Is delayed graft function associated with ureteral stenosis in the kidney transplant recipient? A case-control study

Axel Cayetano-Alcaraz, MD[1]; Juan Sebastian Rodriguez-Alvarez, MD[1]; Mario Vilatobá-Chapa, MD[2]; Josefina Alberú-Gómez, MD[2]; Bernardo Gabilondo-Pliego, MD[1], Francisco Rodríguez-Covarrubias, MD[1]; Luis Eduardo Morales-Buenrostro, MD[3]; Carlos Enrique Méndez-Probst, MD[1]

[1]Department of Urology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico; [2]Department of Transplants, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico; [3]Department of Nephrology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico

Cite as: *Can Urol Assoc J* 2019;13(11):E361-5. http://dx.doi.org/10.5489/cuaj.5794

Published online February 26, 2019

Abstract

Introduction: Ureteral stricture (US) in the kidney transplant recipient is a rare complication that can lead to morbidity and graft loss. Risk factor recognition is crucial in the prevention and management of this entity. Delayed graft function (DGF), as defined by the need for dialysis in the first week after transplantation, has been proposed as a risk factor in previous studies. Our objective is to determine the impact of DGF in US development in kidney transplant patients.
Methods: We designed a matched case-control study. US cases in kidney transplant recipients were identified in the 2008–2017 period. We defined US as the rise in serum creatinine associated with findings suggesting obstruction in ultrasound, scintigraphy, or retrograde pyelogram; any other cause of graft dysfunction was excluded. Controls were defined as kidney transplant recipients from the same population and period without US, matched in a 1:2 fashion by age, sex, and donor type.
Results: From 532 kidney transplant patients, 31 cases and 62 controls were included. Cumulative US incidence was 58 per 1000 cases. When calculating for odds ratio (OR), postoperative urinoma (OR 3.2; 95% confidence interval [CI] 2.36–4.37) and ureteral duplication (OR 3.29; 95% CI 2.40–4.51) were associated with an increased risk for US, while DGF was not found to be statistically significant as a risk factor (OR 3.3; 95% CI 0.96–11.52). No statistically significant differences were found between groups in other pre- and post-transplant-related factors
Conclusions: DGF was not associated with US in our cohort; however, ureteral duplication and postoperative urinoma were associated with an increased risk of graft ureteral stenosis development.

Introduction

Kidney transplantation is the definitive treatment for chronic kidney failure, bearing an improvement in prognosis over dialysis.[1,2] Urological complications are highly relevant, as they may end up in graft loss.[3,4] In particular, ureteral complications have been reported from 4.8–9.2%, with ureteral stenosis (US) rates from 2.4–9.2% of the kidney transplants.[5-7] Additionally, most ureteral complications occur during the first post-transplant year.[5,8,9]

Another feared complication is delayed graft function (DGF), which is associated with an increased risk for graft loss and acute rejection in the first post-transplant year.[10] This complication rate has been reported from 2–50% and 1.6–10% in deceased and living donor transplants, respectively.[11,12] The primary underlying etiology for DGF seems to be ischemia-reperfusion damage.[11]

Some retrospective studies have set a role for DGF as a risk factor for US in renal grafts, along with other variables, such as donor age over 65 years and kidneys with more than two arteries.[5]

We hypothesized that DGF increases the risk for graft US secondary to ischemia-reperfusion damage, pro-fibrotic molecule expression, and ureteral ischemia that promote aberrant scarring.[13,14] Our primary objective was to determine the impact of DGF in US development in kidney transplant patients that underwent transplantation in the 2008–2017 period in a tertiary care hospital. Secondarily, we wanted to calculate the graft US prevalence and describe other risk factors and treatment modalities used for the resolution of this complication.

Methods

We performed a matched case-control study in a single center in Mexico from January 2008 to January 2017. We obtained approval from the local ethics board committee. Data were retrieved from the hospital kidney transplant database. Cases were kidney transplant receptors diagnosed with graft US; controls were patients from the same population that did not develop US during followup.

Case inclusion and exclusion criteria

Cases were included as patients older than 18 years with a kidney transplant performed in this institution, coupled with a confirmed diagnosis of graft US.

We defined graft US as a rise in serum creatinine associated with hydronephrosis on ultrasound, an obstructive curve in scintigraphy, or a retrograde pyelography compatible with ureteral stenosis that were managed surgically (ureteroneocystostomy, Boari flap ureteroneocystostomy, or ureteroureterostomy), endoscopically (retrograde double-J stent catheterization, balloon dilation, or ureterotomy), or by interventional radiology treatment (nephrostomy or antegrade double-J stent catheterization). Any other potential cause, such as rejection (acute or chronic) or obstructive uropathy of other etiology were excluded.

Patients that did not undergo kidney transplantation in our institution were excluded. We eliminated patients with incomplete followup or a followup period of fewer than three months. Cases were matched with controls in a 1:2 fashion by age, sex, donor type, and transplantation period (±5 years).

Control inclusion and exclusion criteria

Controls were selected as kidney transplant recipients from either living or deceased donor older than 18 years that underwent transplantation at our institution during the same followup period of the cases with no graft dysfunction unless concluded to be a DGF. We excluded patients who did not undergo transplantation at our institution. Exclusion criteria were an incomplete followup or a followup period of fewer than three months.

Clinical variables

- *Donor:* Age, sex, blood type, donor type (living or deceased), extended criteria, donor relation (related or unrelated), comorbidities, and glomerular filtration rate (GFR) (calculated with the MDRD formula).
- *Receptor:* Age, sex, blood type, comorbidities, body mass index, smoking status, previous transplantation, HLA mismatch, pre-transplant anti-T panel reactive antibodies (PRA %), donor-specific HLA antibodies, pre-transplant diuresis, induction and maintenance scheme, BK virus infection, CMV infection, five-day followup ultrasonography data (hydronephrosis, perigraft fluid collection, distal intrarenal resistive index), perioperative complications (lymphocele, hematoma, urinoma, urinary fistula, arterial anastomosis stenosis), positive urine culture, acute rejection.
- *Renal graft:* Ischemia time, ≥2 graft arteries, ≥2 graft veins, ureteral duplication, ureteral implant technique, ureteral stent use, surgical bleeding, surgical time, time to stent withdrawal, ureteral stenosis diagnostic method, time to ureteral stenosis development, treatment type (surgical, endoscopic, interventional).
- *Delayed graft function:* Defined as the need for dialysis in the first post-transplant week.[11,15,16]

Sample size

We calculated a sample size of 216 patients, 72 cases and 144 controls. The figures were calculated with a power of 80%, 95% confidence interval (CI), a two control per case proportion, with a 9% estimated control exposure and a minimal odds ratio detection of three (Fleiss, Statistical Methods for Rates and Proportions, formulas 3.18 & 3.19; results obtained from Dean AG, Sullivan KM, Soe MM. OpenEpi: Open Source Epidemiologic Statistics for Public Health. Available at: *www.OpenEpi.com* [updated April 6, 2013]. Accessed April 10, 2017).

Statistical analysis

Data were analyzed with central tendency measures. Quantitative and qualitative data were compared using the student t-test and Chi-square, respectively. A p value under 0.05 was considered statistically significant. We obtained odds ratio (OR) for significant differences with the Mantel-Haenzel test. Statistical Package for the Social Sciences (SPSS®), version 20 was used for calculations.

Results

We reviewed 532 kidney transplantations in the 2008–2017 period; 31 cases and 62 controls were included. Median followup was 60.09 months (interquartile rage [IQR] 46.7). Table 1 describes the basal recipient and donor pre-transplantation characteristics; table 2 describes perioperative transplant variables; and table 3 describes followup kidney receptor characteristics and immunosuppressive schemes.

A ureteral stent was placed in 28 (90.3%) cases, and 54 (87.1%) controls without significant statistical differences (p=0.206); median time for ureteral stent withdrawal was 29.68 days (standard deviation [SD] 15.9) and 34.02 days (SD 20.3) for cases and controls, respectively, also with no statistical significance (p=0.3). Immunosuppressive regimes for induction and maintenance did not show statistical significance among groups.

OR calculations

In the risk estimation tests, urinoma and ureteral duplication were the only variables associated with an increased risk of ureteral stenosis (Table 4).

Table 1. Basal recipient and donor pre-transplantation characteristics

Variable	Cases n=31	Controls n=62	p
Receptor characteristics			
Female gender, n (%)	17 (54.8)	34 (54.8)	1.0
Age, mean (SD)	38.3 (13.5)	37.9 (13.3)	0.9
CKD etiology, n (%)			
Idiopathic	13 (41.9)	22 (35.5)	0.54
Diabetes mellitus	5 (16.1)	15 (24.2)	0.37
Hypertensive	2 (6.5)	0 (0)	0.1
ADPKD	3 (9.7)	6 (9.7)	1.0
SLE	4 (12.9)	6 (9.7)	0.72
Other	4 (12.9)	13 (21.0)	0.343
BMI, mean (SD)	24.2 (3.8)	23.8 (3.8)	0.89
Tobacco use, n (%)	2 (6.5)	7 (11.3)	0.71
≥1 HLA match, n (%)	8 (25.8)	22 (35.5)	0.34
Class 1 PARA, mean (SD)	6.4 (16)	4.9 (12.5)	0.42
Class 2 PARA, mean (SD)	4.3 (11.8)	5.7 (15.9)	0.55
Donor-specific HLA antibodies, n (%)	5 (13.6)	11 (17.7)	0.84
Pretransplant diuresis, n (%)	20 (64.5)	46 (74.2)	0.332
Dialysis to transplant time, months, mean (SD)	36.7 (38.4)	28.8 (28)	0.9
Donor characteristics			
Female gender, n (%)	15 (48.4)	35 (56.5)	0.46
Age, mean (SD)	40.2 (12.3)	38.7 (13.8)	0.58
Donor type, n (%)			
Living	15 (48.4)	30 (48.4)	1.0
Deceased	16 (51.6)	32 (51.6)	
Related donor, n (%)	12 (38.7)	23 (37.1)	0.88
Expanded criteria donor, n (%)	6 (19.4)	4 (6.5)	0.58
Comorbidities, n (%)			
Diabetes mellitus	3(9.7)	3 (4.8)	0.397
Dyslipidemia	3 (9.7)	4 (6.5)	0.682
Hypertension	4 (12.9)	2 (3.2)	0.09
GFR by MDRD, mL/min/1.73 m^2, mean (SD)	87 (45)	98.5 (45.5)	0.57

ADPKD: autosomal dominant polycystic kidney disease; BMI: body mass index; CKD: chronic kidney disease; GFR glomerular filtration rate; HLA: human leukocyte antigen; SD: standard deviation; SLE: systemic lupus erythematosus.

Characteristics of cases with graft ureteral stenosis

The calculated incidence of US was 5.8%, while the incidence rate was 0.093 person-years. The median time for US development was 62 days (IQR 64).

Imaging studies for US diagnosis were distributed as 28 (90.3%), seven (7.5%), and 13 (41.9%) cases for an ultrasound, renal scintigraphy, and retrograde pyelogram, respectively.

US management was surgical in 28 cases (90.3%), balloon dilation and retrograde stenting in two cases (6.4%), and one case required interventional treatment with antegrade stenting. Surgical management included 23 cases (74.2%) with ureteral neocystostomy and five (15.1%) with the Boari flap technique.

Table 2. Kidney transplant perioperative features for cases and controls

Variable	Cases n=31	Controls n= 2	p
Perioperative features			
Ischemia time, minutes, mean (SD)	670.3 (636.3)	676 (611)	0.78
Surgical time, minutes, mean (SD)	306.9 (91.7)	276.4 (71)	0.72
Surgical bleeding, mL, mean (SD)	334.6 (202.1)	323.5 (212)	0.98
≥2 graft arteries, n (%)	6 (19.4)	16 (25.8)	0.47
≥2 graft veins, n (%)	1 (3.2)	3 (4.8)	1.0
Ureteral duplication, n (%)	**4 (12.9)**	**0**	**0.01**
Extravesical implant, n (%)	26 (83.9)	49 (79)	0.57
Delayed graft function, n (%)	**7 (22.6)**	**5 (8.1)**	**0.049**
Perioperative complications, n (%)			
Lymphocele	1 (3.2)	0	0.15
Hematoma	2 (6.5)	4 (6.5)	1.0
Urinoma	**3 (9.7)**	**0**	**0.03**
Urinary fistula	2 (6.5)	0	0.1
Arterial anastomosis stenosis	0	1 (1.6)	1.0

SD: standard deviation.

Discussion

In our sample of 532 kidney transplants performed in the research period, the incidence of US was of 5.8%, with an incidence rate of 0.093 person-years, slightly higher than an international series; for instance, in a series of 2000 transplants performed in a single medical center from 1980 to 2010, the documented US prevalence was 2.7%.[6] A rate of 3.5% in an 894 transplant samples from 1993–2009 was reported by Faenza et al.[5] Karam et al reported a 4.1% rate in

Table 3. Characteristics in the post-transplant followup for cases and controls

Variable	Cases n=31	Controls n=62	p
Post-transplant followup			
Basal post-transplant creatinine, mean (SD)	1.2 (0.35)	1.18 (0.31)	0.39
Post-transplant basal GFR by MDMR, ml/min/1.73 m^2, mean (SD)	71 (32.2)	71 (20.4)	1.0
5-day graft ultrasound anomalies			
Hydronephrosis, n (%)	4 (12.9)	3 (4.8)	0.27
Perigraft fluid collection, n (%)	2 (6.5)	7 (11.3)	0.7
Distal intrarenal resistive index, mean (SD)	0.64 (0.12)	0.65 (0.08)	0.07
CMV infection, n (%)	2 (6.5)	4 (6.5)	1.0
BK virus infection	0	0	—
Positive post-surgery urine culture	29 (29)	23 (37.1%)	0.44

CMV: cytomegalovirus; GFR: glomerular filtration rate; MDMR: Modification of Diet in Renal Disease study; SD: standard deviation.

Table 4. Factors associated with an increased risk of ureteral stenosis development

Variable	Odds ratio (95% CI)
Delayed graft function	3.3 (0.96–11.52)
Urinoma	**3.2 (2.36–4.37)**
Ureteral duplication	**3.29 (2.40–4.51)**

CI: confidence interval

1787 transplants from 1990–2002.[8] More recently, US was reported in 3.39% from a 973 transplant sample performed in the 2004–2014 period, with a mean time to stenosis of 10.6±23.0 months (range 0.5–98).[4]

Time to stenosis occurrence is related to its etiology. Early stenosis can be associated to tissue edema, kink of the ureter, narrow ureter diameter, or extrinsic compression by hematomas or lymphoceles.[17, 18] While the late US can be associated with inappropriate arterial blood supply that results in ischemia and fibrosis.[3] Nevertheless, definitions vary among studies, are not based on international consensus, and tend to be arbitrary.[3,5,6,8] In the present study, early US (defined as less than three months post-transplant) was more common, with a proportion of 74.2% (n=23) and mean time from transplantation to US diagnosis of 62 days (IQR 64). Late US occurred in 25.8% (n=8) of cases. This proportion is similar to the one reported by Faenza et al (81.2% early stenosis vs. 18.8% late stenosis).[5]

DGF is a relatively common, early post-transplant complication, with a rate of up to 50% of deceased donor transplantations.[19] Conversely, its occurrence in living donor transplantations is fairly uncommon, with rates reported from 1.6–10.0%.[11,12] DGF has been associated with graft dysfunction, rejection in the first year, and decreased graft survival.[20] Some studies have proposed DGF as a risk factor for US; in 2006, Karam et al in a single-center, retrospective analysis of 1787 patients with renal transplantation, found that US was correlated to DGF (p=0.016), donor age >65 years (p=0.001), and more than two graft arteries (p=0.009); however, multivariate analysis showed only DGF (OR 1.03; 95% CI 1.01–1.05) and >2 arteries (OR 1.45; 95% CI 1.00–2-00) as an independent risk factors for US.[8] Fontana et al found similar results.[7] Nonetheless, DGF by previous groups was defined as the number of days to reach a GFR of >10 mL/minute, and the study methods did not control potential confounding factors, such as donor age and type.

At the moment, there is no consensus about a superior definition for DGF, but the most commonly used is the need for dialysis in the first post-transplant week; it has been suggested to be adopted as the universal clinical variable for research studies.[15] In our study of matched case-control analysis, although DGF was found to have a statistically significant difference in frequency between cases and controls by Chi-square analysis, we rejected the hypothesis of DGF as a risk factor for US, considering the Mantel-Haenzel analysis did not show a statistically significant effect of exposure (OR 3.3; 95% CI 0.96–11.52). Despite being associated with US in previous studies, our contrasting results may owe to different study design and previous non-standardized definitions for DGF.[7,8] However, the associated factor may not be DGF, per se, but one of the associated mechanisms, such as ischemia-reperfusion damage, which may not always reach a clinical threshold to be considered as such.

The factors that we found for an increased risk of US were perioperative urinoma (OR 3.2; 95% CI 2.36–4.37) and ureteral duplication (UD) (OR 3.29; 95% CI 2.40–4.51). Previous studies did not report perioperative complications as risk factors for US.[7,8] However, urinoma is commonly associated with a ureterovesical (UV) anastomotic leak or distal ureteral ischemia, depending on the occurrence time, leading to periureteral graft fibrosis.[21,22]

On the other hand, UD is a common anatomy variant reported in 1 of 100–500 cases. Mixed results have been reported in small studies, where it may have been associated with an increased incidence of urological complications (10.5%), mainly US;[23] other studies show no difference in perioperative complications.[24] A higher technical difficulty performing the UV anastomosis may explain the association between UD and US.

Since US is regarded as an uncommon complication in renal transplantation, the study design appropriately evaluated the associated risk factors with this entity. Furthermore, the research study period is recent, and distinct renal transplant management aspects (such as patient selection, protocol followup, immunosuppressive schemes, and surgical groups) were standardized since the beginning of the period. Our study limitations are mainly a failure to achieve the optimal sample size owing to the rarity of this entity, as well as its single-center and retrospective nature.

Conclusions

DGF was not associated with ureteral stenosis in our cohort; however, UD and postoperative urinoma were associated with a graft ureteral stenosis development.

Competing interests: The authors report no competing personal or financial interests related to this work.

This paper has been peer-reviewed.

References

1. Wolfe RA, Ashby VB, Milford EL, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *N Engl J Med* 1999;341:1725-30. https://doi.org/10.1056/NEJM199912023412303

2. Schold JD, Buccini LD, Goldfarb DA, et al. Association between kidney transplant center performance and the survival benefit of transplantation vs. dialysis. *Clin J Am Soc Nephrol* 2014;9:1773-80. https://doi.org/10.2215/CJN.02380314
3. Palazzetti A, Oderda M, Dalmasso E, et al. Urological consequences following renal transplantation: A review of the literature. *Urologia* 2015;82:211-8. https://doi.org/10.5301/uro.5000132
4. Gil-Sousa D, Oliveira-Reis D, et al. Ureteral stenosis after renal transplantation — a single-center 10-year experience. *Transplant Proc* 2017;49:777-82. https://doi.org/10.1016/j.transproceed.2017.01.050
5. Faenza A, Nardo B, Fuga G, et al. Urological complications in kidney transplantation: Ureteroneocystostomy vs. uretero-ureterostomy. *Transplant Proc* 2005;37:2518-20. https://doi.org/10.1016/j.transproceed.2005.06.079
6. Eufrasio P, Parada B, Moreira P, et al. Surgical complications in 2000 renal transplants. *Transplant Proc* 2011;43:142-4. https://doi.org/10.1016/j.transproceed.2010.12.009
7. Fontana I, Bertocchi M, Rossi AM, et al. Late ureteral stenosis after kidney transplantation: A single-center experience. *Transplant Proc* 2010;42:1174-5. https://doi.org/10.1016/j.transproceed.2010.03.053
8. Karam G, Hetet JF, Maillet F, et al. Late ureteral stenosis following renal transplantation: Risk factors and impact on patient and graft survival. *Am J Transplant* 2006;6:352-6. https://doi.org/10.1111/j.1600-6143.2005.01181.x
9. Rajpoot DK, Gomez A, Tsang W, et al. Ureteric and urethral stenosis: A complication of BK virus infection in a pediatric renal transplant patient. *Pediatr Transplant* 2007;11:433-5. https://doi.org/10.1111/j.1399-3046.2006.00673.x
10. Yarlagadda SG, Coca SG, Formica RN, et al. Association between delayed graft function and allograft and patient survival: A systematic review and meta-analysis. *Nephrol Dial Transplant* 2009;24:1039-47. https://doi.org/10.1093/ndt/gfn667
11. Perico N, Cattaneo D, Sayegh MH, et al. Delayed graft function in kidney transplantation. *Lancet* 2004;364:1814-27. https://doi.org/10.1016/S0140-6736(04)17406-0
12. Park HS, Hong YA, Kim HG, et al. Delayed graft function in living-donor renal transplantation: 10-year experience. *Transplant Proc* 2012;44:43-6. https://doi.org/10.1016/j.transproceed.2011.11.057
13. Ponticelli C. Ischemia-reperfusion injury: A major protagonist in kidney transplantation. *Nephrol Dial Transplant* 2014;29:1134-40. https://doi.org/10.1093/ndt/gft488
14. Eltzschig HK, Eckle T. Ischemia and reperfusion — from mechanism to translation. *Nat Med* 2011;17:1391-401. https://doi.org/10.1038/nm.2507
15. Mallon DH, Summers DM, Bradley JA, et al. Defining delayed graft function after renal transplantation: Simplest is best. *Transplantation* 2013;96:885-9. https://doi.org/10.1097/TP.0b013e3182a19348
16. Ditonno P, Impedovo SV, Palazzo S, et al. Effects of ischemia-reperfusion injury in kidney transplantation: Risk factors and early and long-term outcomes in a single center. *Transplant Proc* 2013;45:2641-4. https://doi.org/10.1016/j.transproceed.2013.07.025
17. Zagdoun E, Ficheux M, Lobbedez T, et al. Complicated lymphoceles after kidney transplantation. *Transplant Proc* 2010;42:4322-5. https://doi.org/10.1016/j.transproceed.2010.09.127
18. Shoskes DA, Hanbury D, Cranston D, et al. Urological complications in 1000 consecutive renal transplant recipients. *J Urol* 1995;153:18-21. https://doi.org/10.1097/00005392-199501000-00008
19. Schroppel B, Legendre C. Delayed kidney graft function: from mechanism to translation. *Kidney Int* 2014;86:251-8. https://doi.org/10.1038/ki.2014.18
20. Hall IE, Reese PP, Doshi MD, et al. Delayed graft function phenotypes and 12-month kidney transplant outcomes. *Transplantation* 2017;101:1913-23. https://doi.org/10.1097/TP.0000000000001409
21. Berli JU, Montgomery JR, Segev DL, et al. Surgical management of early and late ureteral complications after renal transplantation: techniques and outcomes. *Clin Transplant* 2015;29:26-33. https://doi.org/10.1111/ctr.12478
22. Di Carlo HN, Darras FS. Urologic considerations and complications in kidney transplant recipients. *Adv Chronic Kidney Dis* 2015;22:306-11. https://doi.org/10.1053/j.ackd.2015.04.003
23. Haferkamp A, Dorsam J, Mohring K, et al. Ureteral complications in renal transplantation with more than one donor ureter. *Nephrol Dial Transplant* 1999;14:1521-4. https://doi.org/10.1093/ndt/14.6.1521
24. Ghazanfar A, Zaki MR, Pararajasingam R, et al. Outcome of kidney transplant with double ureter: A multicenter study. *Exp Clin Transplant* 2015;13:152-6.

Correspondence: Dr. Carlos Enrique Méndez-Probst, Department of Urology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico; probstmc@hotmail.com