

## The Effects of Diuresis, Duration of Dialysis and Age on Lower Urinary Tract Function in Urologically Healthy Male Patients on the Waiting List for Kidney Transplant

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**Purpose:** This work investigated the effects of diuresis, duration of dialysis and age on lower urinary tract function in urologically healthy males on the waiting list for kidney transplant.

**Materials and methods:** The study included all men who had kidney transplants at our centre between January 2009 and December 2014 who had normal urological findings prior to inclusion on the list. Diuresis, the duration of haemodialysis, age, and parameters of function of the lower urinary tract as determined by filling and voiding cystometry were evaluated.

**Results:** The study included 127 men (median age, 59 years; median diuresis, 250 mL; median duration of dialysis, 469.5 days). We found that greater diuresis was accompanied by significantly higher FDV, FDV/Cmax, NDV, Cmax and compliance and by significantly lower Pdet.max, PdetQmax and BOOI. Longer duration of dialysis was accompanied by significantly lower FDV, NDV and Cmax, compliance and Qmax.p and with significantly higher Pdet.max, PdetQmax and BOOI. Older age was associated with significantly higher Pdet.max and with significantly lower compliance. Worsening of the basic parameters of the storage function of the lower urinary tract occurred when diuresis decreased to 500–750 mL, when the duration of dialysis was one year and when patients were older than 54 years.

**Conclusion:** In healthy male patients on the waiting list for kidney transplant, there were connections between the occurrence of dysfunctions of the lower urinary tract and diuresis, duration of dialysis and age. Patients should be monitored for dysfunctions of the lower urinary tract before and after transplantation.

**Key words:** age; diuresis; dialysis; kidney transplant; lower urinary tract dysfunction; male; waiting list.

### INTRODUCTION

In patients who are on the waiting list for kidney transplants, changes caused by deterioration of renal function and degenerative processes lead to worsening of the functions of the lower urinary tract (LUT)<sup>(1)</sup>. However, correct function of the LUT is essential for the patient and for graft function following transplantation<sup>(2)</sup>. Although several studies have evaluated the functions of the LUT in patients prior to and after transplantation, the exact relationships between diuresis, duration of haemodialysis and patient age and the occurrence of dysfunctions of the LUT are not yet known. This has not been clarified even in male patients in whom dysfunctions of the LUT could cause an especially serious danger for the graft.

This work investigated the connections between diuresis, duration of dialysis, and age on lower urinary tract function in urologically healthy males who were on the waiting list for kidney transplant. A second objective was to determine the diuresis values, duration of dial-

ysis and age at which the individual parameters of the function of the LUT substantially deteriorated, if indeed they did so. The bigger goal is the identification of male patients without urological diseases and symptoms who are most at risk of developing LUT disorders.

### MATERIALS AND METHODS

The analysis included all men who underwent kidney transplants between January 2009 and December 2014 at our centre who were sent for urological examination and exhibited normal urological findings, except for possible reduced diuresis, before being put on the waiting list for a kidney transplant.

The following men were excluded from the study:

- those whose case histories contained information about surgery of the LUT
- those who at the present time or in the past (for patients with diuresis less than 500 mL) demonstrated medium or serious voiding difficulties based on the questionnaire of the International Prostate Symptom

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**Table 1.** Results of descriptive data for the storage and voiding functions of the lower urinary tract.

Parameters	Median	Lower Quartile	Upper Quartile	Minimum	Maximum
FDV (mL)	89	56	137	5	291
FDV/C max (%)	42	29	58	3	427
NDV (mL)	138	98	213	26	213
NDV/C max (%)	71	55	85	16	713
C max (mL)	211	144	341	22	914
Compliance	14,1	4,4	32,5	0,2	320
Pdet.max (cm H <sub>2</sub> O)	35	17	65	2	221
Qmax.p (mL/s)	15,4	11,2	17,7	9,6	25,2
PVR (mL)	11	0	80	0	910
PdetQmax (cm H <sub>2</sub> O)	52	35	72	12	163
BOOI	37	15	60	6	155
BCI	92	76	113	36	183

Score (i.e. IPSS > 7 on a scale of 0 – 35)

- those who had urological diseases that had potential effects on the LUT

- those for whom uroflowmetry showed a maximal flow rate (Qmax) less than < 15 mL/s (examined only for patients with diuresis greater than 500 mL); the minimum voiding volume in the examination was > 150 mL

- those on pharmacotherapy for LUT symptoms

- those who suffered from neurological diseases or other diseases that might impact LUT function

The following were evaluated for all men:

1. diuresis (mL), which was determined as the average value from a 7-day voiding diary

2. the duration of haemodialysis (days)

3. age (years)

4. the parameters of function of the LUT as evaluated by urodynamic examination performed according to the Good Urodynamic Practice recommendations:

a. storage function parameters as determined by filling cystometry

i. first desire to void (FDV) (mL)

ii. first desire to void/maximal capacity (FDV/Cmax) (normal value > 50% Cmax)

iii. normal desire to void (NDV) (mL)

iv. normal desire to void (NDVCmax) (normal value > 75% Cmax)

v. maximal cystometric capacity (Cmax) (normal value > 350 mL)

vi. detrusor compliance (normal value > 30)

vii. maximal detrusor pressure (Pdet.max) (cm H<sub>2</sub>O)

viii. the presence of uninhibited detrusor contractions

b. voiding parameters as determined using voiding cystometry

i. maximal flow rate (mL/s)

ii. post-voiding residual as measured by ultrasound (mL)

iii. detrusor pressure at maximal flow rate (PdetQmax) (cm H<sub>2</sub>O)

iv. Bladder Outlet Obstruction Index (BOOI = PdetQmax – 2 × Qmax) (normal value < 40)

v. Bladder Contractility Index (BCI = PdetQmax + 5 × Qmax) (normal value > 100)

### Statistical analysis

The following data were evaluated statistically:

- descriptive patient data that were related to diuresis, age and individual urodynamic parameters

- the correlation between diuresis and urodynamic parameters

- the correlation between the duration of dialysis and urodynamic parameters

- and the correlation between age and urodynamic parameters for parameters for which the borderline between normal and pathological values is clearly defined according to the International Continence Society.

Study outcomes:

The area under the curve (AUC = area under ROC curve (receiver operating characteristic curve) is signifying excellent, good, and worthless tests. The accuracy of the test depends on how well the test separates the group being tested into those with and without the disease in question. Accuracy is measured by the area under the ROC curve. An area of 1 represents a perfect test; an area of .5 represents a worthless test. A rough guide for classifying the accuracy of a diagnostic test is the traditional academic point system:

• .90-1 = excellent (A)

• .80-.90 = good (B)

• .70-.80 = fair (C)

• .60-.70 = poor (D)

• .50-.60 = fail (F)

) and confidence intervals (confidence interval (CI) is a type of interval estimate that is computed from the observed data, confidence level is the frequency of possible confidence intervals that contain the true value of their corresponding parameter) were evaluated for diuresis, duration of dialysis and age. When the lower confidence interval for these parameters was less than 0.5, the cut-off values were determined, since these parameters showed the greatest specificity and sensitivity in distinguishing between normal and pathological values for the given parameter. The odds ratios were determined for these parameters.

The basic statistical information, such as averages, standard deviations, scatter, medians, interquartile ranges, and minimum and maximum values were determined for the measured parameters in the entire data set. Selected statistical data were also graphed using Box & Whisker plot diagrams. Spearman's correlation coefficient was used to determine the relationship of the investigated parameters with the non-Gaussian distribution of these variables. Variation in the parameters over time was tested using both the paired Wilcoxon Test and also the Friedman ANOVA test. These results were then controlled using parametric scatter analysis

**Table 2.** The relationships between diuresis and the urodynamic parameters

Parameters	P
FDV (mL)	< .0001
FDV/C max (%)	.08
NDV (mL)	< .0001
NDV/C max (%)	.0098
C max (mL)	< .0001
Compliance	< .0001
Pdet.max (cm H <sub>2</sub> O)	.0005
Qmax.p (mL/s)	.35
PVR (mL)	.33
PdetQmax (cm H <sub>2</sub> O)	.03
BOOI	.04
BCI	.16

**Table 3.** The relationships between the duration of dialysis and the urodynamic parameters

Parameters	P
FDV (mL)	.001
FDV/C max (%)	.2
NDV (mL)	.0001
NDV/C max (%)	.15
C max (mL)	.0001
Compliance	.0002
Pdet.max (cm H <sub>2</sub> O)	.0004
Qmax.p (mL/s)	.0058
PVR (mL)	.97
PdetQmax (cm H <sub>2</sub> O)	.0357
BOOI	.0161
BCI	.64

(repeated design). The differences in the investigated parameters between the monitored groups were tested using the double-selection Wilcoxon test or the Kruskal-Wallis Test.

Differences in the categorical variables between the tested groups were determined using the Chi-squared test or Fisher's exact test. The statistical significance was determined using the limit of  $\alpha = 0.05$ . The statistical analyses were performed using SAS software (SAS Institute Inc., Cary, NC, USA) and STATISTICA software (StatSoft, Inc., Tulsa, OK, USA). The graphs were drawn using SW Statistica (StatSoft, Inc.)

## RESULTS

The study cohort included 127 male patients who had complete information for all of the considered parameters. The median age was 59 years (lower quartile 50 – upper quartile 65). The cause of chronic kidney disease was glomerulonephritis for 21 patients, hypertension nephropathy for 20, diabetic nephropathy for 19, tubulointerstitial nephritis for 19, IgA nephropathy for

12, renal polycystosis for 12, focal segmental glomerulosclerosis for 4 and other or unclear causes for 21. Median diuresis was 250 mL (lower quartile 100–upper quartile 1,000). The median duration of dialysis was 469.5 days (lower quartile 248–upper quartile 1,004). Descriptive data for parameters determined by urodynamic examination

Descriptive data for the storage and voiding functions of the LUT are shown in **Table 1**. Uninhibited detrusor contraction was present in 51 patients (40%).

Correlations between diuresis and urodynamic parameters

**Table 2** shows the relationships between diuresis and the urodynamic parameters related to LUT functions. Evaluation of the storage phase showed that increasing diuresis was accompanied by significant increases in FDV volume, FDV/Cmax, NDV and Cmax and with significantly greater compliance and significantly lower Pdet.max. Evaluation of the voiding phase indicated that the greater the diuresis, the lower the PdetQmax and BOOI values.

Correlations between the duration of dialysis and urodynamic parameters

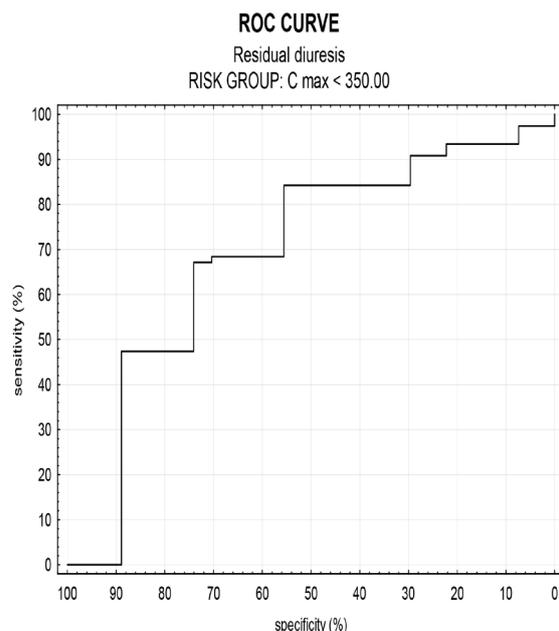
**Table 3** shows the relationships between the duration of dialysis and the urodynamic parameters of the LUT function. Evaluation of the storage phase showed that increasing duration of dialysis was accompanied by significantly lower volumes for FDV, NDV and Cmax, with significantly lower compliance and with significantly greater Pdet.max. Evaluation of voiding showed that greater duration of dialysis was associated with significantly lower Qmax.p and with significantly higher PdetQmax and BOOI values.

Correlations between age and urodynamic parameters

**Table 4** shows the relationships between age and the urodynamic parameters of the LUT function. Evaluation of the storage function showed that increasing patient age was accompanied by significantly higher Pdet.max and with significantly lower compliance. Evaluation of the voiding function showed no significant dependence between age and the parameters of the voiding function of the LUT.

Evaluating the specificity, sensitivity, ROC curve, area under the curve (AUC) and the odds ratio values

For diuresis, the confidence intervals were greater than 0.5 for Cmax and compliance. The cut-off value for distinguishing between normal and pathological values of Cmax was 750 mL, with a sensitivity of 84.2%, a

**Figure 1.** ROC curve for residual diuresis.

**Table 4.** The relationships between age and the urodynamic parameters.

Parameters	P
FDV (mL)	.51
FDV/C max (%)	.18
NDV (mL)	.28
NDV/C max (%)	.16
C max (mL)	.14
Compliance	.0008
Pdet.max (cm H2O)	.0013
Qmax.p (mL/s)	.69
PVR (mL)	.7
PdetQmax (cm H2O)	.73
BOOI	.89
BCI	.63

specificity of 55.6% and an odds ratio of 6.7. At this sensitivity and specificity, patients with diuresis that is less than 750 mL have a 6.7-fold greater risk of having pathological Cmax values than patients with diuresis greater than 750 mL. The cut-off for distinguishing between normal and pathological values of compliance was 500 mL, with a sensitivity of 81.4%, a specificity of 53.3% and an odds ratio of 12.8. At this sensitivity and specificity, patients with diuresis less than 500 mL have a 12.8-fold greater risk of having pathological compliance values than patients with diuresis greater than 500 mL. The results are shown in **Figure 1**.

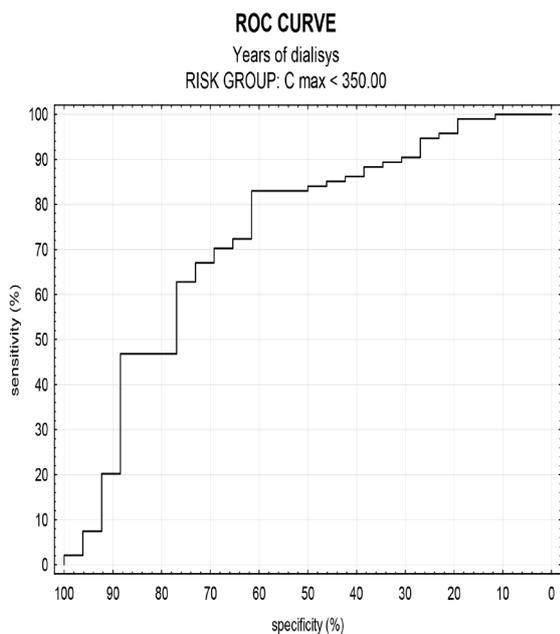
To evaluate the duration of dialysis, the confidence interval was greater than 0.5 for Cmax and BOOI. The cut-off for distinguishing between normal and pathological values of Cmax was 267 days, with a sensitivity of 81.9%, a specificity of 61.5% and an odds ratio of 7.3. At this sensitivity and specificity, patients with duration of dialysis greater than 267 days have a 7.3-fold greater risk of having pathological Cmax values than patients with dialysis duration less than 267 days. The

cut-off for distinguishing between normal and pathological BOOI values was 307 days, with a sensitivity of 75.5%, a specificity of 50.0%, and an odds ratio of 3.1. At this sensitivity and specificity, patients with duration of dialysis greater than 307 days have a 3.1-fold greater risk of having pathological BOOI values than patients with dialysis duration less than 307 days. The results are shown in **Figure 2**.

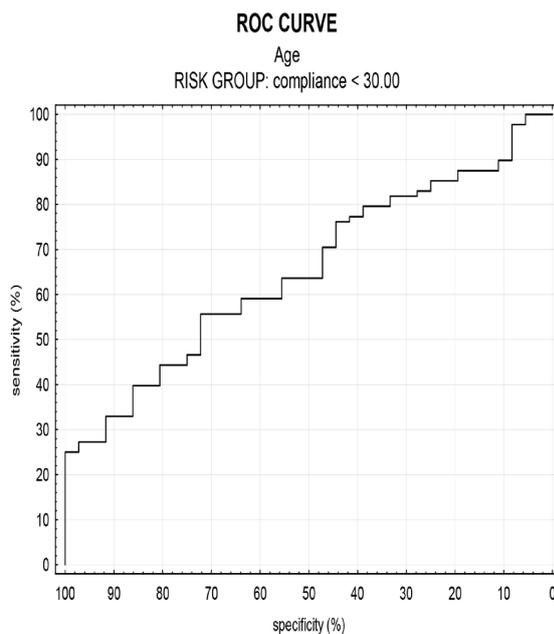
For the age evaluation, the confidence interval was greater than 0.5 for compliance. The cut-off for distinguishing between normal and pathological compliance values was 54 years, with a sensitivity of 76.1%, a specificity of 41.7%, and an odds ratio of 5.2. At this sensitivity and specificity, patients older than 54 years have a 5.2-fold greater risk of pathological compliance values than patients younger than 54 years. The results are shown in **Figure 3**.

### DISCUSSION

The underlying mechanism of LUT dysfunctions in CKD patients have not been completely elucidated yet, however several etiological and risk factors have been discussed. Changes in the diuresis volume, different compound concentration in urine, chronic inflammation, chronic ischaemia, lack of proliferative and protective factors in urine and different reflex between urinary bladder and lower urinary tract outlet might contribute to these effects<sup>(2)</sup>. Dysfunction of the LUT that causes long-term high intravesical pressure and significant post-voiding residual volume can cause vesicoureteral reflux into transplanted kidney and can pose a risk to graft function. Consequently, it is advantageous to diagnose these disorders as soon as possible, ideally prior to transplantation<sup>(2)</sup>. Notably, patients with serious LUT dysfunction, such as reduced maximal detrusor capacity less than 100 mL, have significantly lower graft survival compared to other patients, independent of the patient's immunological status<sup>(1)</sup>. The number of patients in the dialysis program is constantly increasing, primar-



**Figure 2.** ROC curve for duration of dialysis.



**Figure 3.** ROC curve for age.

ily because of the greater number of older patients, both men and women<sup>(3,4)</sup>. Compared to women, men have a greater risk of the occurrence of serious LUT obstruction and other dysfunctions<sup>(5,6)</sup>.

Experimental and clinical studies have repeatedly demonstrated that prolonged reduced diuresis leads to LUT storage and voiding dysfunctions. When this happens, repeated urinary infections or other pathological changes in the bladder can lead to structural rebuilding of all of the layers of the LUT and to serious morphological and functional disorders, such as a contracted bladder with minimal capacity<sup>(1)</sup>. As a result of reduced diuresis, the patient and also the examining physician frequently do not notice any pathological changes in detrusor capacity and compliance in cases of progressing end stage kidney disease (ESKD). Following successful kidney transplant, LUT dysfunction and its symptoms can be fully manifested along with all of their negative consequences<sup>(7)</sup>. Some authors have found that anuria and oliguria are the most important risk factors for urological complications following kidney transplantation<sup>(8)</sup>. Zermann et al. reported that 38% of patients (both men and women) with reduced diuresis who were on the waiting list for kidney transplantation were at risk of low bladder compliance, and 48% were at risk of detrusor hyperactivity<sup>(9)</sup>. Tsunoyama et al. found that patients with ESKD and reduced diuresis who were on the waiting list for kidney transplantation suffered from reduced FS, NS and SS compared to the normal population, while 27% showed detrusor hyperactivity<sup>(10)</sup>. Maximal detrusor capacity less than 100 ml was found for 14% and 34% of patients with reduced diuresis in the studies by Song et al. and Chen et al., respectively<sup>(11,12)</sup>. The voiding function can also be disrupted in patients with reduced diuresis who are on the waiting list for kidney transplantation. In the set of patients studied by Habib Kashi et al., the greatest worsening of LUT function was found for parameters related to both storage and voiding functions<sup>(1)</sup>. Chen et al. found LUT obstruction in 51% of patients<sup>(12)</sup>. This observation is in accordance with our results, as almost all of the storage function parameters and some of the voiding function parameters showed a statistically significant dependence on diuresis volume. We were able to determine a cut-off value for the diuresis volume at which the probability of storage function dysfunction significantly increased. We found that when diuresis decreased to less than 500–750 mL, there was a 6- to 12-fold greater probability of reduced maximal detrusor capacity and compliance.

Previous studies showed that morphological and functional changes in the LUT are dependent on the duration of reduced diuresis<sup>(10)</sup>. The maximal detrusor capacity and compliance also increase with the duration of oliguria or anuria<sup>(12-14)</sup>. According to Martin et al., the capacity of the detrusor decreases to 300 mL after 5 years and to 150 mL after 15 years in patients with ESKD and reduced diuresis<sup>(13)</sup>. According to Dion et al., reduced detrusor compliance after 1 and 10 years of dialysis occurs in 31% and 77% of patients, respectively<sup>(14)</sup>.

These conclusions are in accordance with our results in that we also found that the duration of dialysis and the pathological values of most of the parameters related to storage function showed significant associations with parameters related to voiding function. We found that the risk of the development of reduced bladder ca-

capacity was significant—up to 7-fold—when dialysis lasted longer than 1 year.

Aging occurs at many levels and includes changes at the molecular, cellular and organ levels as well as in cerebral function and in the organism as a whole. The changes associated with aging occur at different times in different individuals; consequently, individuals differ more from each other when they are older versus when they are younger. LUT aging is typically characterized by pathological changes like detrusor hyperactivity, reduced detrusor contractility and the presence of subvesical obstruction. The very complicated changes associated with LUT aging are frequently complicated by concomitant diseases that significantly affect LUT, including vascular, degenerative, metabolic and neurological diseases<sup>(16)</sup>. A number of studies have evaluated the dependence of storage and voiding dysfunction on age. One study that evaluated asymptomatic men and women found that cystometric capacity, maximal detrusor pressure and maximal voiding flow decrease substantially in both sexes with aging<sup>(17)</sup>. Balslev Jorgensen et al. investigated uroflowmetry parameters and found that all of the parameters decrease with age, even in asymptomatic individuals<sup>(18)</sup>. Madersbacher et al. evaluated differences between the sexes by monitoring LUT dysfunction during aging in a symptomatic population. They found a substantial increase in post-voiding residual volume and a decrease in Qmax and detrusor capacity in both sexes during aging<sup>(19)</sup>. Some studies investigated reduced contractility and found a dependence on age<sup>(20)</sup>, while others found no age dependence<sup>(19,21)</sup>.

Our results confirmed those of studies that demonstrated the dependence of storage function parameters on age. We found that detrusor compliance was significantly dependent on patient age and that the risk of deterioration of detrusor compliance increased approximately 5-fold for men who were over 54 years of age. Some studies that evaluated the occurrence of some types of dysfunction and their dependence on age found differences between men and women. The study by Madersbacher et al. found an increase in detrusor hyperactivity that was only dependent on age in men. Among men aged 40 to 60 years, 23% had detrusor hyperactivity, as did 47% of the men who were over 80 years of age<sup>(19)</sup>. Studies of voiding function have repeatedly reported that Qmax is reduced in men over 50 years of age<sup>(22,23)</sup>. Some studies have reported a decrease in Qmax of 1–2 ml/s/5 years<sup>(24-26)</sup>.

Our study only included asymptomatic men who were on the waiting list for kidney transplantation; thus, some of the results may be specific to men. Another potential limitation was our failure to distinguish patients based on the causes of ESKD. However, it was not possible to evaluate these parameters because of the statistically insufficient number of patients.

## CONCLUSIONS

Our results demonstrated that in healthy male patients who were on the waiting list for kidney transplants, there were connections between the occurrence of dysfunctions of the LUT and diuresis, duration of dialysis and age. The basic parameters of the storage function of the LUT worsened when diuresis decreased to 500 – 750 mL, when dialysis was performed for approximately one year and when patients were older than 54 years. Particular care should be taken when examining these

patients, and they should be monitored for dysfunction of the LUT before and after transplantation.

### CONFLICT OF INTEREST

None declared.

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