Impact of Complicated Urinary Tract Infection on Renal Graft Function

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ABSTRACT

Background. Urinary tract infection (UTI) is the most common infectious complication after renal transplantation. It is uncertain whether the development of UTI has an impact on renal graft function. The objective of this study was to evaluate the effects of complicated and recurrent UTI on 2-year renal graft function.

Methods. This was a historical cohort study in renal transplantation patients in a kidney transplant center. All renal transplant recipients from June 2004 to September 2016 were included. A linear regression analysis was performed to study the association between the outcome (variation in estimated glomerular filtration rate [eGFR] by the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation between month 1 and month 24 post-transplant) and the UTI. The approval of the Ethics and Research Committee to carry out this study was obtained.

Results. In total, 276 kidney transplants were performed during the observation period. Of the transplant patients, 193 (69.9%) did not develop a UTI and 83 (30.1%) presented at least 1 complicated UTI. Patients who presented at least 1 UTI had a variation in eGFR during the observation period of −12.6 mL/min/1.73 m^2 (95% confidence interval [CI] −4.5 to −20.7 mL/min/1.73 m^2; $P = .02$), compared with those without a UTI. Said difference persisted in the adjusted model controlling for variables that have an impact on the eGFR. This difference was −10.7 mL/min/1.73 m^2 (95% CI −3.1 to −18.2 mL/min/1.73 m^2; $P = .006$).

Conclusion. The findings suggest that the occurrence of complicated UTI has a negative impact on graft function and that prevention and monitoring of UTIs should be stepped up to avoid their deleterious effects on graft function.

AFTER a renal transplant, urinary tract infection (UTI) is the most common infectious complication, with an incidence of 26% to 76% [1]. Differences in the definition, duration of follow-up, and the variability in the use of post-transplantation antibiotic prophylaxis explain the wide variation in the incidence of UTI in this population [1,2]. This infection is particularly worrying because it does not follow a typical clinical course regarding immunosuppression and surgical denervation of the organ [3], which can generate adverse results, such as reduced graft survival, increased hospitalization costs, and increased multidrug resistance [4].

It is unclear whether the development of UTI has an impact on renal graft function. Recent clinical studies have evaluated this association in transplanted patients, with divergent results. Some have found an association between a single episode of acute pyelonephritis and graft loss at 1 year [5], whereas others have found an association only in

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cases of recurrent UTI [4]; still others have not demonstrated any association [1,6].

The objective of this study was to evaluate the impact of complicated and recurrent UTI on 2-year renal graft function and long-term graft survival in renal transplant recipients.

MATERIALS AND METHODS

Study Design and Population

A historical cohort study was performed in patients undergoing kidney transplant in a kidney transplant center. All living and cadaveric donor kidney transplant recipients from June 2004 to September 2016 were included. Cases of complicated and recurrent UTI were evaluated for 2 years after transplantation. The clinical data of the patients who met the inclusion criteria were obtained from the electronic medical record.

For the study, complicated UTI was defined as the presence of fever, graft pain, malaise or chills, positive urine culture ($>10^5$ CFU/mL), and a diagnosis of pyelonephritis by dimercaptosuccinic acid scintigraphy and/or with urinary irritative symptoms and bacteremia. This definition of UTI was chosen because it is consistent with previous large-scale analyses of post-transplantation UTI [1,7]. Recurrent UTI was defined as more than 3 UTIs in 12 months or more than 2 UTIs in 6 months, regardless of the causative microorganism [4].

The primary point was the impact of complicated and recurrent UTI on the estimated glomerular filtration rate (eGFR) measured by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. We evaluated the Delta eGFR between month 1 and month 24 post-transplantation. The secondary outcome was to assess the impact of urinary infection on graft survival, with follow-up until graft loss.

This study was approved by the institutional research and ethics committee.

Statistical Analysis

Patients were categorized into 3 groups: 1. No UTI; 2. Complicated UTI; and 3. Recurrent UTI. Counts and percentages were used to describe categorical variables, and mean and standard deviation (SD) were used for continuous variables. The comparison between the 2 groups was made using the Student *t* test. Confidence intervals were established at 95%, and a value of $P < .05$ was considered statistically significant.

A linear regression analysis was performed to study the association between the outcome (eGFR variation by CKD-EPI between month 1 and month 24 post-transplant) and the UTI. The variables associated with decreased eGFR were eligible to enter the model, and for the final model only, those with statistical significance were chosen ($P = .05$).

For the multivariate analysis of graft survival, a logistic regression model with selected variables was used, using a stepwise approach. Variables associated with graft loss were eligible to enter the model.

Statistical analysis was performed using the STATA 15 program (StataCorp, College Station, Tex, United States).

RESULTS

During the observation period, 276 kidney transplants were performed. During the first 2 years post-transplant, 193 patients (69.9%) did not develop a UTI and 83 patients (30.1%) presented with at least 1 complicated UTI. Thirty-five of the UTI patients presented with recurrent UTI (42.1%). The mean time from transplantation to the initial UTI was 188.3 days (± SD 130.6); 44 of the 83 UTI patients developed acute kidney injury during the episode, 28 of whom were classified as Kidney Disease Improving Global Outcomes (KDIGO) 1, 11 as KDIGO 2, and 5 as KDIGO 3.

Baseline, demographic, and clinical characteristics of the transplanted population were compared based on the UTI status, and are presented in Table 1. We found that kidney transplant recipients with at least 1 episode of UTI were more likely to be women, with hypertension as a cause of kidney disease, transplanted from an expanded criteria donor, with serology for cytomegalovirus D+/R+, induction with basiliximab, and with delayed graft function.

Impact on eGFR

The analysis was performed using a linear regression model, taking into account all the variables that could affect eGFR, controlled by age, expanded criteria, delayed graft function, presence of rejection, cadaveric donor, human leukocyte antigen mismatch, the receiving of tacrolimus as a strategy for initial post-transplant immunosuppression, and sex. It was evidenced that patients presenting with at least 1 UTI had a variation in eGFR during the observation period of −12.6 mL/min/1.73 m^2 (95% confidence interval [CI] −4.5 to −20.7 mL/min/1.73 m^2; $P = .02$), compared with those without a UTI. When performing an adjusted model controlling for those variables with statistical significance, there was still evidence of a greater delta of loss in eGFR between the first month and month 24 post-transplant in the UTI −10.7 mL/min/1.73 m^2 (95% CI −3.1 to −18.2 mL/min/1.73 m^2; $P = .006$) group (Table 2). Figure 1 shows the average GFR during the observation period.

Graft Outcomes

To evaluate the graft survival outcome, we followed patients up for an average of 74.1 months (+/- SD 43.9) and documented that the main risk factors associated with graft function loss were expanded criteria donor (odds ratio [OR] 9.8, 95% CI, 2.33-40.1; $P = .002$) and presence of acute rejection (OR 4.3, 95% CI, 1.5-12.3; $P = .006$). Having at least 1 UTI was associated with more significant graft loss (OR 2.5, 95% CI, 0.9-7.0; $P = .84$). Nevertheless, it did not reach statistical significance.

Microbiology

A total of 157 UTI episodes were documented. Gram-negative pathogens caused most infections and more than half were caused by *Escherichia coli* (51.6%), with *Klebsiella pneumoniae* being the second most common cause (12.1%). The presence of gram-positive pathogens was uncommon.

DISCUSSION

We examined a cohort of renal transplant recipients managed in a single center, and we found that 30.1% of them presented with at least 1 complicated UTI after

Table 1. Sociodemographic, Clinical, and Outcome Characteristics

	No UTI (n = 193)	Complicated UTI (n = 83)	Recurrent UTI (n = 35)*
Demographic data of recipients			
Age (y), mean (±SD)	45.2 (13.5)	45.1 (13.5)	45.1 (13.6)
Women, n (%)	57 (29.5)	51 (61.4)	25 (71.4)
Cause of kidney disease, n (%)			
Hypertension	36 (18.7)	22 (26.5)	13 (37.1)
Type 2 diabetes mellitus	5 (2.6)	1 (1.2)	0 (0.0)
Type 2 diabetes mellitus and hypertension	19 (9.8)	9 (10.8)	2 (5.7)
Glomerulonephritis	32 (16.6)	15 (18.1)	4 (11.4)
Polycystic disease	10 (5.2)	4 (4.8)	2 (5.7)
Lupus and/or vasculitis	7 (3.6)	5 (6.0)	1 (2.9)
Reflux nephropathy	4 (2.1)	6 (7.2)	4 (11.4)
Other/Unknown	80 (41.5)	21 (25.3)	9 (25.7)
Kidney replacement therapy, n (%)			
Hemodialysis	145 (75.1)	55 (66.3)	22 (62.9)
Peritoneal dialysis	41 (21.2)	25 (30.1)	12 (34.3)
Pre-dialysis	7 (3.6)	3 (3.6)	1 (2.9)
Previous transplant, n (%)	20 (10.4)	6 (7.2)	2 (5.7)
Demographic data of donors			
Age (years), mean (±SD)	38.4 (14.5)	38.4 (14.7)	38.4 (14.8)
Cadaveric donor, n (%)	183 (94.8)	75 (90.4)	33 (94.3)
Expanded criteria donor, n (%)	11 (5.7)	9 (10.8)	7 (17.1)
CMV D+/R-, n (%)	13 (6.7)	9 (10.8)	3 (8.6)
Transplant characteristics			
Type of induction, n (%)			
Thymoglobulin	70 (36.3)	19 (22.9)	7 (20.0)
Basiliximab	113 (58.5)	57 (68.7)	25 (71.4)
Other	10 (5.2)	7 (8.4)	3 (8.6)
Cold ischemia time (h), mean (±SD)	12.5 (5.2)	12.6 (5.2)	12.6 (5.2)
Immunologic risk PRA >20%, n (%)	28 (14.5)	7 (8.4)	1 (2.9)
Double-J catheter, n (%)	49 (25.4)	21 (25.3)	6 (17.1)
Number of bladder-catheter days, mean (±SD)	6.5 (5.2)	6.3 (4.1)	6.5 (5.1)
Antibiotic prophylaxis, n (%)	169 (87.6)	73 (88.0)	29 (82.9)
Delayed graft function, n (%)	26 (13.5)	12 (14.5)	8 (22.9)
Follow-up			
Immunosuppression, n (%)			
Tac – MMF – Steroids	116 (60.1)	46 (55.4)	23 (65.7)
CsA- MMF – Steroids	69 (35.8)	35 (42.2)	11 (31.4)
Other	8 (4.1)	2 (2.4)	1 (2.9)
1 month post-transplant eGFR CKD-EPI (mL/min/1.73 m^2), mean (± SD)†	59.0 (24.6)	62.5 (27.4)	59.7 (27.7)
1 year post-transplant eGFR CKD-EPI (mL/min/1.73 m^2), mean (± SD)†	58.4 (28.4)	56.9 (29.3)	54.1 (32.5)
2 years post-transplant eGFR CKD-EPI (mL/min/1.73 m^2), mean (± SD)†	57.6 (28.9)	53.2 (31.2)	48.2 (34.8)
Graft loss at 2 years, n (%)	10 (5.2)	5 (6.0)	2 (5.7)
Mortality at 2 years, n (%)	9 (4.7)	3 (3.6)	2 (5.7)

Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CMV, cytomegalovirus; CsA, cyclosporine; eGFR, estimated glomerular filtration rate; h, hours; m, meter; mL, milliliters; min, minutes; MMF, mycophenolate mofetil; PRA, panel-reactive antibody; SD, standard deviation; Tac, tacrolimus; UTI, urinary tract infection

*Recurrent UTI patients are included in the complicated UTI group.

†Patients who lost the renal graft or did not continue their follow-up were assigned a GFR of 0 mL/min.

transplantation. In the linear regression model, those who presented the event had a higher delta eGFR with the CKD-EPI equation between month 1 and month 24 compared with those who did not show UTI, and the eGFR was significantly lower in the first group. This difference was maintained after controlling for well-known factors that negatively impact renal graft function.

Other researchers have evaluated the impact of UTI on renal graft function and have found conflicting results. Fiorante et al assessed the influence of acute pyelonephritis on graft results and found that this condition does not impair long-term graft function [8]. Ariza-Heredia et al found that patients presenting with at least 1 episode of UTI had a lower GFR, measured by nuclear medicine studies

Table 2. Linear Regression Model of Variables Evaluated as Predictors of Change in eGFR by CKD-EPI in Renal Transplant Recipients

	Delta eGFR in mL/min/1.73 m^2 Between Month 1 and Month 24 Post-transplant Coefficient	95% CI	*P* value
UTI	−10.7	−3.1 to −18.2	.006
Acute graft rejection	−13.0	−4.6 to −21.5	.003
Delayed graft function	19.2	8.2 to 30.1	.001
Initial tacrolimus post-transplant	−12.7	−5.5 to −20.0	.001

Abbreviations: CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; UTI, urinary tract infection.

(iothalamate) than those without infection. Nevertheless, they found no differences in the eGFR with the Modification of Diet in Renal Disease (MDRD)-4 equation [1]. Camargo et al evaluated the impact on graft function and found no differences in eGFR at 1 year [9].

In line with our findings, a study by Pelle et al documented that acute pyelonephritis had a negative impact on eGFR with the MDRD-4 equation [10]. Bodro et al analyzed 867 transplanted patients and found that those who developed graft pyelonephritis had a more considerable deterioration of renal function evaluated at 1 year [5]. Ooms et al evaluated 417 patients and 28% developed UTI; for those patients, the eGFR using the MDRD-4 equation was significantly lower compared with patients who did not develop a UTI [11]. Britt et al analyzed a large cohort of renal transplant recipients with 2469 patients; they documented that a UTI was significantly associated with a worse graft function as estimated by the MDRD-4, compared with those who did not have a UTI, especially in the case of recurrent UTI [4].

It is striking that, although it has been described that the incidence of post-renal transplant UTI decreases over time and that the majority of episodes occur in the early post-transplant period [12–14], in our study the average time for UTI onset was 6.3 months, which may be related to the results.

Abbott et al documented that late UTI was associated with renal graft loss and increased mortality [15]. Subsequently, a review by Martin-Gandul et al showed that the impact of UTI on graft dysfunction appears to be different depending on the period of onset of infection: early during the first 3 months vs late-onset. They found that an early UTI has been reported as a risk factor associated with the development of bacteremia and rejection, whereas a late recurrent UTI seems to be related to an increased risk of renal graft dysfunction and loss [16].

When we reviewed the effect of the immunosuppressive regimen, the use of tacrolimus was associated with higher delta eGFR between month 1 and month 24. The innate immune response is critical for controlling urinary tract bacterial infections [17]. A recent study documented that the use of tacrolimus has a negative effect on the toll-like receptor activation pathway, generating a defect in the functionality of bladder macrophages and granulocytes, conditioning a deterioration in the antimicrobial defense against UTI [18]. Therefore the immunosuppressive effect of tacrolimus could condition an increase in urinary infection rates, and the latter may be related to the impact documented on the eGFR.

Regarding graft loss, we found that having at least 1 UTI is associated with an increase in this event compared with those who do not present with a UTI. Nevertheless, this increased risk was not statistically significant (OR 2.5; 95% CI 0.9-7.0; $P = .84$). This is probably owing to the small number of patients who lost the graft, with an average follow-up period of 75.7 months (± SD 43).

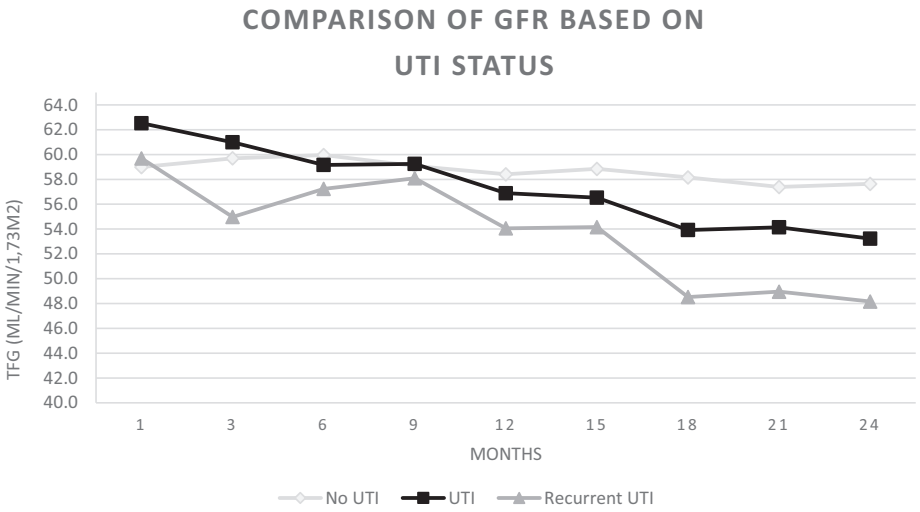

Fig 1. Comparison of eGFR by CKD-EPI based on UTI status after renal transplantation. CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; UTI, urinary tract infection.

The etiologic agents were isolated in 82% of the episodes. Most cases were related to gram-negative bacillus infection, which is similar to the prevalence found in other studies [7,19–23].

The present study has some limitations. It was a single-center study with a limited cohort of patients. Although we evaluated all transplanted patients, this was a retrospective study, and it cannot be ruled out that some data may be missing. Nevertheless, it provides crucial data on the impact of UTIs on renal function.

CONCLUSIONS

The findings suggest that the occurrence of complicated UTI has a negative impact on graft function, and it is necessary to take extreme measures to prevent and monitor UTI to avoid harmful consequences on graft function. The recorded impact of tacrolimus on the eGFR may be related to a dysfunction in the antimicrobial defense against UTI, and the latter may be responsible for the lower eGFR in this group.

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