# Lower Urinary Tract Symptoms in Kidney Transplant Recipients and Timing of Treatment With TURP: Impact on Renal Graft Survival and Function

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ABSTRACT

Background. With the aging of recipients of renal transplantation (RT) one of the emerging issues is the incidence of low urinary tract symptoms (LUTS), which may have negative consequences on the graft survival and function. The aim of our study was to assess the influence of LUTS and the treatment with transurethral resection of the prostate (TURP) on the outcome of RT.

Materials and Methods. We collected data from men over 55 who underwent RT at our center from January 2007 to December 2016. We analyzed the incidence of LUTS; the rate of treatment with TURP; the eGFR (estimated glomerular filtration rate) at 6 months and 1, 3, and 5 years from transplantation; and graft survival.

Results. Fifty-five patients out of 268 experienced LUTS, and 19 of them had a bladder outlet obstruction (BOO). Patients experiencing BOO had a significantly higher hazard ratio (HR) of graft failure (HR 5.7, CI 1.56-21.4) compared to the other recipients. Of the 18 patients treated with TURP, 10 received the procedure within 6 months from the LUTS onset. They had a significantly absolute eGFR improvement at 6 months from the intervention (+14.25 mL/min ± 8.10) compared to the patients treated later (-8.4 mL/min ± 14.43).

Discussion. We showed the negative effects of LUTS on kidney graft function and survival. Although TURP is the standard therapy for such an issue, the best timing for it still has to be defined. Our experience supports the need for an early treatment of the LUTS for promoting the outcome of the RT.

DUE to the increase in elderly patients undergoing RT (renal transplantation), some age-related issues may ensue and risk compromising the overall success of the intervention [1,2].

One important threat is represented by the benign prostatic hyperplasia (BPH), which is one of the most common causes of lower urinary tract symptoms (LUTS) in middle-aged and elderly men. LUTS are generally due to issues related to the urinary storage (overactive bladder, increased urinary frequency, nocturia, urinary urgency, and urinary incontinence) or voiding (slow/weak stream, hesitancy and terminal dribble, incomplete emptying, and postmicturition dribble) [3]. The symptoms related to the latter group are certainly the most frequent in the general population, as approximately 50% to 60% of men older than 60 experience BPH and related LUTS [4]. However, since patients on dialysis are often oliguric or anuric, LUTS remain unnoticed and emerge only after the restoration of diuresis following RT. The occurrence of bladder outlet obstruction (BOO) and lower urinary tract infections (UTIs) may have severe detrimental effects on graft function and renal outcomes [5]; therefore, such problems

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0041-1345/19
https://doi.org/10.1016/j.transproceed.2019.02.072

should be detected and addressed as soon as they present [6].

Currently, transurethral resection of the prostate (TURP) is considered the gold standard for treatment of LUTS caused by BPH. Whereas its safety has been proven worldwide in the general population, complications such as UTIs and bleeding requiring blood transfusion are possible and can be particularly challenging to manage in transplanted patients [7]. In the published data, an increased risk of urosepsis following TURP performed after RT has been reported among the early complications, possibly due to the required immunosuppressive therapy [8]. In the long run, urethral strictures can also ensue after TURP, especially when the procedure is delayed and the patients have undergone several traumatic catheterizations and recurrent infections [9].

All these events related to the BPH and its treatment may be associated with significant rates of morbidity and prolonged hospitalization [8]. The aim of this study is to report the incidence of LUTS in a population of male elderly kidney transplant recipients and describe their outcome in terms of graft function and survival according to the timing of the urologic treatment.

## MATERIALS AND METHODS

### Study Design

This retrospective observational study included all consecutive male patients over the age of 55 who underwent a kidney transplantation at the Kidney and Pancreas Transplantation Unit of the Hospital of Padua from January 2007 to December 2016. Patients were followed up from the date of transplantation until the last follow-up visit or the loss of graft function. We excluded from the analysis all patients who presented urogenital malformations in the records before the kidney transplantation.

Data on recipients', donors', and transplantations' characteristics were collected: time from transplantation to the onset of LUTS, type of treatment used, time from the onset of LUTS and the TURP in the patients who underwent that procedure, recipient age, time on waiting list, time on dialysis, number of retransplantations in the recipients at the time of LUTS onset, type of donor (living, deceased, and marginal donor), occurrence of delayed graft function (DGF), episodes of acute rejection, and the type of immunosuppressive regimen (both for the induction and for the maintenance period).

DGF was defined as the need of dialysis in the first week after transplantation; the immunologic episode was recognized as acute rejection either when biopsy proven or when the antirejection treatment was started based on clinical suspicion. Graft survival was defined as return to dialysis or retransplantation. Patients lost at the follow-up with functioning graft were included in this analysis.

### Clinical Outcomes

The primary endpoint was to assess the effect of LUTS after kidney transplantation in terms of long-term renal function and graft survival. The renal function was assessed by eGFR at 1 and 6 months and 1, 3, and 5 years.

The secondary outcomes included the assessment of renal function and graft survival for the patients treated with TURP according to the timing of the procedure, within or after 6 months from the RT.

### Statistical Analysis

Continuous variables were reported as mean ± standard deviation. Categorical variables were summarized as the number and the percentage of cases. For comparison of categorical variables between groups, $\chi^2$ test or Fisher's exact test was used. To compare continuous variables between groups, the Mann-Whitney U test was applied. Graft survival curves were estimated using the Kaplan-Meier method and compared between groups using the log-rank test. The univariate Cox regression model was performed to identify risk factors of graft failure. $P$ values were calculated using two-tailed tests and considered statistically significant if less than .05. All analysis were performed using R software (version 3.4.3, The R Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

### Baseline Characteristics of Donors, Recipients, and Features of the Transplant

Of the 268 male kidney transplant recipients considered in the time period, 55 (20.5%) experienced low urinary tract obstructive symptoms (LUTS); 18 had urinary tract infections, and 18 with dysuria and 19 with acute bladder outlet obstruction (BOO) occurred. The mean time from transplantation to the beginning of LUTS was 14.23 months (± 19.28); however, 35 of the patients experienced LUTS within 6 months from RT and 30 of them within 3 months.

The main characteristics of the recipients, of the donors, and of the transplantations are shown in Table 1, according to the group of patients (LUTS vs asymptomatic patients). The 2 groups were similar in regard to the age at transplant and the type of donors (extended criteria donors and living donors). The only differences were observed in the percentage of retransplanted recipients, which was higher in the group with LUTS (18.18%) compared to that without LUTS (4.23%), and for the time on dialysis before transplantation, which was significantly longer for the LUTS group (49.04 ± 39.41 months) than for the asymptomatic recipients (35.11 ± 29.48). The immunosuppression regimen for both induction and maintenance was not significantly different between the 2 groups, according to our standard practice [10]. The postoperative incidence of DGF and acute rejection was also comparable among the groups, although slightly higher numbers of both events were reported for the group of LUTS (respectively 8.18% and 14.55% for DGF and acute rejection in the LUTS vs 15.02% and 9.39% in the not-LUTS group).

### Influence of LUTS on Graft Survival and Renal Function

*Graft survival.* When analyzing the graft survival of the recipients experiencing LUTS vs those without LUTS, we saw a trend toward lower survival rates for the former group (98.2%, 93.8%, and 90.2% at 1, 3, and 5 years post-transplantation, respectively) compared to the latter group (100%, 98.7%, and 95.7% at 1, 3, and 5 years post-transplantation, respectively, $P = .3$) (Fig 1A). When

**Table 1. Baseline Variables Related to the Recipients' and Donors' Characteristics and to the Transplantation Features**

| Characteristics of Recipients, Donors, and Transplantations | Patients With LUTS (55) | Patients Without LUTS (213) | *P* Value |
|---|---|---|---|
| Recipient Characteristics | | | |
| Age at transplantation (years) mean ± SD | 60.89 ± 6.58 | 60.28 ± 6.38 | .558* |
| Time in waiting list (months) mean ± SD | 24.15 ± 29.41 | 17.30 ± 18.63 | .169* |
| Patients on dialysis | | | |
| • n, % | 51 (92.73%) | 191 (89.67%) | .495† |
| • Time on dialysis (months) mean ± SD | 49.04 ± 39.41 | 35.11 ± 29.48 | .03247‡ |
| Retransplantations n, % | 10 (18.18%) | 9 (4.23%) | .00127‡ |
| Donor Characteristics | | | |
| Expanded criteria donor n, % | 28 (50.91%) | 112 (52.58%) | .825† |
| Living donor transplantation n, % | 7 (12.73%) | 42 (19.72%) | .232† |
| Transplantation Features | | | |
| DGF n, % | 10 (18.18%) | 32 (15.02%) | .566† |
| Acute rejection n, % | 8 (14.55%) | 20 (9.39%) | .265† |
| Induction immunosuppression | | | |
| • Thymoglobulin n, % | 46 (83.64%) | 163 (76.52%) | .257† |
| • Basiliximab n, % | 9 (16.36%) | 47 (22.07%) | .354† |
| Maintenance immunosuppression | | | |
| • CNI + steroids + MMF n, % | 30 (54.55%) | 97 (45.54%) | .233† |
| • CNI + steroids + mTORI n, % | 25 (45.45%) | 116 (54.46%) | |

Abbreviations: CNI, calcineurin inhibitor; DGF, delayed graft function; LUTS, lower urinary tract symptoms; MMF, mycophenolate mofetil; mTORI, mammalian target of rapamycin inhibitor; SD, standard deviation.
*Mann-Whitney test.
†$\chi^2$ test.
‡Fisher's exact test.

considering the patients presenting with acute bladder outlet obstruction as the main urinary symptom, we observed a significant decrease in 1, 3, and 5 years post-transplant graft survival, with figures, respectively, of 94.7%, 88%, and 70.4% for patients with acute BOO vs 100%, 98.4%, and 96% for those without that clinical presentation ($P = .003$) (Fig 1B). We then performed a Cox regression for graft survival analysis on the whole population of recipients (Table 2). We observed that both time on dialysis and the BOO were associated with a significantly higher hazard ratio of graft failure over time. Particularly, the HR of graft failure was increased by 5.7 times in the group of patients suffering a BOO compared to all the other patients, with a CI of 1.56 to 21.4.

*Renal function.* We compared the graft function in term of eGFR at 1, 6, and 12 months and at 3 and 5 years from transplantation between the group of patients who had experienced LUTS and the group who had not experienced it. A general not-significant trend toward higher levels of eGFR was observed in the group without LUTS at every time point.

### Influence of the Treatment With TURP on Graft Survival and Renal Function in the Subset of Patients With LUTS

Among the patients with LUTS, 34 were started on alpha blockers drugs, 18 underwent transurethral resection of the prostate, and 3 were managed with other treatments. When the chosen therapy was pharmaceutical, the patients were immediately put under treatment. By contrast, when they were treated with the procedure of transurethral resection of prostate (TURP), there was a latency time, from the beginning of the symptoms to the actual intervention, of 8.43 months (± 8.77). Of the 18 patients who performed the TURP, 10 had the procedure within 6 months from the diagnosis and only 5 within 3 months.

*Graft survival.* We compared the graft survival between the group of patients who underwent TURP vs those who did not. We found a slightly higher rate of graft survival in the group not undergoing TURP with 1-, 3-, and 5-year graft survival of 100%, 96%, and 84%, respectively, compared to a graft survival of 88.9% at 1 year from the beginning of the urinary symptoms, which remained the same for the remaining follow-up ($P = .58$).

*Renal function.* In order to assess whether the timing of TURP had any effect on the renal function, we compared the variation in eGFR assessed before the TURP and after 6 months and 1 and 2 years from the procedure. We observed a significant improvement in the eGFR at 6 months from the TURP when it was performed within 6 months from the beginning of the LUTS. The group of patients treated within that time period had a mean increase in the eGFR of 14.25 mL/min (± 8.10) compared to the group of patients treated later, who experienced a mean reduction in eGFR of 8.4 mL/min (± 14.43) ($P = .016$). When looking at the effect at 1 and 2 years from the procedure, we did not see a significant difference in the variation of eGFR between the 2 groups.

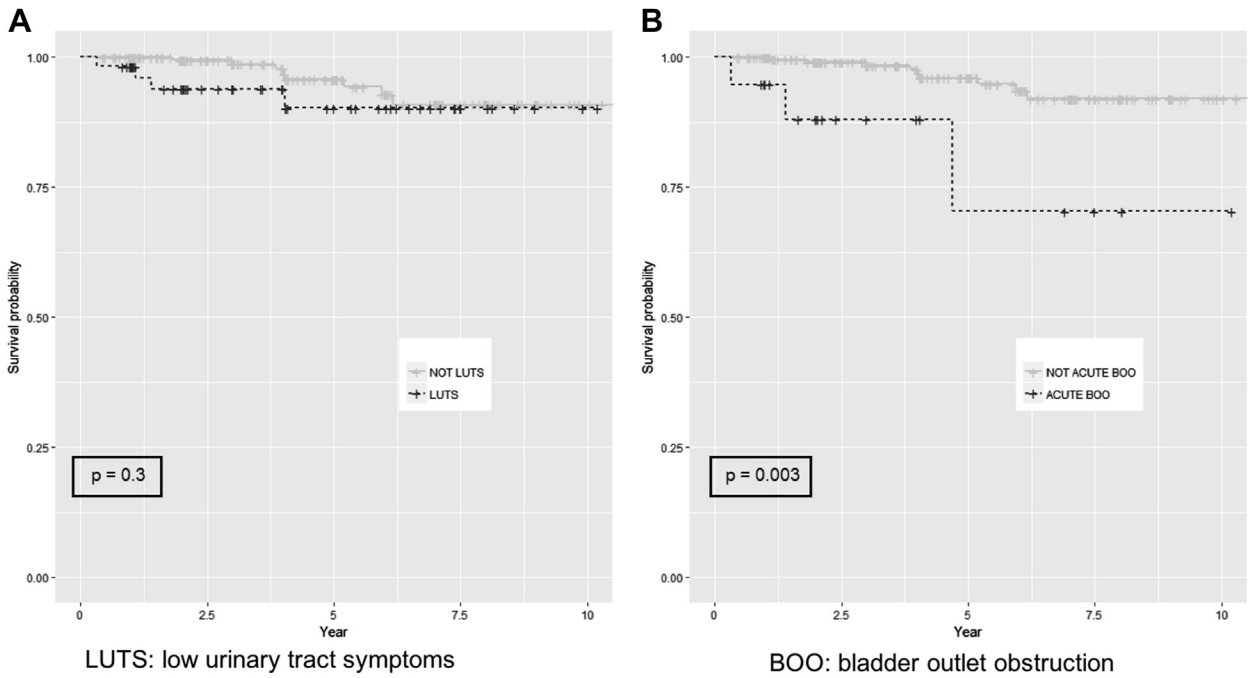


**Fig 1.** Kaplan-Meier graft survival curves from the time of transplantation to graft loss. **(A)** Comparison between patients with and without LUTS; **(B)** comparison between patients presenting with and without BOO.

## DISCUSSION

In the new era of kidney transplantation, physicians and surgeons need to manage an elderly population of recipients. A large American study published in 2009 showed that the incidence of BPH at 3 years from the kidney transplant was 9.7% in a group of male recipients, highly superior to the commonly acknowledged 10-year incidence of around 1% in the general population [11,12]. In our study, we only included male patients who were more than 55 at the time of transplantation; therefore, it is not surprising that we observed a much higher incidence of the disease, with more than 20% of our patients suffering of LUTS at a mean time of 14 months from transplantation. A higher percentage of retransplantations and a longer dialytic period in the group of men who experienced LUTS is probably due to the longer period of anuria, typical of sensitized patients. This condition may mask symptoms related to BPH or reduced bladder compliance, which present only at the restoration of urine output after the transplantation. Although the problem of urinary retention is quite common and many physicians are familiar with it, ascertaining it in the transplanted patients may be more challenging. First of all, LUTS can occur not only right after the removal of the bladder catheter, as we generally expect, but also some days or weeks afterward, when the patient has been discharged home and is seen by the doctor in the outpatient clinic. Moreover, chronic retention of urine may be asymptomatic and therefore not reported by the patient or may only present with slight increase in creatinine [13]. This factor is particularly important since the rate of retransplantation and sensitization among these patients is increased. As a result, it is not uncommon to face the clinical dilemma of a sensitized aged transplanted man presenting with a mild decline in the renal function, reporting mild LUTS. As the main danger in these cases is an immunologic event, a renal biopsy or the treatment of the suspected rejection are often the first steps in most of the transplantation centers. However, we should acknowledge the possibility of a urinary retention and excluding its occurrence in first place may be advantageous.

One of the most dreadful complications of BPH in the general population is renal failure [14]; however, only 1 study analyzed the long-term outcome of BPH in kidney

**Table 2. Univariate Cox Regression Analyses to Identify Risk Factors of Graft Failure in the Whole Patient Cohort**

| Univariate Analyses | | |
|---|---|---|
| Factors | HR (95% CI) | *P* Value |
| LUTS | 1.87 (0.56–6.22) | .3068 |
| Recipient age | 1.04 (0.95–1.13) | .373 |
| Donor age | 1.03 (0.98–1.09) | .21 |
| Time on dialysis | 1.02 (1.003–1.03) | .0147 |
| Events of acute rejection | 3.033 (0.90–10.18) | .0725 |
| Retransplantation | 2.33 (0.30–18.23) | .421 |
| Events of acute urinary retention | 5.778 (1.56–21.4) | .00864 |

Abbreviations: CI, confidence interval; HR, hazard ratio; LUTS, lower urinary tract symptoms.

transplant recipients [11]. In this paper, Hurst et al observed a 36% increased rate of graft failure for RT recipients with BPH compared to those without such a diagnosis.

In our population, patients with bladder outlet obstruction were over 5 times more likely to have a graft failure compared to those without, and this risk was increased at least 1.5 times. Moreover, we also observed a reduction in the renal function of patients suffering from LUTS compared to those without such symptoms, although the difference was not statistically significant, probably due to the low sample size of the LUTS group.

BPH is only one of the causes of LUTS in kidney transplant recipients. Mokos et al, in their study of patients undergoing TURP or TUIP (transurethral prostate incision) after the RT, reported that 37% of them did not have a BPH but a bladder neck constriction [15]. This is supported by other studies that have compared the volume of the resected prostates from kidney transplant recipients with the specimens collected from operations on the general population, finding lower weights of preoperative prostate and of resected gland in the group of transplanted patients [15,16].These evidences support the thesis that chronic retention may ensue even in cases of a slightly enlarged gland, suggesting that particular attention is needed in order to early detect and possibly treat LUTS.

A few studies have been published in the last 10 years about the results of TURP on kidney transplant recipients [13]. Volpe et al reported their experience of TURP on 32 patients after a median time of 6 months from the kidney transplantation, showing a significant improvement in renal function after the operation [6]. More recently Sarier et al confirmed such results [4], and, in a different publication, the same authors compared the 2 procedures of TURP and TUIP, finding similar results in term of postoperative incidence of acute urinary retention, UTIs, and reoperations but lower rates of retrograde ejaculation in favor of the TUIP procedure [16].

What is still a matter of debate is the timing of TURP after the beginning of LUTS. None of the studies consider the time elapsed from the initial urinary symptoms and the actual performance of the procedure.

In our patients, we compared the improvement in renal function after the TURP according to the timing of the procedure. For all the reasons mentioned previously, it is very common that kidney transplant recipients wait several months before undergoing the scheduled intervention. We found a significantly improved eGFR at 6 months after the TURP in the group of patients treated within 6 months from the beginning of urinary symptoms, compared to those treated later. However, such a trend was not confirmed in the following timepoints, probably due to the low numbers of patients in each group.

Since the TURP is a frequent procedure, it is common for the patients to wait a long time before the scheduled intervention is actually performed. However, a timely solution of the urinary symptoms is so vital not only for the function but for the actual survival of the renal grafts; therefore, it seems particularly important to establish dedicated pathways for the urological management of kidney transplant recipients in order to reduce the waiting time before the operation.

## CONCLUSION

This paper reports the experience of a single transplantation center in the detection and treatment of LUTS in male kidney transplant recipients. It has the merit of drawing the attention on the important problem of the impact of LUTS and of the timing of the treatment on the renal graft function and survival. However, the study presents a few limitatitions as well. First, it is retrospective with the potentials for confounders and some bias on data collection. Second, the number of patients who experienced the analyzed events was small. This hampered the estimation of multivariate modeling able to adjust for patient-related factors that could potentially affect the survival time of a patient in order to avoid overfitting. Finally some of the patients' medical records were not complete, hence limiting the information at our disposal.

From the available evidences, LUTS seem to impact not only on the renal graft function but also on its survival. LUTS in kidney transplant recipients may be misleading, and better assessment methods should be collegially discussed in order to promptly detect chronic retention and eventually treat them. TURP or TUIP are the main treatment methods; although the correct timing for these procedures is still unclarified, it seems that an early intervention may be justified by outcomes.

## REFERENCES

[1] Matas AJ, Smith JM, Skeans MA, Thompson B, Gustafson SK, Stewart DE, et al. OPTN/SRTR 2013 annual data report: kidney. Am J Transplant 2015;(Suppl 2):1–34. https://doi.org/10.1111/ajt.13195.

[2] Legeai C, Andrianasolo RM, Moranne O, Snanoudj R, Hourmant M, Bauwens M, et al. Benefits of kidney transplantation for a national cohort of patients aged 70 years and older starting renal replacement therapy. Am J Transplant. 2018;18:2695–707. https://doi.org/10.1111/ajt.15110.

[3] Coyne KS, Sexton CC, Thompson CL, Milsom I, Irwin D, Kopp ZS, et al. The prevalence of lower urinary tract symptoms (LUTS) in the USA, the UK and Sweden: results from the Epidemiology of LUTS (EpiLUTS) study. BJU Int. 2009;104:352–60. https://doi.org/10.1111/j.1464-410X.2009.08427.x.

[4] Sarier M, Tekin S, Duman İ, Yuksel Y, Demir M, Alptekinkaya F, et al. Results of transurethral resection of the prostate in renal transplant recipients: a single center experience. World J Urol. 2018;36:99–103. https://doi.org/10.1007/s00345-017-2094-5.

[5] Mitsui T, Shimoda N, Morita K, Tanaka H, Moriya K, Nonomura K. Lower urinary tract symptoms and their impact on quality of life after successful renal transplantation. Int J Urol. 2009;16:388–92. https://doi.org/10.1111/j.1442-2042.2009.02252.x.

[6] Volpe A, Billia M, Quaglia M, Vidali M, Marchioro G, Ceratti G, et al. Transurethral resection of the prostate in kidney transplant recipients: urological and renal functional outcomes at long-term follow-up. BJU Int. 2013;112:386–93. https://doi.org/10.1111/bju.12030.

[7] Rassweiler J, Teber D, Kuntz R, Hofmann R. Complications of transurethral resection of the prostate (TURP)—incidence, management, and prevention. Eur Urol. 2006;50:969–80.

[8] Reinberg Y, Manivel JC, Sidi AA, Ercole CJ. Transurethral resection of prostate immediately after renal transplantation. Urology. 1992;39:319–21.

[9] Fenton AS, Morey AF, Aviles R, Garcia CR. Anterior urethral strictures: etiology and characteristics. Urology. 2005;65:1055–8.

[10] Rigotti P, Capovilla G, Di Bella C, Silvestre C, Donato P, Baldan N, et al. A single-center experience with 200 dual kidney transplantations. Clin Transplant. 2014;28:1433–40. https://doi.org/10.1111/ctr.12475.

[11] Hurst FP, Neff RT, Falta EM, Jindal RM, Lentine KL, Swanson JS, et al. Incidence, predictors, and associated outcomes of prostatism after kidney transplantation. Clin J Am Soc Nephr. 2009;4:329–36. https://doi.org/10.2215/CJN.04370808.

[12] Koziolek MJ, Wolfram M, Müller GA, Scheel AK, Strutz F, Scheuermann EH, et al. Benign prostatic hyperplasia (BPH) requiring transurethral resection in freshly transplanted renal allograft recipients. Clin Nephrol. 2004;62:8.

[13] Mokos I, Kastelan Z, Basić-Jukić N, Kes P, Pasini J. Transurethral incision/resection of the prostate (TUIP/TURP) in operative treatment of repeated bladder outlet obstruction early after kidney transplantation. Acta Clin Croat. 2011;50:381–4.

[14] Rule A, Lieber M, Jacobsen S. Is benign prostatic hyperplasia a risk factor for chronic renal failure? J Urol. 2005;173:691–6.

[15] Gratzke C, Pahde A, Dickmann M, Reich O, Seitz M, Jauch K, et al. Predictive factors for urinary retention following kidney transplantation in male patients. Scand J Urol Nephrol. 2012;46:44–7. https://doi.org/10.3109/00365599.2011.633225.

[16] Sarier M, Duman I, Kilic S, Yuksel Y, Demir M, Aslan M, et al. Comparative results of transurethral incision with transurethral resection of the prostate in renal transplant recipients with benign prostate hyperplasia. Urol J. 2018;15:209–13. https://doi.org/10.22037/uj.v0i0.4074.