Structural Analysis of Urological Complications after Renal Transplantation from a Living Related Donor

F. R. Nasirov, F. A. Akilov, Sh. T. Mukhtarov, S. S. Kariev, D. Kh. Mirkhamidov, Z. T. Matkarimov, N. M. Rakhimov, M. M. Khasanov

Republican Specialized Scientific and Practical Medical Center of Urology, Tashkent, Uzbekistan

Abstract **Aim** of the research was to study the frequency and structure of urological complications in the early and long-term period after related renal transplantation. **Material and methods.** The study was based on the results of examination and treatment of 162 adult recipients ($\geq$ 18 years) with urological complications after a related renal transplantation, who were on outpatient and inpatient treatment at the Republican Specialized Scientific and Practical Medical Center of Urology and at the Republican Specialized Scientific and Practical Medical Center of Surgery named after acad. V. Vakhidov for the period from June 2010 to May 2023. The features of the spread and structure of the major (ureteral stenosis/stricture, vesicoureteral reflux, urine leakage, transplanted kidney lithiasis) and minor (urinary tract infection, asymptomatic bacteriuria, lymphocele) urological complications in the early and long-term period after a related renal transplantation were studied. **Results.** We analyzed a cohort of 840 recipients after related renal transplantation and determined that the prevalence of urological complications after related renal transplantation is 19.3%, with a higher frequency of occurrence (14.3%) in the early and near (0-3 months) period, manifested by the main (ureteral stenosis/stricture (1.3%), urine leakage (0.5%) and vesicoureteral reflux (2.1%)) and small (urinary tract infection (7.6%), asymptomatic bacteriuria (2.4%), lymphocele (5.2%) and stone formation (0.1%)) complications. **Conclusion.** Urological complications are frequent complications of related renal transplantation and represent a serious burden for the patient and the healthcare system, and may require invasive procedures or repeated surgeries. At the same time, they often have an asymptomatic course, clinical manifestations are nonspecific and often delay from the moment of onset.

Keywords Renal transplantation from a living related donor, Urological complications, Prevalence, Structure

1. Introduction

Renal transplantation (RT) is the gold standard for the treatment of chronic kidney disease (CKD) and has a significant impact on the life quality [1]. Renal transplant recipients are at risk of developing various postoperative complications against the background of receiving immunosuppressive drugs and concomitant pathologies associated with long-term CKD [2-3].

Major and minor urological complications (UCs) are the second cause of morbidity after RT and rejection episodes, and may be associated with graft loss and mortality [3-6]. Main or major UCs include urine leakage, ureteral stenosis, bladder outlet obstruction, vesicoureteral reflux (VUR) and graft lithiasis [6-7]. The development of UOs is associated with a longer hospital stay, higher overall costs and often requires additional interventions. [1,8-9]. They can develop at any time after RT with a favorable prognosis in cases where the disease has been detected and timely treatment has been initiated [5,10].

The total recorded incidence of UCs after RT varies from 2.5% to 14%, depending on the series and the criteria used to determine them [2,3-4]. Numerous predictors of UCs have been documented, such as donor age, renal artery variants, recipient male sex, cytomegalovirus (CMV) infection, delayed graft function and extensive periureteric connective tissue dissection [11]. This incidence has decreased in recent years due to the use of double J-stents, adaptation of the extravesical ureteroneocystostomy technique by Leach-Gregoire, improvements in perfusion-preserving kidney harvesting techniques and decreased use of steroids [10,12-14].

Aim of the research was to study the frequency and structure of urological complications in the early and long-term period after related renal transplantation.
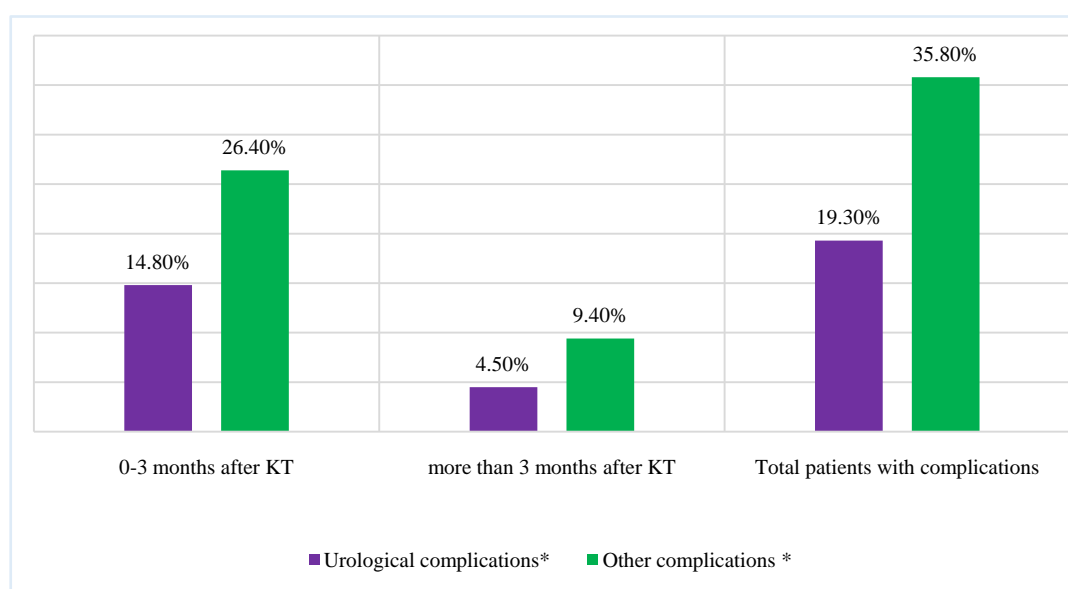
2. Material and Methods

The study was based on the results of examination and treatment of 162 adult recipients ($\geq$ 18 years) with urological complications after a related renal transplantation, who were on outpatient and inpatient treatment at the Republican Specialized Scientific and Practical Medical Center of

Urology and at the Republican Specialized Scientific and Practical Medical Center of Surgery named after acad. V. Vakhidov for the period from June 2010 to May 2023. The mean age of recipients with UOs was 34.5 years (from 20 to 63 years). Young patients (from 18 to 44 years) predominated among the recipients – 84.0% (136 from 162). Middle-aged recipients (45-59 years) made up 15.4% (25 from 162). Only 1 (0.6%) recipient was elderly. In most cases, the surgeries were performed on male recipients – 124 (76,5%) observations.

The mean age of donors was 40.4 years (from 18 to 63 years). Young patients also predominated among donors (from 18 to 44 years) – 62.9% (102 from 162). Middle-aged donors (from 45 to 59 years) made up 34.0% (55 from 162).
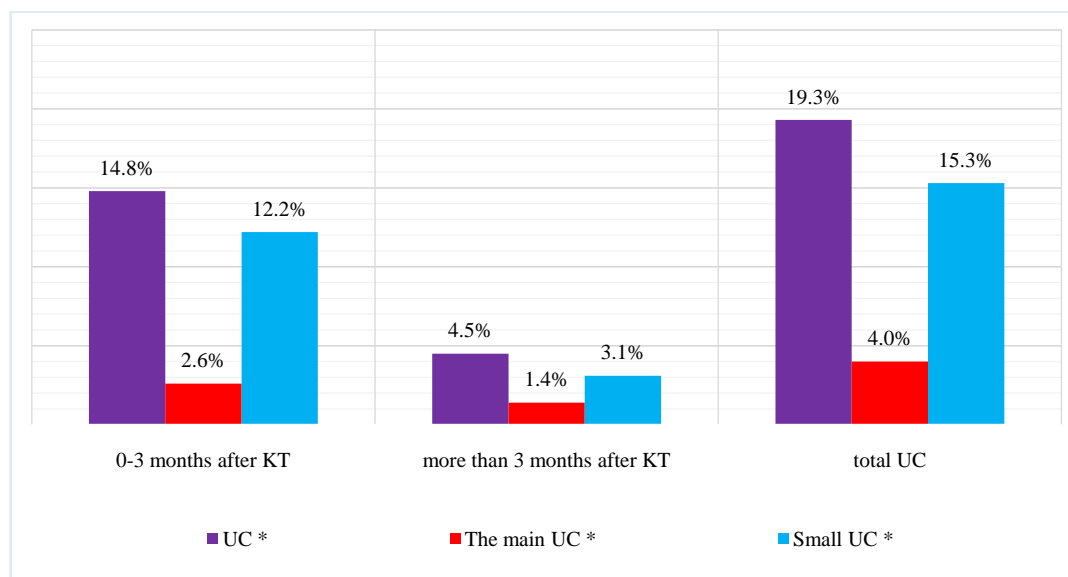
Всего 5 (3,1%) доноров были пожилого возраста. Male donors accounted for slightly more than half of the (50.6%; 82 from162) cases. Kidney donors were most often first-line relatives – fathers (17.3%), mothers (24.7%), brothers (24.1%) and sisters (21.0%).

A significant majority of patients (90.7%; 147 from 162) were operated on due to end-stage CKD as a result of chronic glomerulonephritis. In other cases, indications for RT, i.e. the cause that led to the terminal stage of CKD, were polycystic kidney disease (2.5%; 4 from 162), chronic pyelonephritis (1.2%; 2 from 162), type 2 diabetes mellitus (0.6%; 1 from 162), various abnormalities of the urinary system (0.6%; 1 from 162) and in 4 (2.5%) recipients the etiology of CKD was not established.

*Note: * - calculations were made from the total number of recipients after KT (840) taken for 100%*

Figure 1. The frequency of complications in the early and long-term period after related RT

*Note: * - calculations were made from the total number of recipients after KT (840) taken for 100%.*

Figure 2. Prevalence of major and minor UCs at various times after related RT

3. Results

UCs had a greater occurrence frequency in the early and immediate period after the related RT. In total, the prevalence of UCs after related RT was 19.3% (162 from 840), which determined them as a significant factor affecting the clinical course of the post-transplant period. The early and immediate period (0-3 months after RT) was characterized by the development of UCs in 14.8% (124 from 840) of cases, the frequency of which in the long-term period (more than 3 months after RT) made up 4.5% (38 from 840) (Fig. 1).

Based on an analysis of the literature, we also included ureteral stricture, urine leakage and vesicoureteral reflux as the main UCs. Minor UCs included urinary tract infection, asymptomatic bacteriuria and lymphocele.

As it can be seen from Fig. 2, in the early and immediate period, minor UCs prevailed with a statistically significant difference ($p=0.002$), making up 12.2% (103 from 840), while major UCs were diagnosed in 2.6% (21 from 840) cases.

Thus, in total, among 840 kidney transplant recipients, UCs were diagnosed in 124 (14.8%) patients within 3 months after surgery (Tab. 1). In the long-term period (3 months or more after RT), this number increased to 162 (19.3%), as it is shown in Table 2.

Table 1. Types and frequency of UCs in the early and immediate (0-3 months) follow-up period after related RT

Types of complication	n=840 RT
Ureteral stricture, n (%)	4 (0.5%)
Urine leakage, n (%)	3 (0.4%)
Vesicoureteral reflux, n (%)	14 (1.7%)
Urinary tract infection, n (%)	49 (5.8%)
Asymptomatic bacteriuria, n (%)	16 (1.9%)
Lymphocele, n (%)	38 (4.5%)
Total UCs, n (%)	124 (14.8%)

Table 2. Types and frequency of UCs in the long-term (more than 3 months) follow-up period after a related RT

Type of complications	n=840 RT
Ureteral stricture, n (%)	7 (0.8%)
Urine leakage, n (%)	1 (0.1%)
Vesicoureteral reflux, n (%)	4 (0.5%)
Stone formation	1 (0.1%)
Urinary tract infection, n (%)	15 (1.8%)
Asymptomatic bacteriuria, n (%)	4 (0.5%)
Lymphocele, n (%)	6 (0.7%)
Total UCs, n (%)	38 (4.5%)

Urine leakage mainly occurred during the first 3 months, including in 3 (0.4%) patients. The number of patients with ureteral obstruction after 3 months made up 4 (0.5%) and increased to 7 (0.8%) in the long-term period. Vesicoureteral reflux was also more common in the first 3 months after related RT - 1.7% (14 from 840) versus 0.5% (4 from 840) in the long–term period.

The incidence of urinary tract infections decreased as the posttransplantation period increased from 5.8% (49 from 840) to 1.8% (15 from 840), as well as the prevalence of asymptomatic bacteriuria (a decrease from 1.9% in the early to 0.5% in the long-term period was noted).

A significant difference was also noted in the incidence of cases with lymphocele. So, if in the early and immediate period after related RT there were 4.5% of recipients with lymphocele (38 from 840), then in the long-term period their number decreased to 0.7% (6 from 840).

In our cohort of patients, 1 (0.1%) case of stone formation (presence of concretion in the graft or nephrolithiasis of the transplanted kidney) was registered in the long-term period after a related RT.

Thus, in the structure of UCs of both the early and long-term period after related RT, urinary tract infection (UTI) remains clinically significant pathology, followed by asymptomatic bacteriuria (ABU), lymphocele and ureteral stricture.

The results we obtained confirmed the fact that ureteral stenosis can be developed both in the early (<3 months) and in the late (>3 months) post- transplantation period in kidney recipients. First of all, this is due to inappropriate devascularization of the ureter in the postoperative period.

Among 11 of our recipients with ureteral stenosis, 10 cases revealed stenosis/obstruction of the ureteral-vesicular anastomosis and 1 case of stenosis/obstruction of the pelvic-ureteral anastomosis, and there were no cases with stenosis/obstruction of the ureter itself. In 4 patients, a secondary infection was developed with acute pain in the side from the transplanted kidney, nausea and hyperthermia up to 39 °C.

Urine leakage (early – 3 cases, later – 4 cases) was defined as the accumulation of urine around the transplanted kidney and ureter, requiring surgical intervention and/or percutaneous nephrostomy.

Table 3. Bacterial isolates from urine samples of 84 kidney transplant recipients with UTI and ABU

	UTI	ABU	*n*
E. coli	28	14	*42*
E. faecalis	8	18	*26*
E. faecium	10	12	*22*
Klebsiella pneumoniae	12	1	*13*
Pseudomonas aeruginosa	3	4	*7*
Klebsiella oxytoca	1	3	*4*
Enterobacter cloacae	2	2	*4*
Serratia marcescens	2	1	*3*
Citrobacter species	1	1	*2*
Proteus mirabilis	2	-	*2*
Klebsiella variicola	1	-	*1*
Ureaplasma urealyticum	1	-	*1*
Raoultella planticola	-	1	*1*
Acinetobacter baumanii	-	1	*1*

We also retrospectively reviewed the cards of 84 recipients with UTI (n=64) and ABU (n=20), where the most common pathogens found in urine samples after RT were Escherichia coli, E. Faecium, Enterococcus faecalis and Klebsiella pneumonia (Tab. 3).

Urosepsis was developed in 2 cases. E. coli was the leading pathogen and was detected in 42 cultures, followed by E. faecium (n=22) and E. faecalis (n=26). 71 uropathogenic bacteria were cultured from 64 cultures obtained at UTI. Mixed cultures of two uropathogenic cultures were recorded in 5 cases. In 1 patient, four separate episodes of UTI were developed and four different bacteria grew (E. coli sensitive to fosfomycin, E. faecium resistant to vancomycin, E. faecium, and another strain of E. coli). Culture results differed significantly between UTI and ABU. Gram-negative bacteria were more often detected at UTI, whereas gram-positive bacteria were more often observed in episodes of ABU.

From these 84 kidney transplant recipients with UTI and ABU, 54 (64.3%) patients received one course of antibiotics, 22 (26.2%) patients received two courses, 6 (7.1%) received three courses and 2 (2.4%) patients received four courses of antibiotics. A total of 12 patients were found to have multi-resistant gram-negative bacteria (MRGN). All 12 were 3-MRGN (E. coli n=9, Enterobacter cloacae n=2, Citrobacter species, n=1).

We evaluated the nature of resistance in bacteria grown from urine samples of recipients. E. coli was resistant to ampicillin/sulbactam in 69.0% (29 out offrom 42), to fluoroquinolones - in 52.4% (22 from 42), to TMP-SMX - in 62% (26 from 42), to the 3rd generation of cephalosporins - in 19% (8 from 42), to piperacillin/ tazobactam - in 16.7% (7 from 42). At the same time, gram-positive bacteria E. faecalis (n=26) were also most often isolated from recipients with UTI and ABU, which was resistant to ampicillin/ sulbactam by 0%, to piperacillin/tazobactam by 0% and to carbapenems by 4%.

4. Discussion

Thus, the frequency, nature and features of the clinical course of UCs after related RT were studied, which allowed to carry out their structural analysis, the role and place in the cohort of all complications of the post-transplant period.

It is reported that new RT surgical methods have reduced the incidence of UCs [8,11]. We analyzed a cohort of 840 recipients after related RT and determined that the prevalence of UCs after related RT was 19.3%, with a higher incidence (14.3%) in the early and immediate (0-3 months) period, manifested by the main (ureteral stenosis/stricture (1.3%), urine leakage (0.5%) and vesicoureteral reflux (2.1%)) and minor (UTI (7.6%), ABU (2.4%), lymphocele (5.2%) and stone formation (0.1%)) complications, which was comparable to the data presented in other publications [7,11,15].

Ureteral stenosis/stricture is one of the most formidable UCs after RT and may be associated with previous urinary incontinence or be an independent manifestation. A total of 11 cases of ureteral stenosis/stricture were registered (1.3%), which were diagnosed within 0-3 months (0.5%) or with late treatment (0.8%) for more than 3 months after RT.

Ciancio et al. identified urine leakage and ureteral stenosis as the main UCs when analyzing 500 RT results [8]. Another study with 635 RTs confirmed similar results [4]. Urine leakage and UTI occur more in the early stages of the disease and are most common. Graft lithiasis can be present at any time after RT and has been reported in the literature with an incidence ranging from 0.4% to 4.4% [16].

In our study, ureteral stenosis/strictures were surgically restored using a new ureteroneocystostomy with a double J-catheter laparoscopically and by open methods. Lithiasis of the transplanted kidney was not accompanied by complete obstruction, and our approach was drug treatment.

We conducted a detailed analysis of UTI and ABU, and determined that the most common pathogens found in urine samples after RT were Escherichia coli, Enterococcus faecalis, E. faecium and Klebsiella pneumoniae.

5. Conclusions

UCs are frequent complications of related RT and pose a serious burden to the patient and the healthcare system and may require invasive procedures or repeated surgeries. At the same time, UCs after related RT are often asymptomatic, clinical manifestations are nonspecific and often delay from the moment of onset.

The authors declare no conflict of interest.

This study does not include the involvement of any budgetary, grant or other funds.

The article is published for the first time and is part of a scientific work.

REFERENCES

[1] Araújo JC, Barbosa RWDS, Machado MF, et al. Clinical impact of surgical complications in kidney transplant recipients in a reference hospital in Salvador, Bahia, Brazil. Transplant Proc. 2016; 48(7): 2301–2305. doi: 10.1016/j.transproceed.2016.06.017.

[2] Slagt I. Urological complications in kidney transplantation. Transl Androl Urol. 2015; 45(1): 25–31.

[3] Di Carlo HN, Darras FS. Urologic considerations and complications in kidney transplant recipients. Adv Chronic Kidney Dis. 2015; 22(4): 306–311. doi: 10.1053/j.ackd.2015.04.003.

[4] Rahnemai-Azar AA, Gilchrist BF, Kayler LK. Independent risk factors for early urologic complications after kidney transplantation. Clin Transplant. 2015; 29(5): 403–408. doi: 10.1111/ctr.12530.

[5] Buttigieg J, Agius-Anastasi A, Sharma A, Halawa A. Early urological complications after kidney transplantation: an overview. World J Transplant. 2018; 8(5): 142–149. doi: 10.5500/wjt.v8.i5.142.

[6] Nie Z, Zhang K, Huo W, Li Q, Zhu F, Jin F. Comparison of urological complications with primary ureteroureterostomy versus conventional ureteroneocystostomy. Clin Transplant. 2010; 24(5): 615–619. doi: 10.1111/j.1399-0012.2009.01134.x.

[7] Bruintjes MHD, D'ancona FCH, Zhu X, Hoitsma AJ, Warlé MC. An update on early urological complications in kidney transplantation: a national cohort study. Ann Transplant. 2019; 24: 617–624. doi: 10.12659/AOT.920086.

[8] Ciancio G, Farag A, Gonzalez J, Vincenzi P, Gaynor JJ. Results of a previously unreported extravesical ureteroneocystostomy technique without ureteral stenting in 500 consecutive kidney transplant recipients. PLoS One. 2021; 16: 1–20. doi: 10.1371/journal.pone.0244248.

[9] Choate HR, Mihalko LA, Choate BT. Urologic complications in renal transplants. Transl Androl Urol. 2019; 8(2): 141–147. doi: 10.21037/tau.2018.11.13.

[10] Saeb-Parsy K, Kosmoliaptsis V, Sharples LD, et al. Donor type does not influence the incidence of major urologic complications after kidney transplantation. Transplantation. 2010; 90(10): 1085–1090. doi: 10.1097/TP.0B013E3181F7C031.

[11] Slagt IKB, IJzermans JNM, Visser LJ, Weimar W, Roodnat JI, Terkivatan T. Independent risk factors for urological complications after deceased donor kidney transplantation. PLoS One. 2014; 9(3): e91211. doi: 10.1371/JOURNAL.PONE.0091211.

[12] Bruintjes MHD, Langenhuijsen JF, Kusters A, Hilbrands LB, d'Ancona FCH, Warlé MC. Double J stent is superior to externally draining ureteric stent in enhancing recovery after kidney transplantation – a prospective cohort study. Int J Surg. 2019; 71: 175–181. doi: 10.1016/j.ijsu.2019.09.031.

[13] Vogel T, Utech M, Schmidt F, et al. Double-J versus external ureteral stents in kidney transplantation: a retrospective analysis. Nephrourol Mon. 2015; 7(4): 0–4. doi: 10.5812/numonthly.27820.

[14] Sarier M, Yayar O, Yavuz A, Turgut H, Kukul E. Update on the management of urological problems following kidney transplantation. Urol Int. 2021; 105(7–8): 541–547. doi: 10.1159/000512885.

[15] Neri F, Tsivian M, Coccolini F, et al. Urological complications after kidney transplantation: experience of more than 1000 transplantations. Transplant Proc. 2009; 41(4): 1224–1226. doi:10.1016/J.TRANSPROCEED.2009.03.044.

[16] Harraz AM, Kamal AI, Shokeir AA. Urolithiasis in renal transplant donors and recipients: an update. Int J Surg. 2016; 36(PD): 693–697. doi: 10.1016/j.ijsu.2016.11.032.3.