Impact of Urinary Tract Infection on the Outcome of Allograft Renal Transplantation in Egypt

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Abstract: Introduction: Kidney transplantation is the best available replacement therapy for patients with end stage renal disease (ESRD). Successful renal transplantation allows freedom from the lifestyle restrictions and complications associated with dialysis. In addition, over the long term, it is more cost-efficient than dialysis. Infection is still the most frequent cause of death in the early post transplantation period. Infections are reported to be the second most common cause of death in renal transplant patients. Urinary tract infection (UTI) is the most common infection in renal transplant recipients**,** ranging from 6% to 86% and accounting for approximately 40–50% of all infectious complications. **Objectives:** The aim was to study incidence, risk factors and etiology of UTI and its effect on the outcome of renal transplantation among Egyptian patients. **Patients and methods:** This retrospective study was conducted on randomly selected 300 allograft renal transplant recipients attended Ain Shams Specialized Hospital, National Institute of Nephrology and Nasser Institute. Patients were subjected to full history taking and laboratory investigations; Kidney function test (KFT), estimated glomerular filtration rate (eGFR), urine analysis, urine culture and sensitivity, Complete blood count (CBC). Statistical analysis of data was performed using the SPSS software version 15.0. **Results:** The study included 300 allograft renal transplant recipients; 71.7% males and 28.3% females; their mean age (years) was 41±12.1. The mean follow up duration (months) was 35.47±1.44. Pyuria (WBC/HPF >10) was detected in 137 (45.6%) patients, and 66 (22%) patients were diagnosed as having UTI by positive urinary culture. 54/66 (81.8%) patients developed UTI during the 1st 6 months post-transplantation, while 12/66 (18.2%) after 6 months. And 37/66 (56.1%) patients developed recurrent UTI episodes. The most common etiology of ESRD among patients with UTI was hypertension (26/66). The most common causative organism of UTI was *E. Coli* (41%). Out of the 66 UTI patients; 18 (27.3%) developed acute rejection (p=0.5). Only 25/300 (8.3%) patients had pre-transplantation UTI, out of who only 8/25 (32%) developed post-transplantation UTI (p=0.2). Out of the patients who developed post-transplantation surgical complications, only 10/30 (33.2%) developed UTI (p=0.1). Only 19/300 underwent nephrectomy of native kidney; 6/19 of them developed UTI; 3/6 (50%) pre-transplantation and 3/6 (50%) post-transplantation (p=0.02). Also UTI was more associated with patients who underwent unilateral nephrectomy (5/6). It was noticed that UTI was more prevalent after the first transplantation (62/66) than after the second transplantation (4/66) (p=0.4). Out of the 43 CMV-positive patients; 10/43 (23.3%) developed UTI (p=0.8). The mean GFR was significantly lower among patients with UTI than among those without UTI (54.98±25.34 and 62.34±26.22 respectively, p=0.04). The incidence of lost graft among UTI patients was significantly higher than among those without UTI (10.6% and 3.8%, p=0.03). Presence of UTI didn't significantly affect 5 years graft survival (p=0.6). **Conclusio**n: UTI is a common post-renal transplantation complication which has a negative impact on graft function and survival. Pre-transplantation nephrectomy decreases the incidence of post-transplantation UTI.

[Essam M. Khedr, Aber H. Baki Attallah, Sahar M. Shawki and Cherry R. Kamel **Effect of UTI on the Outcome of Allograft Renal Transplantation in Egypt**] *J Am Sci* 2012; 8(1s):93-98]. (ISSN: 1545-1003). http://www.jofamericanscience.org. 15

Keywords: UTI, renal transplantation, graft function, graft survival, pre-transplantation nephrectomy, Egypt.

1. Introduction

Renal transplantation has become a well-established, highly successful therapy for chronic ESRD. Successful renal transplantation strictly depends on good control of rejection and better prevention and treatment of infections, which remain serious threats.[1]

Renal graft recipients are at greatest risk of infections that may compromise the transplant outcome and may represent a serious danger to the patient's life. Infectious complications after renal transplantation are associated with significant morbidity. They are still the most frequent cause of death in the early post-transplantation period.[2,3]

After the first 6 months from transplantation, the kidney transplant function becomes the main predictor of risk for infections.[4] About 75% of patients have excellent allograft function and require low maintenance immunosuppressive therapy; these develop infections at a frequency comparable to that in the general population. Fifteen percent have a moderate graft function and have a higher incidence of viral infections.[5] The remaining 10% with poor allograft function and frequent episodes of acute and

chronic rejections carry the highest risk for development of opportunistic infections.[6]

Although several factors influence the risk of infections following transplantation, key factors include the degree of human leukocyte antigens (HLA) mismatch, the net state of immune-suppression, early renal function, early rejection episodes, and donor kidney source.[7]

Urological maneuvers post renal transplantation (indwelling catheters) also carry the risk of increased incidence of UTI's.[8] It is mentioned that antibiotic prophylaxis as well as early removal of indwelling catheters may lower the incidence of post renal transplantation UTI's.[9]

The long-term effect of UTI on graft and patient survival is debatable. While some studies demonstrated an increased risk of chronic rejection with urinary tract infections,[10] others failed to show that effect.[11, 12] Although the incidence of UTI is increased in patients with urologic complications, no differences in long-term graft or patient survival were seen in multiple studies addressing this problem.[13, 14, 15]

The aim of this retrospective study was to study the incidence, risk factors and etiology of UTI and its effect on the outcome of renal transplantation among Egyptian patients.

2. Patients and Methods

Patients

This retrospective study was conducted on randomly selected 300 allograft renal transplant recipients attended Ain Shams Specialized Hospital, National Institute of Nephrology and Nasser Institute.

Treatment protocol:

Fifteen patients of them had induction therapy either with Anti-Thymocyte Globulin (ATG) or Basiliximab, patients were maintained on triple immune-suppressive therapy, the most commonly used protocol was corticosteroid (CS), cyclosporine (CsA), mycophenolate mofetil (MMF)/ mycophenolic acid (MPA). Patients who received induction therapy were given prophylaxis with systemic antifungal, and also were given antiviral prophylaxis against cytomegalovirus (CMV) for 3 months.

All patients received prophylactic intravenous third generation cephalosporin for 5 days post-operative. Patients were given (sulphamethaxazole/trimethoprim) (800 mg/160 mg) for 3 months prophylaxis against Pneumocystitis carinii pneumonia, and against UTI.

Methods

Each patient was subjected to:

1) Full clinical history taking; personal, present and past history.
2) Laboratory investigations

a- KFT (serum creatinine and blood urea)
b- Estimated glomerular filtration rate (eGFR) using (MDRD) Modification of Diet in Renal Disease equation.
c- Complete blood count (CBC)
d- Urine analysis
e- Urine culture and sensitivity

Pyuria was defined as the presence of at least 10 white blood cells per high-power field (WBC/HPF) of unspun midstream urine.[16] UTI was defined as urine culture containing more than 10^5 colonies.[17]

Graft dysfunction was defined as more than 20% rise in serum creatinine after diagnosing UTI[18], or is an estimated glomerular filtration rate (eGFR) <40ml/min.[19] Graft survival time was defined as the time between the date of transplantation and the date of graft failure. Graft failure was defined as one of the following events: return to dialysis, re-transplantation or death with functioning graft.[20]

Statistical analysis

Statistical analysis of data was performed using the SPSS software version 15.0 (SPSS Inc., Chicago, IL, USA). Data were expressed as mean± standard deviation (SD) values or as frequencies (percentages). Mean values were compared using the Student's t-test or paired t-test for continuous variables. Non-continuous variables were compared using Chi-square test. Graft survival rates were determined by Kaplan-Meier analysis and the log-rank method. All tests were two-tailed, and statistical significance was established at p values of ≤ 0.05.

3. Results

The study included 300 allograft renal transplant recipients; 215 (71.7%) males and 85 (28.3%) females; their mean age was 41±12.1SD. Post-transplantation pyuria was detected in 137 (45.6%) patients, 66 (22%) had UTI by positive urinary culture, as in fig. 1.

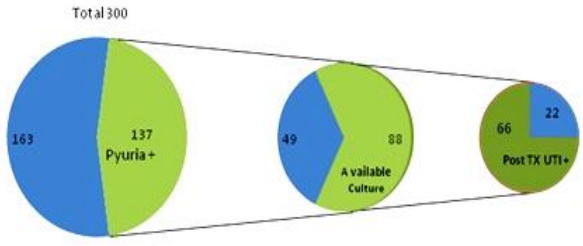

Figure 1: Prevalence of pyuria, post TX UTI in the study.

Escherichia coli (E. coli) was the most commonly isolated organism by urine culture followed by Pseudomonas (19.7%) and Klebsiella

(19.7%), while *Streptococcus agalactiae* (1.5%) and Citrobacter (1.5%) were the least commonly isolated organisms. 54/66 (81.8%) patients developed UTI during the 1st 6 months post-transplantation, while 12/66 (18.2%) after 6 months. And 37/66 (56.1%) patients developed recurrent UTI episodes.

Comparison between UTI group (66 patients) and non UTI group (234 patients) showed insignificant differences as regards to sex and age (p>0.05). The eGFR was significantly lower among UTI group (p≤0.05). As regards to the etiology of ESRD; the incidence of UTI was significantly higher among patients with obstructive uropathy (OU) (p≤0.05). Insignificant differences between the two groups were found as regards the past history of Bilharziasis, reflux or hepatitis C virus (HCV) (p>0.05). Insignificant differences between both groups were found as regards immnuno-suppression, acute rejection, pre-transplantation UTI, surgical complications and CMV (p>0.05). Out of the studied 300 patients, 19 patients underwent native kidney nephrectomy, 6 of them developed UTI, and those patients who underwent pre-transplantation nephrectomy showed significantly lower incidence of UTI (p≤0.05). Incidence of lost graft was higher among UTI group than non UTI group (p≤0.05) (Table 1).

Regarding 5 years graft survival among UTI group, 3 (4.5%) patients lost graft, while 8 (3.4%) patients of the non UTI group lost graft and the difference was statistically insignificant (p=0.6), as in fig.2. The mean graft survival time among UTI group was insignificantly lower than among non UTI group (57.39 and 57.84 respectively, p=0.84). There was insignificant effect of post-transplantation UTI on 5 years graft survival rate.

Table 1: Comparison between UTI and non UTI groups of patients

	UTI group(n=66)	Non UTI group(n=234)	*p*-value
Male (%)	48 (72.7%)	167 (71.4%)	0.8
Age (years)	43.4±11.29	40.32±12.25	0.06
Duration of dialysis (months)	18.5±14.2	17.99±23.46	0.8
Follow up duration (months)	41.54±33.91	33.75±31.04	0.07
eGFR	54.98±25.34	62.34±22	**0.04**
Serum creatinine	1.99±1.61	1.66±1.38	0.13
Etiology of ESRD			
Hypertension (%)	26 (39.4%)	88 (37.6%)	0.79
Diabetes mellitus (%)	11 (16.7)	25 (10.7%)	0.18
PKD (%)	6 (9.1%)	15 (6.4%)	0.45
OU (%)	14 (21.2%)	16 (6.8%)	**0.001**
CPN (%)	4 (6.1%)	16 (6.8%)	0.82
CGN (%)	7 (10.6%)	29 (12.4%)	0.69
CIN (%)	2 (3%)	5 (2.1%)	0.67
Unknown (%)	7 (10.6%)	39 (16.7%)	0.22
Others (%)	1 (1.5%)	11 (4.7%)	0.24
Bilharziasis (%)	9 (13.6%)	17 (7.3%)	0.1
Reflux (%)	5 (7.6%)	7 (3%)	0.09
HCV-positive (%)	14 (21.2)	64 (27.4%)	0.31
Immuno-suppression			
Induction (%)	3 (4.5%)	12 (5.1%)	0.84
Maintenance			
CS-CsA-MMF (%)	41 (62.1%)	146 (62.4)	
CS-CsA-AZA (%)	16 (24.4%)	50 (21.4%)	
CS-SRL-MMF (%)	3 (4.5%)	7 (3%)	0.37
CS-TAC-MMF (%)	4 (6.1%)	29 (12.4%)	
CS-EVER-MMF (%)	2 (3%)	2 (0.9%)	
Acute rejection (%)	18 (27.3%)	56 (23.9)	0.5
Pre-transplantation UTI (%)	8 (12.1%)	17 (7.3%)	0.2
Surgical complications (%)	10 (15.2%)	20 (8.5%)	0.11
Native kidney nephrectomy			
Pre-transplantation (%)	3/6 (50%)	11/13 (84.6%)	**0.01**
Unilateral (%)	5/6 (83.3%)	10 /13 (76.7%)	0.75
Second re-transplantation (%)	4 (6.1%)	9 (3.8%)	0.43
CMV-positive (%)	10 (15.2%)	33 (14.1%)	0.83
Overall lost graft (%)	7 (10.6%)	9 (3.8%)	**0.03**

PKD= polycystic kidney disease, OU=obstructive uropathy, CPN= chronic pyelonephritis, CGN=chronic glomerulonephritis, CIN=chronic interstitial nephritis, AZA=azathioprine, SRL=sirolimus, EVER= everolimus.

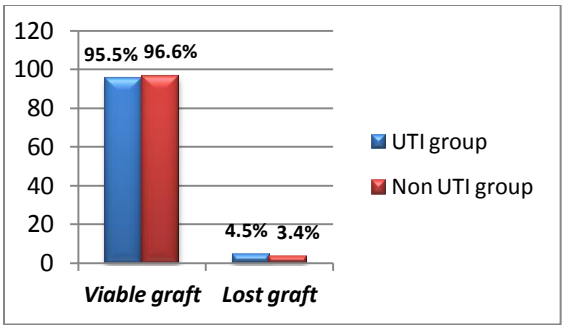

Figure 2: 5 years graft survival

4. Discussion

The prevalence of UTI among the studied 300 allograft renal transplant recipients was 22%. And there were insignificant differences between UTI and non UTI groups of patients as regards to age and sex. This coincides with Iqbal *et al.,* [21] who found that the prevalence of UTI in their study was 33%, and found insignificant differences between UTI (66 patients) and non UTI (134 patients) groups of patients as regards to age and sex (*p*= 0.51 and p=0.31 respectively).

Regarding the mean duration of pre-transplantation dialysis, in our study there was insignificant difference between UTI and non UTI groups of patients. And this also coincides with Iqbal *et al.,* [21] who found no statistically significant difference between the studied groups as regards to the duration of dialysis (12±14 and 11±15 respectively, *p*=0.83).

Most UTI episodes occur during the first three months post transplantation.[22,23] An earlier study from SIUT reported UTI in 65% recipients in the first three months of post transplantation.[24] The present study showed that 81.8% patients developed UTI during 1st 6 months post-transplantation, while 18.2% after 6 months.

The most common isolated organisms in our study were *E. coli* (40.9%) followed by other gram negative organisms such as Pseudomonas (19.7%) and Klebsiella (19.7%). Also Iqbal *et al.,* [21] found *E. coli* (51%) as a leading cause of UTI, followed by Pseudomonas (18%) and Klebsiella (14%).

Diabetic nephropathy has been widely reported to be associated with increased risk of UTI.[13] This was not observed in our study as no significant association between pre-transplant diabetes and increased risk of urinary tract infection was found. This could be due to the small number of diabetic patients in the study group. Other causes of ESRD were not found to be a significant cause for increasing the risk of post transplant urinary tract infections in our renal transplant recipients.

In this study, patients with structural abnormalities such as reflux uropathy and bladder outlet obstruction developed UTI, but the association was insignificant as regards to reflux and this can be explained by that 4 patients of those with reflux showed minor degree of reflux (grades I-II) only discovered by micturating cystourethrography (MCUG), while significant association was found as regards to obstructive uropathy. This is partially consistent with the results of Chuang *et al.,* [25] who reported a high incidence of UTI in patients with structural abnormalities.

In our study the risk of post-transplantation UTI didn't significantly increases with history of Bilharziasis. And this disagrees with Mahmoud *et al.,* [26] who found significant association between the incidence of UTI and Schistosoma infection among graft recipients. The difference might be explained by the smaller number of patients with history of Schistosomiasis in our study (26) in comparison to 136 recipients with Schistosomiasis in their study.

In our study, the incidence of post-operative UTI among patients with history of pre-operative UTI was 8/25 (32%) in comparison to 58/275 (21%) of patients without pre-operative UTI. Also Rizvi *et al.,* [27] found that the incidence of post-operative bacterial UTI was 31.6% (6 of 19) among patients with pre-operative UTI compared with 6.2% (6 of 81) among patients without pre-transplant UTI.

The mean serum creatinine was not significantly higher among patients who developed UTI in comparison to those without UTI, while the eGFR significantly decreased among patients with UTI. This disagrees with Iqbal *et al.,* [21] who found that mean creatinine level was significantly higher among UTI group in comparison to those without (1.52±0.38 and 1.12±0.28, *p*<0.001).

In our study UTI was found to significantly decrease overall graft survival, and this might be explained by *E. coli* that expresses P fimbriae. These virulence factors, or unknown uropathic factors, may contribute to the effects of calcineurin inhibitors, endotoxin and limited symptoms resulting in a significant deterioration of renal allograft function. [28]

Five year graft survival was 95.5% in positive group, 96.6% in negative group with no significant difference. And this agreed with Lyerová *et al.,* [29] who found no significant differences in graft survival during 5 years between patients with UTI and without UTI.

Conclusion

UTI is a common post-renal transplantation complication which has a negative impact on graft function and overall survival. Pre-transplantation nephrectomy decreases the incidence of post-transplantation UTI. Obstructive uropathy were significant risk factors for UTI among allograft

kidney transplant recipient. Pre-transplantation nephrectomy significantly decreases the incidence of post-transplantation UTI.

Acknowledgments

We acknowledge Dr.Mohamad Said, M.B.B.Ch**,** Faculty of Medicine**,** Ain Shams University for her helpful work during recruitment of cases, comments & discussion.

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