical approach in pediatric renal transplant patients with reflux: a retospective analysis and description of technique. *J Urol* 2006; 176: 1582–7

11 **Prat V, Horcickova M, Matousovic K et al.** Urinary tract infection in renal transplant patients. *Infection* 1985; 13: 207–10

12 **Coulthard MG, Keir MJ.** Reflux nephropathy in kidney

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transplants demonstrated by dimercaptosuccinic acid scanning. *Transplantation* 2006; 82: 205–10

13 **Pichler R, Buttazzoni A, Rehder P et al.** Endoscopic application of dextranomer/hyaluronic acid copolymer in the treatment of vesico-ureteric reflux after renal transplantation. *BJU Int* 2011; 107: 1967–72

14 **Neuhaus TJ, Schwöbel M, Schlumpf R et al.** Pyelonephritis and vesicoureteral reflux after renal transplantation in young children. *J Urol* 1997; 157: 1400–3

15 **Skoog SJ, Peters CA, Arant BS Jr et al.** Pediatric vesicoureteral reflux guidelines panel summary report: clinical practice guidelines for screening siblings of children with vesicoureteral reflux and neonates/infants with prenatal hydronephrosis. *J Urol* 2010; 184: 1145–51

16 **Bruno R, François C, Marwan D et al.** Vesicoureteral reflux after kidney transplantation in children. *Nephrol Dial Transplant* 2000; 15: 1852

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Abbreviations: RUR, redo ureteric reimplantation; VCUG, voiding cysto-urethrography; e-RUR, extravesical RUR.