Transurethral resection of the prostate in kidney transplant recipients: urological and renal functional outcomes at long-term follow-up

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Objectives

- To assess prospectively the safety and efficacy of transurethral resection of the prostate (TURP) for the treatment of lower urinary tract symptoms attributable to benign prostatic hyperplasia (BPH) in patients who have undergone renal transplantation (RT).
- To assess the impact of TURP on renal graft function.

Patients and Methods

- Urological and renal functional outcomes of TURP performed in RT recipients for treatment of lower urinary tract obstruction attributable to BPH were prospectively assessed in a series of 32 consecutive patients with follow-up of ≥48 months.
- Maximum urinary flow rate (Q_{max}) at uroflowmetry, International Prostate Symptom Score (IPSS), post-void residual urine volume (PVR), haemoglobin and serum creatinine (sCr) levels were recorded before TURP and 1, 6, 24 and 48 months after the procedure. The trends in these variables after TURP were evaluated.
- Early and delayed complications were assessed and graded according to the Clavien classification system.

Results

- TURP was performed at a mean of 6 months after RT.
- No intraoperative complications occurred. Seven postoperative complications were observed (21.9%): two Clavien grade II and five Clavien grade IIIa.
- Q_{max}, IPSS and PVR improved significantly after surgery and the improvement was maintained until 48 months. No patient required a repeat TURP during follow-up.
- SCr levels significantly decreased 1 and 6 months after TURP and did not significantly increase at long-term follow-up.

Conclusions

- TURP for lower urinary tract obstruction attributable to BPH in RT recipients is safe and effective since it improves urinary flow, bladder emptying and related urinary symptoms.
- TURP allows an early significant improvement of graft function that is maintained at a follow-up of 48 months.

Keywords

benign prostatic hyperplasia, bladder outlet obstruction, lower urinary tract symptoms, renal functional outcomes, renal transplantation, transurethral resection

Introduction

The mean age of patients undergoing renal transplantation (RT) has been increasing in recent years [1,2]. According to the 2006 United States Renal Data System Annual Report, the proportion of RT recipients >60 years old increased from 10.4% in 1994 to 20.7% in 2004 [3]. This reflects the increasing age of the overall population and of patients on renal replacement therapy [1,2].

Functional outcomes of transplanted kidneys in elderly patients are satisfactory overall [4,5] and recent studies on series of older RT recipients reported similar graft survival rates compared with those observed for younger recipients [6–9]; however, the widespread use of extended-criteria donors in this setting ('old-for-old' allocation) makes these grafts prone to developing chronic interstitial fibrosis owing to calcineurin-inhibitor nephrotoxicity or chronic urinary tract obstruction [10,11].

Benign prostatic hyperplasia is a common disease in elderly men. It is estimated that in the USA >70% of men aged 60–69 years are affected by BPH [12]. The incidence of bladder outlet obstruction (BOO) attributable to benign prostatic hyperplasia (BPH) among RT recipients is often underestimated as patients undergoing dialysis are oliguric

or anuric. Nevertheless, after RT and restoration of diuresis, urinary obstruction and related lower urinary tract symptoms (LUTS) become evident [13], being responsible for patient bother and risk for graft function.

Today, TURP is considered to be the 'gold standard' treatment for LUTS attributable to BPH and its safety and efficacy have been confirmed in large series [14,15]. Studies in the literature have reported that TURP after RT is a safe procedure, but these studies were focused only on urological outcomes and had a short mean follow-up. Furthermore, to our knowledge, no information is available about the effects of TURP on renal functional outcomes after RT.

The aim of the present prospective study was to evaluate the long-term safety and efficacy of TURP performed after RT and to assess the impact of this procedure on graft function.

Patients and Methods

Patients

From November 1998 to July 2009, 636 patients with end-stage renal disease (246 women and 390 men) underwent cadaveric or living donor RT at our centre. Immunosuppressive therapy was based on steroids, mycophenolate mofetil and cyclosporine in the first 51 patients and on steroids, mycophenolate mofetil (or mycophenolic acid) and tacrolimus in the remaining patients. An induction was performed in all patients with basiliximab (20 mg on postoperative day 0 and 4) and calcineurin inhibitor introduction was either immediate or delayed until serum creatinine (sCr) decreased below 2 mg/dL. A histological evaluation of the graft according to Karpinsky score was performed in all donors aged >50 years before transplantation [16].

Overall, 103/314 (32.8%) male patients >40 years developed LUTS after RT. In all cases medical treatment with α-blockers (tamsulosine or alfuzosine) and/or 5-α reductase inhibitors (5-ARIs; finasteride or dutasteride) was initially recommended. Notably, 17/103 patients (16.5%) had already been on treatment with an α-blocker (doxazosin) for hypertension before development of significant LUTS and were given additional 5-ARIs when needed.

Patients underwent urological evaluation at 3 and 6 months after the start of medical therapy and every 12 months thereafter. According to our internal guidelines, TURP was indicated during follow-up in case of urinary retention requiring a permanent indwelling urethral catheter or in the presence of post-void residual urine volume (PVR) >100 mL, maximum urinary flow rate (Q_{max}) ≤10 mL/s, increased (≥3 points) International Prostate Symptom Score (IPSS), new onset of significant hydronephrosis at transplant ultrasonography or increasing sCr values in the absence of other reasons for worsening renal function.

Urological Assessment before TURP

Before TURP all patients underwent a thorough urological evaluation. Digital rectal examination (DRE), serum PSA testing, IPSS assessment, urine analysis with cultures and sensitivity, TRUS, uroflowmetry and PVR measurement were carried out in all patients. Urodynamic tests were performed in selected patients. When a prostate cancer was suspected based on elevated PSA values and/or suspicious DRE, patients were scheduled for prostate biopsy. Patients with evidence of prostate cancer at pathology or with LUTS attributable to neurological disorders at urodynamic tests were excluded from the study.

Nephrological Assessment before TURP

A thorough nephrological evaluation was carried out before TURP to exclude other causes of renal impairment and to identify the best time for intervention. In all patients with persistently impaired renal function and proteinuria, TURP was deferred so that renal biopsy and adequate treatment (e.g. steroid pulse therapy in the presence of acute rejection) could be performed as needed. Only patients without evidence of active nephrological problems underwent TURP. In all patients, immunosuppressive therapy was assessed before intervention; in mTOR-treated patients the drug was withdrawn at least 1 week before TURP and re-started at least 1 week afterwards to avoid interference with surgical healing. Steroid dose and tacrolimus levels were increased in these cases to provide sufficient immunosupression in the perioperative period. Steroids were administered i.v. on the day of intervention (switch from oral prednisone to an equivalent dose of i.v. methylprednisolone) and then restarted orally in all patients.

TURP Technique

We performed TURP under spinal or general anaesthesia. Perioperative antibiotic prophylaxis was performed 30 min before the procedure and continued on the first postoperative day. We used ampicilline-sulbactam 3 g if no urinary tract infection (UTI) was detected at preoperative cultures and other antibiotics according to sensitivity tests in the case of positive cultures. TURP was performed by different surgeons using a 26 F continuous-flow monopolar or bipolar resectoscope according to the standard techniques. The decision to perform a monopolar or bipolar TURP was based on the estimated adenoma volume at TRUS and on surgeon preference. At the end of the procedure a 22–24 F Dufour catheter was placed with

continuous bladder irrigation until the morning after surgery. The catheter was removed on the second postoperative day if the urine was clear. PVR was always tested before patient discharge.

For each patient we collected the following preoperative variables: serum PSA, IPSS, Q_{max} at uroflowmetry, PVR, haemoglobin (Hb) and sCr levels. For patients with an indwelling urethral catheter before TURP, we considered the sCr level measured before the catheter was placed to be the preoperative sCr. Recorded operative variables included type of resection (monopolar vs bipolar), operating time and volume of prostate tissue resected. Length of hospital stay, catheterization time and pathology of the tissue resected were also collected. Postoperative complications were recorded and graded according to the Clavien–Dindo classification [17]. Early and delayed complications were defined as those that occurred <24 h and >24 h after TURP, respectively.

Follow-up

Patients with a minimum follow-up of 48 months after TURP were considered eligible for the study. Follow-up consisted of physical examination, DRE, urine analysis with cultures, uroflowmetry, PVR measurement and IPSS at 1, 6, 24 and 48 months. Proteinuria, Hb and sCr levels were tested according to the same time schedule.

Statistical Analysis

Statistical analyses and graphics were performed using SPSS v. 15.0 (SPSS Inc., Chicago, IL, USA) and Statistica v. 7 (StatSoft Inc., Tulsa, OK, USA). Normality distribution was assessed using the Kolmogorov–Smirnov and the Shapiro–Wilk tests, and visually by histogram and kernel density plot. In the presence of skewness and considerable departure from normal distribution, data were expressed as median values with interquartile ranges (IQRs). Differences in Hb between two paired samples (before and after TURP) were performed using the Wilcoxon signed-rank method. Friedman's test was used to compare levels of sCr, PVR, and Q_{max} before and after 1, 6, 24 and 48 months. Changes in sCr were also evaluated in relation to the sCr critical difference, which indicates, for a stated probability level, the change needed between two serial results from the same individual to be significantly different; sCr critical difference was calculated according to the following formula:

$$CD\% = 2.77 \times \left(CVi^2 + CVa^2\right)^{1/2},$$

with 2.77 depending on the selected probability of 95%, and where CD% represents the sCR critical difference, and CVi and CVa indicate the intra-individual variation and analytical variation, respectively, specifically related to the laboratory where tests were performed. For a CVi and CVa of 4.3% and 3.8%, respectively, the sCr critical difference was 15.9%.

Results

A total of 32 patients who underwent TURP after RT at our centre with a minimum follow-up of 48 months were included in the study. The median (IQR) time between RT and TURP was 6 (3–14) months. Patient characteristics are shown in Table 1. Overall, five patients had an indwelling urethral catheter placed before TURP and four patients underwent urodynamic tests without evidence of neurogenic voiding disorders. No patient had significant hydronephrosis of the transplanted kidney before TURP.

Thirteen patients (40.6%) underwent a biopsy of the transplanted kidney before TURP because of persistently impaired renal function and proteinuria. Immunological lesions were seen in five patients (three cases of chronic transplant glomerulopathy and two cases of acute cell-mediated rejection) and required treatment before TURP. Nephrotoxicity lesions were observed in five patients and aspecific lesions in the remaining ones. At the time of intervention all patients were receiving steroids with a median (IQR) prednisone dose of 5 (2.5–10) mg/day. Thirty out of 32 (93.8%) patients were on a calcineurin inhibitor-based regimen (tacrolimus in all patients except one, who was on cyclosporine A) and 7/32 (21.9%) were taking an mTOR-inhibitor (rapamycin). Furthermore, 9/32 (28.1%) patients were under treatment with antiplatelet agents which were withdrawn 1 week before TURP and replaced with low-molecular-weight heparin until 2 weeks after TURP. No patient was on anticoagulant therapy.

In 21 (65.6%) and 11 cases (34.4%), TURP was performed with a monopolar and bipolar resectoscope, respectively. The median (IQR) operating time was 41 (33–56) min and the median (IQR) volume of tissue resected was 28 (22–34) g. The median (IQR) catheterization time and hospital stay

Table 1 Preoperative characteristics of the 32 patients in the study.

Characteristic	Median (IQR)
Age, years	58 (48–64)
Time on dialysis before RT, months	54 (22–81)
Residual diuresis before RT, mL	100 (50–200)
Preoperative Q_{max}, mL/s	9 (4.3–10)
Preoperative IPSS	15 (12–19)
Preoperative PVR, mL	140 (80–200)
Preoperative PSA, ng/mL	1.24 (0.5–1.45)
Volume of adenoma at TRUS, mL	26 (16–36)
Preoperative sCr, mg/dL	2.4 (1.8–2.7)
Preoperative proteinuria, g	0.2 (0.1–0.4)
Preoperative Hb level, g/dL	11.8 (9.9–13.2)

were 1 (1–2) and 3 (3–4) days, respectively. Pathology confirmed BPH in all cases and no incidental carcinoma was detected.

No intraoperative complications were observed. Postoperative complications were observed in seven patients (21.9% [Table 2]). Early complications occurred in two patients (6.3%). A patient with history of beta-thalassemia developed fever >38 °C on the first postoperative day. The antibiotic therapy was changed with resolution of hyperthermia. Another patient experienced persistent haematuria with a decrease in Hb levels (7 g/dL) and underwent blood transfusions. No transurethral resection syndrome occurred in the postoperative period. Delayed complications occurred in five patients (15.6%). Three patients developed acute urinary retention at catheter removal. In all patients, a 16-F Foley urethral catheter was placed and maintained for 48 h with no further episodes of retention. Two patients developed a bulbar urethral stricture 6 months after the procedure. In both cases the stricture was successfully treated with laser visual internal urethrotomy. No patient required repeat endoscopic procedures during follow-up. All early complications were Clavien grade II and all delayed complications were Clavien grade IIIa.

The median (IQR) follow-up was 64 (48–125) months. Preoperative and postoperative variables at the different follow-up points are shown in Table 3. Postoperative Q_{max} was significantly higher ($P < 0.001$), and IPSS and PVR were significantly lower than preoperative values ($P < 0.001$). Q_{max}, IPSS and PVR values remained stable until 48 months (Fig. 1). No significant Hb reduction was observed after TURP, while Hb level was significantly higher at 24 and 48 months follow-up compared with the preoperative value ($P < 0.001$).

Patients' sCr levels were significantly lower 1 and 6 months after TURP ($P < 0.001$) and were slightly higher at 24 and 48 months (Fig. 2); however, sCr at 48 months after TURP was still significantly lower compared with preoperative values and not significantly different compared with sCr values recorded at 6- and 24-month follow-ups. It is noteworthy that 52 and 79% of patients had a reduction in sCr levels beyond the critical difference after 1 and 6 months, respectively.

A comparative analysis with a control group of age-matched transplanted patients who did not undergo

Table 2 Early (<24 h after TURP) and delayed (>24 h after TURP) complications ($n = 32$).

Complication	*n* (%)	Treatment	Clavien grade
Early			
Anaemia	1 (3.1)	Blood transfusion	II
Hypertermia (>38 °C)	1 (3.1)	Antibiotic therapy	II
Delayed			
Acute urinary retention	3 (9.4)	Bladder catheterization	IIIa
Bulbar urethral stricture	2 (6.2)	Visual internal urethrotomy	IIIa

Fig. 1 Trend in peak flow rate (Q_{max}) at uroflowmetry during follow-up of TURP.

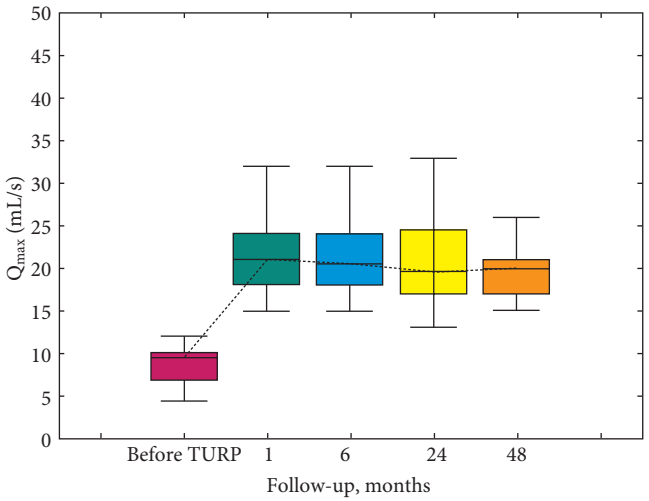
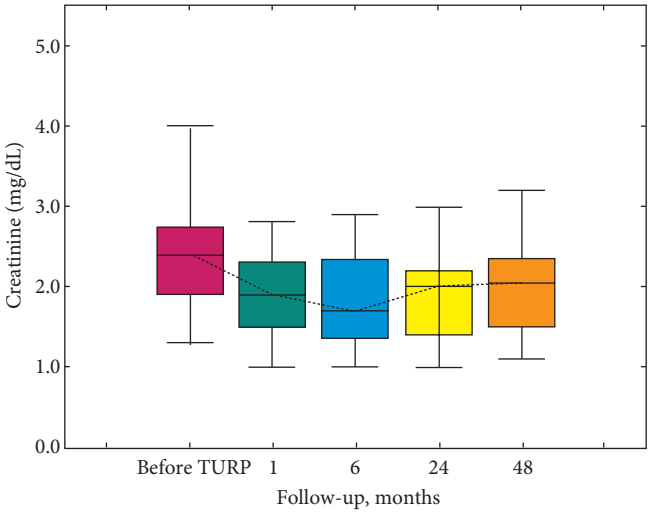


Table 3 Urological and renal functional outcomes during follow-up of TURP.

	Preoperative	1 Month	6 Months	24 Months	48 Months
Median (IQR; min–max) IPSS	15 (12–19; 11–20)	4* (0–5; 0–6)	3* (0-4; 0–5)	4* (0–6; 0–6)	3* (0–6; 0–6)
Median (IQR; min–max) Q_{max}, mL/s	9.5 (7.0–10.0; 4.3–27.0)	21.0* (18–24; 16–32)	20.5* (18-24; 16–32)	19.5* (17–24.7; 17–33)	20* (16.5–22; 15–44)
Median (IQR; min–max) PVR, mL	100 (100–150, 70–400)	0* (0–0; 0–40)	0* (0–0; 0–0)	0* (0–0; 0–50)	0* (0–0; 0–50)
Median (IQR; min–max) Hb, g/dL	11.8 (9.9–13.2, 8.9–16.6)	11.5 (10.1–13.4, 8.3–14.8)	12.0 (11.5–14.2, 9.9–16.0)	12.8*† (11.7–14.5; 9.5–16)	13.0*† (12.0–14.0, 11.0–16.6)
Median (IQR; min–max) SCr, mg/dL	2.4 (1.85–2.77; 1.2–8.8)	1.9* (1.5–2.35, 1.0–3.1)	1.7* (1.2–2.1, 1.0–3.0)	2* (1.4–2.3; 1.0–2.8)	2* (1.5–2.3, 0.8–2.4)

**Significant vs preoperative ($P < 0.001$). †Significant vs postoperative with correction for multiple comparisons ($P < 0.001$).*

Fig. 2 Trend in sCr levels during follow-up of TURP.



TURP showed that sCr was significantly higher in patients awaiting TURP compared with control patients 6 months after RT (2.63 vs 1.69 mg/dL, $P < 0.001$). Conversely, there was no significant difference between the sCr levels of patients who underwent TURP and those of control patients at 48-month follow-up (sCr = 1.9 vs 1.69 mg/dL, $P = 0.13$).

Five patients (15.6%) underwent a renal biopsy for clinical reasons after TURP; immunological lesions (chronic transplant glomerulopathy) were detected in one patient, while aspecific chronic vasculopathy without signs of chronic rejection was the predominant finding in the remaining patients.

Discussion

The incidence of end-stage renal disease increases with advancing age. Owing to low survival rates and the comparatively poor quality of life of patients in dialysis, RT has been increasingly performed in older patients over the past decade [1,2].

Although transplantation has been shown to be a good option for renal replacement therapy also in this category of patients [5–7], with graft survival outcomes that are similar to those of younger recipients, older RT recipients are more likely to have comorbidities that can affect graft survival and patient quality of life. BPH is a chronic condition that is associated with progressive LUTS attributable to BOO in aging men. These symptoms affect ~75% of patients in the seventh decade of life [12]. It is therefore not surprising that Tsaur et al. [18] reported a high incidence of voiding dysfunctions largely attributable to urinary obstruction caused by BPH in male RT recipients aged ≥60 years. LUTS are frequently experienced in this category of patients after RT while their presence is generally underestimated in patients with uraemia of the same age in dialysis owing to the decreased or absent diuresis [13]. The presence of severe BOO is worrisome in transplanted patients since this condition can lead to urinary retention with high PVR levels, recurrent UTIs and progressive deterioration of renal function. The median sCr level of patients in our series before TURP was found to be significantly higher than the median sCr level of an age-matched population without signs of chronic urinary obstruction 6 months after transplantation. Chronic urinary obstruction can affect graft function, either by increasing urethral resistances to urinary flow or by affecting glomerular filtration rate (GFR) [19].

The current gold standard treatment for BPH and related symptoms is TURP [15]. This is based on consistent data in the literature supporting the safety and efficacy of this procedure [14]. Although transurethral incision of the prostate is performed by some authors to relieve BOO after RT [20], at our centre TURP is the preferred option for the treatment of LUTS attributable to BPH in transplanted patients.

Only few, retrospective series of TURP in RT recipients have been reported in the literature. In 1992, Reinberg et al. [21] retrospectively compared the functional outcomes of eight patients who underwent TURP within 10 days of RT with those of another group of patients who did not undergo prostate surgery, and observed no significant difference between the groups in terms of graft and patient survival; however, there was a 25% incidence of major postoperative complications after TURP (including one mortality). With the improvement in TURP technique, other authors subsequently reported the efficacy of TURP in the treatment of BOO after RT without significant risk of complications in the presence of preoperative and postoperative sterile urinary cultures [22,23]. Although these studies were based on a low number of cases, a single institutional study very recently reported 70 patients who underwent TURP for urinary retention after RT. The authors identified patient age >60 years and duration of dialysis >120 months as significant predictors of urinary retention requiring TURP in this category of patients [24]. Finally, in a retrospective chart review of a large cohort of 23 622 recipients, Hurst et al. [25] observed that 7.3% of patients underwent TURP after RT. At multivariate analysis, BPH was independently associated with the incidence of acute urinary retention episodes, UTIs and graft loss.

All these studies were retrospective, focused mainly on the assessment of urological outcomes and have a relatively short follow-up. The present study represents, to our knowledge, the first prospective assessment of long-term urological and functional results of TURP after RT.

In the present series, 32.8% of male recipients aged >40 years developed LUTS after RT, which is consistent with the observations of Tsaur et al. [18] and emphasizes the clinical importance of chronic urinary obstruction management in transplanted patients.

Most patients with LUTS attributable to BPH can be initially treated with medical therapy, either with α-blockers, 5-ARIs or a combination of both [15]. At our centre, patients are scheduled for TURP only after clinical evidence of failure of a trial of medical treatment. This represents our policy both in the general population and in transplant recipients with LUTS. We believe this is appropriate to avoid surgical overtreatment of patients with moderate urinary obstruction and at the same time to select patients that are most likely to benefit from endoscopic resection.

In the present series, TURP was confirmed as a safe procedure. No cases of transurethral resection syndrome occurred. This can be explained by the relatively low median size of the adenomas resected and by the employment of continuous flow resectoscopes and bipolar technology for TURP of larger prostates. Minor (Clavien grade II) early complications were observed only in two patients, including one case of bleeding requiring blood transfusion and one of fever requiring modification of the antibiotic regimen.

According to major urological guidelines the duration of perioperative prophylaxis for a TURP should be ideally minimized to a single preoperative dose [26]; however, because of the higher risk of infections in the transplanted, immunocompromised population, we preferred to extend the administration of i.v. antibiotics to the entire first postoperative day. Our policy seemed to be effective as only one case of UTI (3.1%) was observed postoperatively in the present series.

Delayed postoperative complications were observed in 15.6% of cases, including three urinary retentions after catheter removal and two urethral strictures. All these complications required an invasive treatment (re-insertion of a urethral catheter or visual internal urethrotomy under regional anaesthesia) and are therefore classified as Clavien grade IIIa; however, all cases of postoperative urinary retention were attributable to oedema or clots and resolved spontaneously after a few days of further catheterization. No re-TURP was needed during follow-up, confirming the success of the procedure. The higher incidence of postoperative strictures compared with other series of TURP in the general population may be simply attributable to the small number of patients in the present study [27].

Regarding urological outcomes, the present study clearly confirms the clinical efficacy of TURP in RT recipients. Urinary flow, bladder emptying and related urinary symptoms improved significantly after TURP and this improvement was maintained at long-term follow-up. In particular, median Q_{max} at uroflowmetry increased from 9.5 mL/s preoperatively to 21 mL/s postoperatively ($P < 0.001$), and median IPSS score decreased from 15 preoperatively to 4 postoperatively ($P < 0.001$). No significant decrease in Q_{max} or increase in IPSS score was observed at 24- or 48-month follow-up (Table 3; Fig. 2). Five out of 32 (15.6%) patients continued chronic treatment with α-blockers (doxazosin) for hypertension after TURP, potentially biasing the results, but as these men were taking the same drug before TURP, this was unlikely to have had a significant influence on the degree of improvement of the urological outcomes.

Until now, no prospective and thorough assessment of the efficacy of TURP on renal function at short- and long-term follow-up has been available in the literature. The present study shows that renal function of transplanted patients who underwent TURP for LUTS attributable to BPH improves at short-term follow-up. In fact, median sCr levels showed a significant and progressive decline in the first 6 months after TURP (2.4 mg/dL preoperatively; 1.9 mg/dL 1 month after TURP; and 1.7 mg/dL 6 months after TURP; $P < 0.001$). The median sCr level subsequently slightly increased (2 mg/dL at 24–48 months), but remained comparable with that observed in the postoperative period confirming a satisfactory long-term graft function. Since urological outcomes were stable over time confirming the absence of recurrent urinary obstruction, the relative increase in sCr levels 24–48 months after RT is probably explained by the onset of new conditions affecting renal function. Furthermore, no significant difference in sCr levels at long-term follow-up was observed between patients who underwent TURP after RT in the present series and an age-matched population of transplanted patients without signs of chronic urinary obstruction. Although the two groups were not matched for immunological parameters, immunosuppressive protocol and comorbidities such as diabetes and cardiovascular disease, this also suggests that the beneficial effects of TURP on renal function are maintained over time.

In summary, the present study confirms the safety and long-term efficacy of TURP in the treatment of BPH after RT. TURP relieves BOO and significantly decreases related LUTS in the postoperative period. The benefits for urological outcomes are maintained until 48 months. Furthermore, the study shows a significant improvement of sCr levels in the postoperative months, with no significant worsening at long-term follow-up. Larger series of TURP in RT recipients with urodynamic confirmation of the presence and degree of urinary obstruction are needed to confirm our findings.

Conflict of Interest

None declared.

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Abbreviations: RT, renal transplantation; Q_{max}, maximum urinary flow rate; PVR, post-void residual urine volume; sCr, serum creatinine; 5-ARI, 5-α reductase inhibitor; Hb, haemoglobin; IQR, interquartile range.