



Title	Risk Factors for Lower Urinary Tract Dysfunction and Symptoms After Successful Renal Transplantation
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Risk Factors for Lower Urinary Tract Dysfunction and Symptoms After Successful Renal Transplantation

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Background: We investigated risk factors for lower urinary tract (LUT) dysfunction and LUT symptoms in patients who successfully underwent renal transplantation (RTX).

Material/Methods: Ninety-five patients (54 males and 41 females) undergoing RTX (median age: 45 years old) at Hokkaido University Hospital were included in this study. Uroflowmetry (UFM), postvoid residual urine volume (PVR), and 24-h bladder diaries were performed. We analyzed risk factors for voiding dysfunction, urinary frequency, polyuria, nocturia, and nocturnal polyuria after RTX using logistic regression analysis.

Results: End-stage renal disease arose from diabetes mellitus in 18 patients (19%). Pre-transplant dialysis had been carried out in 74 patients. Voiding dysfunction as assessed by UFM and PVR was observed in 24 patients (27%). Based on the 24-h bladder diaries, we identified frequent micturition in 29 patients (35%), polyuria in 44 (54%), nocturia in 30 (37%), and nocturnal polyuria in 46 (56%). A multivariable logistic regression analysis revealed that diabetes mellitus, which may cause autonomic disorders, was a risk factor for voiding dysfunction and nocturnal polyuria. A risk factor for frequent micturition and nocturia was older age at RTX. Being female was a risk factor for polyuria, which suggested that fluid intake in relation to body weight was higher in females.

Conclusions: LUT dysfunction and LUT symptoms were not uncommon in patients who successfully underwent RTX. LUT dysfunction and LUT symptoms need to be considered in patients with risk factors such as diabetes mellitus, older age at RTX, and being female, even after successful RTX.

MeSH Keywords: **Diabetes Mellitus • Kidney Transplantation • Lower Urinary Tract Symptoms • Risk Factors • Urinary Bladder, Overactive • Urinary Tract Physiological Phenomena**

Abbreviations: **CI** – confidence interval; **ESRD** – end-stage renal disease; **LUT** – lower urinary tract; **OR** – odds ratio; **PVR** – postvoid residual urine volume; **QOL** – quality of life; **RTX** – renal transplantation; **UFM** – uroflowmetry.

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Background

Renal transplantation (RTX) has broadly been accepted as an ultimate treatment for end-stage renal disease (ESRD). The long-term outcome of allograft survival has continuously been improved to more satisfactory levels because of recent developments in immunosuppressive therapies, with previous studies reporting that RTX improved the quality of life (QOL) of patients with ESRD [1–3]. However, the demand for kidney donors is markedly larger than their supply in Japan because of the shortage of deceased donors. Therefore, >80% of RTX in Japan are performed from living donors. Although some patients can undergo preemptive or early RTX because of a related living kidney donor or cadaveric kidney donor, most patients in Japan require long-term renal replacement therapies, such as hemodialysis or peritoneal dialysis.

Although detrusor overactivity, voiding dysfunction, and decreases in bladder capacity and bladder compliance were previously reported in patients as the duration of dialysis increased [4,5], the lower urinary tract (LUT) immediately adapts storage and voiding functions to variable urine volumes following successful RTX. In non-neurogenic patients, adaptation of the LUT typically occurs within 6 months of RTX [6] if the glomerular filtration rate and urine output fully recover. However, some patients develop LUT dysfunction and LUT symptoms, which can impact on QOL [7–9]. Particularly, more than a half of patients with RTX frequent micturition and nocturia, which persisted for many years [10,11]. Furthermore, patients who undergo RTX are instructed to take ample amounts of fluid in order to preserve renal function; however, this may affect LUT symptoms. We previously showed that some patients who successfully underwent RTX developed nocturnal polyuria and nocturia, which affected their QOL [9]. On the other hand, LUT dysfunction may cause urinary tract infection [8], which could affect survival of renal graft [12–14]. Thus, we need to focus on LUT dysfunction and LUT symptoms after successful RTX, because it is currently an important issue to improve the QOL of patients with RTX as well as a survival rate of renal graft.

Few studies have examined LUT dysfunction and LUT symptoms following RTX. In the present study, we investigated risk factors for LUT dysfunction and LUT symptoms in patients who successfully underwent RTX. This study addressed important points that need to be considered for LUT dysfunction and LUT symptoms after RTX.

Material and Methods

Ninety-five patients (54 males and 41 females) who underwent RTX at Hokkaido University Hospital between September 1991 and July 2013 were enrolled in the present study. All patients had

a follow-up period of 6 months or longer after RT, because adaptation of the LUT typically occurs within 6 months of RTX [6].

LUT function and micturition behavior were assessed using uroflowmetry (UFM), postvoid residual urine volume (PVR) at 6.0–184 months (median: 27.1), and 24-hr bladder diaries at 6.3–184 months (median: 38.6). The methods of urodynamics referred to documents of the International Continence Society [15] and micturition function was assessed by UFM and PVR. Voiding dysfunction was defined as follows; less than 5% of a maximum flow rate in a Liverpool nomogram [16], abnormal flow patterns such as obstructive, strain, and intermittent, or more than 50 mL of PVR. To assess micturition behavior, a 24-hr bladder diary was kept for 3 days. Frequent micturition was defined as voiding 10 times or more/day. Polyuria was defined as the production of more than 40 mL/kg of urine in 24 hrs [17]. Nocturia was defined as voiding 2 times or more between the time when an individual went to bed with the intention of sleeping and the time of waking with the intention of rising. Nocturnal urine volume was the total volume of urine passed between the time when the individual went to bed with the intention of sleeping and the time of waking with the intention of rising, which excluded the last void before going to bed, but included the first void after rising in the morning [15]. Nocturnal polyuria was defined as a nocturnal polyuria index (NPI: nocturnal urine volume/24-hr urine volume) of >0.33 [17]. The protocol for the present research project has been approved by a suitably constituted Ethics Committee of the Institution in Hokkaido University Hospital (No. #014-425).

Statistical analyses were performed using the Student's *t*-test and Chi-square test as a univariate analysis, and a multivariable logistic regression analysis was also used to investigate risk factors related to LUT dysfunction and LUT symptoms after RTX. The odds ratio (OR) along with the 95% confidence interval (CI) were also examined. Significance levels were set to 0.05 for all comparisons.

Results

The median age at RTX was 45 years (13–68 years) and the follow-up period after RTX was between 6.0 and 184 months. The median serum creatinine level at the most recent visit was 1.2 mg/dL (0.6–3.7). Body mass index at the most recent visit was 14.2–33.2 (median: 21.0). Serum creatinine level or body mass index at the most recent visit did not affect voiding function and micturition behavior. Pre-transplant dialysis had been carried out in 74 patients (78%) with a median duration of 5.0 years (0.1–32 years). Diabetes mellitus as an original disease for ESRD was noted in 18 patients (19%), and other original diseases were chronic glomerulonephritis in 32 patients (34%), IgA nephropathy in 14 (15%), autosomal

Table 1. Risk factors for voiding dysfunction.

	Univariate						p-value	OR	Multivariate	
	Voiding dysfunction (+)			Voiding dysfunction (-)					95% CI	p-value
	Mean	50 th	25 th -75 th	Mean	50 th	25 th -75 th				
Age at RTX (y/o)	45.4	46.5	34.6-56.1	41.2	41.8	31.1-59.8	0.217	1.021	0.979-1.067	0.327
Pre-transplant dialysis (years)	7.2	3.6	1.1-7.0	5.8	2.5	0-10.0	0.478	1.027	0.961-1.095	0.414
Follow-up period after RTX (months)	48.1	22.4	11.7-76.0	46.6	28.2	12.6-57.5	0.900	1.006	0.994-1.018	0.323
Gender (Female/Male)	8/16		29/35				0.311	0.757	0.259-2.124	0.599
Diabetes mellitus (%)	33.3		10.9				0.023	3.922	1.043-15.231	0.042

OR – odds ratio; CI – confidence interval.

dominant polycystic kidney disease in 5 (5%), nephrotic syndrome in 4 (4%), congenital renal hypoplasia in 3 (3%), reflux nephropathy in 2 (2%), and others or unknown in 17 (18%). The incidence of diabetes mellitus was analyzed as one risk factor because it can affect voiding function and micturition behavior.

Voiding dysfunction

Voiding dysfunction as assessed by UFM and PVR was observed in 24 out of 88 patients (27%, 16 males and 8 females). The univariate analysis revealed that the frequency of voiding dysfunction was higher in RTX patients with diabetic nephropathy ($p=0.023$). No significant differences were observed in gender, age at RTX, the period of pre-transplant dialysis, or the follow-up period after RTX between patients with and without voiding dysfunction. The multivariate logistic regression analysis revealed that diabetes mellitus as an original disease for ESRD was the only risk factor for voiding dysfunction, and also that the risk of voiding dysfunction after RTX was 3.92-fold higher in patients with diabetes mellitus than in patients without diabetes mellitus (95%CI: 1.043-15.231, $p=0.042$) (Table 1).

Urinary frequency

The 24-hr bladder diaries led to the identification of frequent micturition in 29 out of 82 patients (35%, 14 males and 15 females). The univariate analysis showed that the incidence of frequent micturition was higher in patients who underwent RTX at an older age ($p=0.010$) and had a longer pre-transplant dialysis period ($p=0.047$). No significant differences were observed in gender, the follow-up period after RTX, or diabetes mellitus as original disease for ESRD between patients with and

without frequent micturition. The multivariate analysis identified an older age at RTX as the only risk factor for frequent micturition after RTX, and the OR for frequent micturition after RTX was 1.05 for every 1 year increase in age at RTX (95% CI: 1.008-1.102, $p=0.018$). On the other hand, the incidence of frequent micturition after RTX was lower in patients with diabetes mellitus than in patients without diabetes mellitus (OR: 0.248, 95%CI: 0.047-0.984, $p=0.047$) (Table 2).

Polyuria

The 24-hr bladder diaries showed that urine volume for 24 hrs varied from 1320 mL to 5130 mL (median: 2355 mL). In the present study, 44 out of 82 patients (54%) developed polyuria after RTX (16 males and 28 females). The univariate analysis revealed urine volume per weight for 24 hrs was higher in females than in males ($p=0.001$). Other factors, such as age at RTX, the period of pre-transplant dialysis, the follow-up period after RTX, or diabetes mellitus, did not affect the incidence of polyuria. The multivariate analysis also showed that being female was the only risk factor for polyuria, and the OR for polyuria after RTX was 4.61-fold higher in females than in males (95% CI: 1.789-12.619, $p=0.001$) (Table 3).

Nocturia

The 24-hr bladder diaries led to the identification of nocturia in 30 out of 82 patients (37%, 14 males and 16 females). The univariate analysis revealed that the incidence of nocturia was higher in patients who underwent RTX at an older age ($p=0.001$) and received pre-transplant dialysis for a longer period ($p=0.008$). No significant differences were observed

Table 2. Risk factors for frequent micturition.

	Univariate						Multivariate			
	Frequent micturition (+)			Frequent micturition (-)			p-value	OR	95% CI	p-value
	Mean	50 th	25 th –75 th	Mean	50 th	25 th –75 th				
Age at RTX (y/o)	50.0	51.6	41.5–57.2	41.7	43.4	33.4–53.4	0.010	1.051	1.008–1.102	0.018
Pre-transplant dialysis (years)	9.1	5.0	1.1–17.2	5.4	2.5	0.4–7.6	0.047	1.030	0.972–1.096	0.323
Follow-up period after RTX (months)	46.0	36.1	12.7–53.1	57.7	40.6	19.4–86.1	0.290	0.793	0.085–6.586	0.793
Gender (Female/Male)		15/14			23/30		0.772	1.008	0.376–2.731	0.988
Diabetes mellitus (%)		9.7			23.5		0.116	0.248	0.047–0.984	0.047

OR – odds ratio; CI – confidence interval.

Table 3. Risk factors for polyuria.

	Univariate						Multivariate			
	Polyuria (+)			Polyuria (-)			p-value	OR	95% CI	p-value
	Mean	50 th	25 th –75 th	Mean	50 th	25 th –75 th				
Age at RTX (y/o)	45.7	47.7	35.2–56.3	43.6	45.3	33.4–53.5	0.513	1.000	0.960–1.040	0.975
Pre-transplant dialysis (years)	7.3	4.0	1.1–10.5	6.2	3.8	0–10.0	0.549	1.001	0.948–1.073	0.808
Follow-up period after RTX (months)	44.9	33.3	13.5–52.5	62.9	45.8	18.2–121.9	0.091	0.991	0.979–1.003	0.147
Gender (Female/Male)		28/16			10/28		0.001	4.607	1.789–12.619	0.001
Diabetes mellitus (%)		15.9			21.0		0.548	0.688	0.188–2.500	0.567

OR – odds ratio; CI – confidence interval.

in other factors between patients with and without nocturia. The multivariate analysis showed that an older age at RTX was the only risk factor for nocturia, and the OR of nocturia after RTX was 1.08 for every 1 year increase in age at RTX (95% CI: 1.030–1.142, $p=0.001$) (Table 4).

Nocturnal polyuria

The 24-hr bladder diaries showed that nocturnal urine volume varied between 200mL and 1900mL (median: 745mL) while NP_i varied between 0.12 and 0.57 (median: 0.35). In the

present study, 46 out of 82 patients (56%) developed nocturnal polyuria after RTX (24 males and 22 females). The univariate analysis showed that the incidence of nocturnal polyuria was higher in RTX patients who underwent RTX at an older age ($p=0.0119$), received pre-transplant dialysis for a longer duration ($p=0.042$), and had diabetic nephropathy ($p=0.008$). No significant differences were observed in gender or the follow-up period after RTX between patients with and without nocturnal polyuria. The multivariate analysis showed that diabetes mellitus was the only risk factor for nocturnal polyuria, and the risk of nocturnal polyuria after RTX was 7.04-fold

Table 4. Risk factors for nocturia.

	Univariate						p-value	OR	Multivariate	
	Nocturia (+)			Nocturia (-)					95% CI	p-value
	Mean	50 th	25 th –75 th	Mean	50 th	25 th –75 th				
Age at RTX (y/o)	52.3	51.8	47.0–61.0	40.5	40.6	32.0–53.2	0.001	1.080	1.030–1.142	0.001
Pre-transplant dialysis (years)	10.0	5.0	1.2–16.9	5.0	2.3	0–6.8	0.008	1.055	0.948–1.127	0.085
Follow-up period after RTX (months)	43.3	30.6	12.9–55.1	59.0	40.0	19.2–83.5	0.157	1.001	0.987–1.015	0.842
Gender (Female/Male)		16/14			22/30		0.335	1.675	0.595–4.857	0.329
Diabetes mellitus (%)		16.7			19.2		0.772	0.7023	0.168–2.701	0.610

OR – odds ratio; CI – confidence interval.

Table 5. Risk factors for nocturnal polyuria.

	Univariate						p-value	OR	Multivariate	
	Nocturnal polyuria (+)			Nocturnal polyuria (-)					95% CI	p-value
	Mean	50 th	25 th –75 th	Mean	50 th	25 th –75 th				
Age at RTX (y/o)	48.3	47.8	39.0–56.3	40.6	40.6	30.6–53.5	0.012	1.027	0.974–1.072	0.188
Pre-transplant dialysis (years)	8.4	5.0	1.0–13.9	4.7	2.4	0–5.4	0.042	1.062	0.999–1.140	0.055
Follow-up period after RTX (months)	45.2	24.2	12.9–55.1	63.6	31.4	31.5–83.9	0.082	0.791	0.099–5.918	0.820
Gender (Female/Male)		22/24			16/20		0.761	1.308	0.488–3.564	0.593
Diabetes mellitus (%)		28.3			5.6		0.008	7.040	1.595–50.569	0.008

OR – odds ratio; CI – confidence interval.

higher in patients with diabetes than in patients without diabetes (95%CI: 1.595-50.569, p=0.008) (Table 5).

Discussion

LUT function and micturition behavior were assessed using UFM, PVR, and 24-h bladder diaries in the present study. Voiding dysfunction as assessed by UFM and PVR was detected in 24 patients (27%). Frequent micturition, polyuria, nocturia, and nocturnal polyuria were identified in 35%, 54%, 37%,

and 56% of patients who successfully underwent RTX, respectively. Diabetes mellitus was identified as a risk factor for both voiding dysfunction and nocturnal polyuria, which indicated that autonomic disorders associated with diabetes mellitus may cause voiding dysfunction and nocturnal polyuria. Older age at RTX was a risk factor for both frequent micturition and nocturia, which may related to decreased bladder volume with aging. Furthermore, being female was a risk factor for polyuria, which suggests that fluid intake in relation to body weight was higher in females. Thus, LUT dysfunction and LUT symptoms were not uncommon in patients who successfully underwent

RTX, and LUT dysfunction and LUT symptoms need to be considered patients with risk factors even after successful RTX.

Most patients require long-term renal replacement therapies in Japan, and the longer duration of dialysis may affect LUT function due to the development of oliguria or anuria in patients with ESRD. Previous studies reported decreases in bladder capacity and bladder compliance, detrusor overactivity, and voiding dysfunction in patients who received dialysis for a longer period [4,5]. However, most of these abnormalities in urodynamic parameters subside after RTX with improvement in urine output by the renal graft [6,18]. However, some patients may have persistent LUT dysfunction or LUT symptoms even after successful RTX. Zermann et al. reported that frequent micturition and nocturia were the main LUT symptoms in patients who successfully underwent RTX, and have been attributed to a high fluid intake and long-term defunctionalized urinary bladder during renal replacement therapy [19]. Dion et al. reported that low urine output before RTX was predictive of LUT symptoms, which were not uncommon after RTX [20]. Voiding dysfunction has also been frequently observed in patients who underwent RTX [7–9]. Thus, screening for LUT symptoms and LUT dysfunction is important, even in patients who successfully underwent RTX, because they may induce urinary tract infections and vesicoureteral reflux and their related complications.

Predictive factors have not yet been elucidated for LUT dysfunction or LUT symptoms after RTX. In the present study, we identified diabetes mellitus as a risk factor for both voiding dysfunction and nocturnal polyuria, older age at RTX as a risk factor for both frequent micturition and nocturia, and being female as a risk factor for polyuria. Diabetes mellitus may cause autonomic disorders and nephropathy. The autonomic disorders associated with diabetes mellitus have been implicated in the development of LUT dysfunction in some diabetic patients [21]. Nocturnal polyuria is involved in many factors, e.g., third-space fluid sequestration, loss of the circadian control of urine output, obstructive sleep apnea, and renal tubular dysfunction [22]. Since third-space fluid sequestration may be caused by autonomic disorders, particularly diabetic neuropathy, diabetes mellitus was involved in the development of nocturnal polyuria in the present study. A longer duration of pre-transplant dialysis also appeared to be important (95%CI: 0.999–1.140, $p=0.055$), and further studies are needed to confirm this. Regarding nocturia and frequent micturition, nocturia without nocturnal polyuria may arise from LUT dysfunction [22], which may involve the same pathology as frequent micturition. Frequent micturition and nocturia are common in older people [23], and may be related to a decrease in functional bladder capacity with age. In the present study, multivariate analysis revealed that the incidence of frequent micturition and nocturia increased with older age at RTX, whereas univariate

analysis showed that longer duration of pre-transplant dialysis also played a role in the development of frequent micturition and nocturia. A decrease in functional capacity after RTX may be mainly caused by aging and not a disused bladder during dialysis. In the present study, functional bladder capacity from the 24-h bladder diaries was negatively correlated with age at RTX ($r=0.231$, $p=0.036$). On the other hand, only the multivariate analysis, and not the univariate analysis, showed that the incidence of frequent micturition after RTX decreased in patients with diabetes mellitus. We speculated that this result was involved in some potential confounding factors, and further studies are needed to clarify this. Being female was a risk factor for polyuria, which suggests that fluid intake in relation to body weight was higher in females and may have been a consequence of patients who underwent RTX being instructed to drink ample amounts of fluid.

LUT dysfunction and LUT symptoms generally affect QOL, and attempts to diagnose and treat these have typically improved QOL [23]. A previous study reported that LUT dysfunction and LUT symptoms did not significantly affect the QOL of patients who underwent RTX [19], except for nocturia and nocturnal polyuria [9]. However, these findings are controversial because patients who underwent RTX do not need renal replacement therapy and may perceive changes in LUT symptoms as positive. Since LUT dysfunction and LUT symptoms are not uncommon after RTX, they need to be examined in more detail using non-invasive methods, even in patients who successfully underwent RTX. LUT dysfunction and LUT symptoms may increase susceptibility to urinary tract infections and vesicoureteral reflux, which affects renal graft function and mortality in patients with RTX [24,25]. We herein identified the risk factors for LUT dysfunction and LUT symptoms following successful RTX; therefore, appropriate management and treatments is needed for RTX patients with these risk factors. In fact, the previous reports revealed that pharmacological treatments effectively relieve LUT symptoms and are safe for renal graft function. These treatments can improve the QOL of patients with RTX [26,27].

As a limitation of the present study, first, we investigated LUT dysfunction and LUT symptoms in a cross-sectional, but not longitudinal manner. LUT dysfunction and LUT symptoms may change over time after RTX. Second, we did not evaluate LUT symptoms using specific questionnaires. Furthermore, we did not sufficiently evaluate the QOL of patients, which may be affected by LUT dysfunction and LUT symptoms. We should have used established questionnaires regarding LUT symptoms and the QOL of patients. Third, we did not evaluate the significance of pharmacological treatments for LUT dysfunction and LUT symptoms in patients with RTX, which is a very important issue. Fourth, we did not perform urodynamic studies except UFM and PVR in patients who complained of severe

LUT symptoms. In addition to UFM and PVR, other urodynamic studies may be necessary to assess LUT function in detail in patients who complain of severe or persistent LUT symptoms. Therefore, further studies are warranted.

Conclusions

This assessment of voiding dysfunction, frequent micturition, polyuria, nocturia, and nocturnal polyuria in patients who successfully underwent RTX revealed that LUT dysfunction and

LUT symptoms were not uncommon in these patients. LUT dysfunction and LUT symptoms need to be considered in patients with risk factors such as diabetes mellitus, older age at RTX, and being female, even after successful RTX.

Conflicts of interest

None of the contributing authors have any conflicts of interest, including specific financial interests or relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

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