Lower urinary tract dysfunction after renal transplantation in children and adults

Voor niertransplantatiepatiënten

The studies presented in this thesis have been performed at the Radboud University Nijmegen Medical Centre. Part 1 of this thesis was conducted in cooperation with the Departments of Urology, Department of Nephrology, Centre for Quality of Care Research, Nursing Science Section, Epidemiology and Biostatistics and Radboud University Nijmegen: Department of Economics.
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Contents

Chapter 1

General introduction

This thesis

The research presented in this thesis started with a question asked by a staff nurse working at the department of nephrology. She wondered how bladder function develops over time after renal transplantation. Some of her recently transplanted patients suffered from frequency and she did not know what information and advice to give them. A literature search made clear that hardly any information on the prevalence and nature, of lower urinary tract dysfunction after renal transplantation was available. Especially, information was lacking on how bladder function would develop over time. This thesis explores the function of the lower urinary tract after renal transplantation both in children and adults.

Renal transplantation: the treatment of choice for patients with renal failure

There are three types of renal replacement therapy for patients with failing kidneys: hemodialysis, peritoneal dialysis, and renal transplantation. All three forms of therapy are, however, incomplete solutions, providing an extension of life, but restoring neither full life expectancy nor complete quality of life.[1] There is no doubt that the quality of life of a transplant patient with minimal complications is much better than that of even the most well-adjusted dialysis patient.[1] Therefore, for patients with renal failure, transplantation remains the treatment of choice and is commonly performed nowadays.[2] Unfortunately, the demand for donor kidneys is larger than the supply. In The Netherlands, the average waiting period for a donor kidney is about 4 years.[3] Therefore, these patients usually require hemodialysis or peritoneal dialysis.

The last few decades, kidney transplantation has become more safe and successful. Graft survival rates at 10 years are between 40% and 80%, depending on factors influencing graft outcome like HLA matching, donor age, race, original disease, early renal function, and early rejection.[4] As graft survival becomes longer, research into factors that may involve a risk for graft survival on the long term becomes more and more important. This thesis aims to contribute to this field by providing insight into the prevalence and nature of bladder dysfunction after renal transplantation.

Clinical setting: renal transplantation in the Netherlands

In the Netherlands, about 40.000 people suffer from kidney disease, of which around 11.000 depend on renal replacement therapy; either renal transplantation or dialysis.[3] Presently, 5000 people depend on dialysis, which they receive in one of the 60 Dutch dialysis centres.[3] In the last decade, the number of patients who depend on dialysis has increased with 3.5% per year. Every year, 20% of the patients who undergo dialysis die. Anno 2006, about one thousand Dutch patients are waiting for a renal transplantation.[3] Mean waiting time for transplantation with a kidney from a deceased donor is about 4.5

years. In 1998, when the Act on Organ Donation was introduced, the waiting time for a renal graft was 2.5 years. Due to this long waiting time for a deceased donor kidney, the number of transplantations with kidneys from living donors has increased during recent years.

Since 1966, when the first renal transplantation was performed in the Netherlands, over 12.000 people underwent a renal transplantation. In 2005, 492 people received a renal transplant in one of the 7 renal transplant centres.[3] Only 4 renal transplant centers perform transplantations in children. Each year about 25 children receive a renal transplant. The Radboud University Nijmegen Medical Centre (UMCN) is one of the renal transplant centers that performs transplantations in both adults and children. In the UMCN the first transplantation in adults was carried out in 1968. Nine years later, in 1977, the UMCN also started to perform renal transplantations in children. Nowadays, the yearly number of renal transplant recipients at the UMCN is around 120, including about 10 pediatric recipients.

Bladder function before and after transplantation

A normal bladder acts as a low-pressure, good-volume urinary reservoir, that is continent, sterile and empties freely and completely.[5] Table 1 shows the criteria that the bladder should meet after renal transplantation to enable the transplant to function well.

Table 1. Criteria for a normal bladder[4]

Criteria for usable bladder	Adults	Children	Instrument
Bladder capacity	$\geq$ 300 mL $\leq$ 500 mL	(age/2 + 6) x 28.35	Frequency volume chart
Bladder pressure	$\leq$ 40 cm H_2O	$\leq$ 40 cm H_2O	Urodynamic studies
Sterile	Urinary Tract Infection = > 10^5 CFU/mL clean voided midstream specimen		Cultures
Emptying freely	> 18-25 mL/s		Uroflowmetry
Emptying completely	< 40% of total bladder volume at free flow	Post Void Residual < 20 mL	Free flow and transabdominal ultrasonography

Giving the waiting period for a kidney graft, when no living donor is available, patients suffering from end stage renal disease usually have to undergo hemodialysis or peritoneal dialysis for a prolonged period of time. In dialysis patients, the amount of urine produced can still be normal, but over time it often becomes strongly reduced. Therefore, many patients will make little use of the lower urinary tract during the last period preceding transplantation. Results from our own studies show that almost half (between 40% and 50%) of the patients had a urine production $\leq$150 mL/24 hrs and that about one third (between 29% and 39%) had no urine production at the time of transplantation.

The bladder is a hollow muscular organ with reservoir and evacuation functions. It is a well-known fact that, when the detrusor is not used for a longer period this may have

consequences for these functions.[6,7] Therefore, bladders may not meet the criteria for a normal bladder at the time of transplantation. Furthermore, there are a number of patients with end stage renal disease due to underlying urological disease. In our pediatric study group, 30% of the patients had an underlying urological disease. In the adult study group this was around 10%. Consequently, disturbances in bladder function during the first phase after transplantation can be expected.

Because urological follow-up generally is only done in patients with an underlying urological disease, the assumption seems to be that after transplantation the bladder will recover without problems. However, not much research on bladder function after renal transplantation has been done. Furthermore, the evidence that is available does not unequivocally support the assumption that after transplantation the bladder will recover without problems.[6-9] Serrano et al. studied five male renal recipients with a dysfunctional bladder during a longer period (range 15 to 26 years) before transplantation.[6] Bladder rehabilitation was accomplished by bladder cycling through a suprapubic tube or urethral catheter. A progressive increase in bladder capacity was noted in all 5 patients within the first 3 months after transplantation. Based on these results Serrano et al. concluded that bladders can be successfully rehabilitated after 26 years of defunctionalization. Al Khudair and Mansi reported a case of a 17-year old boy, who had been receiving hemodialysis for 9 years.[7] They found the boy's bladder capacity to increase with 240 mL in 3 months (from 80 to 320 mL), as a result of bladder cycling. However, Reinberg et al. stated in a survey on urological aspects related to renal transplantation that resumption of bladder function does not always goes smoothly and they mention complications like incontinence, frequency, vesicoureteral reflux, and hydronephrosis.[8] They also concluded that bladder function, in particular in cases of thick walled bladders due to outlet obstruction in children with urethral valves, would not recover easily.[8] Also Errando et al., who performed bladder cycling in 9 patients with low compliance, found the urodynamic studies to be normalized in only 3 cases.[9] Of the other cases, 2 showed improvement, and 4 patients, with extremely low compliance, remained unchanged.[9] These studies demonstrate that after transplantation bladder function may recover easily in some cases, but that in other cases, full recovery of the bladder function is not automatically achieved. It therefore would be very useful if we could find indicators that can predict which bladder will recover and which one will not.

Unfortunately, this is not yet possible.[10-12] Urological assessment before transplantation is not helpful, because the actual bladder function before transplantation does not provide a reliable indication of the degree to which the bladder will recover after transplantation. This lack of predicting indicators implies that we cannot beforehand identify which individual needs early therapeutic intervention.[10-12] Only after transplantation it can be assessed whether and to what extent normal bladder function has been achieved. However,

assessment of bladder function after transplantation is not routine practice. Currently, urological follow-up after renal transplantation is only done in urological high-risk populations, like patients with an underlying urological disease or patients with recurrent urinary tract infections. No comprehensive study of bladder function in non high-risk renal recipients has been conducted.

The relation between bladder dysfunction and renal graft function

Several studies have indicated that bladder dysfunction after renal transplantation may have a negative effect on the function of the transplanted kidney.[13-15] Parkhouse et al. reported a relation between persistent bladder dysfunction in boys treated for posterior urethral valves (n=114) and poor long-term renal function outcome.[13] Several other studies also showed that boys with posterior urethral valves and a voiding disorder are at risk of renal function deterioration.[12,14,15] Luke et al.,[16] comparing the long-term outcomes of graft survival between children with a dysfunctional lower urinary tract (n=20) and children with a normal lower urinary tract (n=61), found that high pressure in the lower urinary tract negatively affects graft survival. Taken together, the results of these studies indicate that in urological high-risk populations such as children with posterior urethral valves, there are two deciding factors that may cause deterioration of renal graft function: high pressure in the lower urinary tract and post void residual urine due to voiding disorder.

On the effects of bladder dysfunction on renal transplant function in patients with a non-urologic underlying disease much less is known. Some studies addressed the effect of urinary tract infections (UTI) after renal transplantation on transplant deterioration in more extensive populations. However, the clinical relevance of UTI occurring after renal transplantation for transplant functioning is still under debate. Several studies concluded that UTI after renal transplantation was a benign complication[17-19], but other studies found that UTI after renal transplantation in a general population were significantly associated with an increased risk of death.[20,21] As dysfunction of the lower urinary tract is the major cause of urinary tract infections, further research is needed to investigate the prevalence of a dysfunctional lower urinary tract in renal transplant recipients.

Aim of the thesis

The aim of this thesis is to study the function of the lower urinary tract in both children and adult renal transplant patients. The general research questions in this thesis are:

1. What is the prevalence and nature of lower urinary tract symptoms after renal transplantation in adults?
2. What are the causes of frequency and nocturia after renal transplantation in adults?
3. What is the prevalence and nature of LUTS after renal transplantation in children?

4. What are the causes of LUTS after renal transplantation in children?
5. What are the consequences of LUTS for the function of the renal graft?

Outline of the thesis

In the next chapter, the results are presented of a study on the prevalence on lower urinary tract symptoms (LUTS) in adult renal graft recipients during the first year following renal transplantation, and compared with the results from a control group. For this study, data on LUTS were gathered with a written questionnaire.

In chapter 3 we present the results of a follow-up study aimed at determining the changes in LUTS over time after renal transplantation. In the third year following transplantation, we once more approached the patients from the previous study and again determined the occurrence of LUTS. We compared the occurrence of LUTS in the study group at 3 years after transplantation with their own micturition behavior at one year after transplantation and with the control group.

Chapter 4 describes the results of a study on potential causes of frequency and nocturia after renal transplantation. An inventory of symptoms of dysfunction of the lower urinary tract was made not only with the questionnaire used in the earlier studies but also with frequency volume charts, medical records, and urinary cultures. To explore the causes of frequency and nocturia, Structural Equations Modeling (SEM) was used to estimate the effects of multiple potential causes and related factors simultaneously.

In chapter 5 we report about a study on the prevalence of LUTS after transplantation in 30 children, consisting of 9 children (30%) undergoing renal transplantation with an underlying urological disease and 21 children (70%) with an underlying nephrological disease. The focus of the study was the presence of LUTS in children with an underlying nephrological disease. Furthermore we report about the relationship between the demographic and clinical characteristics of these children and the occurrence of LUTS. Data were gathered using a written questionnaire, frequency volume chart, free uroflowmetry, transabdominal ultrasonography, and medical records.

In chapter 6 the results are presented of a study on the relationship between symptoms of dysfunction of the lower urinary tract after transplantation and renal transplant function, in the 21 renal transplant children with an underlying nephrologic disease. For this study the existing data set with information about the children's characteristics and bladder function was enriched with medical record data about the occurrence of lower urinary tract infections after transplantation and with data about renal graft function.

Chapter 7 deals with the general discussion and conclusion. This chapter describes the possible consequences of our findings and gives an overview of research questions to be answered in the future.

References

1. Winearls CG, Mason PD. Chronic renal failure: renal replacement therapy. In: Kidney transplantation, principles and practice. Morris PJ. W.B. Saunders Company, 2001: 32-44.
2. Hamilton D. A history in kidney transplantation. In: Kidney transplantation, principles and practice. Morris PJ. W.B. Saunders Company, 2001: 1-7.
3. www.nierstichting.nl
4. Terasaki PI, Cecka JM, Gjertson DW, Cho Y, Takemoto S, Cohn M. A ten-year prediction for kidney transplant survival. In: Clinical Transplants (Terasaki PI, Cecka JM et al.). Los Angeles: U.C.L.A. Tissue Typing Laboratory, 1993: 105.
5. Rudge CJ. Transplantation in the abnormal bladder. In: Kidney transplantation, principles and practice. Morris PJ. W.B. Saunders Company, 1994: 138-148.
6. Serrano DP, Flechner SM, Modlin CS, et al. Transplantation into the long-term defunctionalized bladder. J Urol 1996; 156: 885–888.
7. Al Khudair WK, Mansi MK. Rehabilitation of longterm defunctionalized bladder for renal transplantation. Transpl Int 1998; 11: 452–454.
8. Reinberg Y, Gonzalez R, Fryd D, et al. The outcome of renal transplantation in children with posterior urethral valves. J Urol 1988; 140: 1491.
9. Errando C, Batista JE, Caparros J, et al. Urodynamic evaluation and management prior to renal transplantation. Eur Urol 2000; 38: 415–418.
10. MacGregor P, Novick AC, Cunningham R, et al. Renal transplantation in end-stage renal disease patients with existing urinary diversion. J Urol 1986; 135(4): 686-8.
11. Dinneen MD, Duffy PG. Posterior urethral valves. Br J Urol 1996; 78: 275.
12. Salomon L, Fontaine E, Guest G, et al. Role of the bladder in delayed failure of kidney transplants in boys with posterior urethral valves. J Urol 2000; 163: 1282–1285.
13. Parkhouse HF, Barratt TM, Dillon MJ, et al. Long-term outcome of boys with posterior urethral valves. Br J Urol 1988; 62: 59–62.
14. Groenewegen AA, Sukhai RN, Nauta J, et al. Results of renal transplantation in boys treated for posterior urethral valves. J Urol 1993; 149: 1517–1520.
15. Ghanem MA, Wolffenbuttel KP, de Vylder A, et al. Long-term bladder dysfunction and renal function in boys with posterior urethral valves based on urodynamic findings. J Urol 2004; 171: 2409–2412.
16. Luke PPW, Herz DB, Bellinger MF, et al. Long term results of pediatric renal transplantation into a dysfunctional lower urinary tract. Transplantation 2003; 76: 1578–1582.
17. Lyerova L, Lacha J, Skibova J, et al. Urinary tract infection in patients with urological complications after renal transplantation with respect to long-term function and allograft survival. Ann Transplant 2001; 6: 19–20.
18. Mueller T, Resinger C, Ruffingshofer D, et al. Urinary tract infections beyond the early post-transplant period in pediatric renal graft recipients. Wien Klin Wochenschr 2003; 115: 385–388.
19. Takai K, Aoki A, Suga A, et al. Urinary tract infections following renal transplantation. Transplant Proc 1998; 30: 3140–3141.
20. Abbot KC, Swanson J, Richter ER, et al. Late urinary tract infection after renal transplantation in the United States. Am J Kidney Dis 2004; 44: 353–362.
21. Chuang P, Parikh CR, Langone A. Urinary tract infections after renal transplantation: a retrospective review at two US transplant centers. Clin Transplant 2005; 19: 230–235.

Part 1:

Lower Urinary Tract Symptoms after renal transplantation in adults

Chapter 2

Lower urinary tract symptoms after renal transplantation

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Abstract

Purpose: We investigated the prevalence and nature of lower urinary tract symptoms after renal transplantation. In addition, we studied how these symptoms affect the quality of life and whether function of the lower urinary tract before transplantation was related to postoperative occurrence of lower urinary tract symptoms.

Materials and Methods: Data were gathered by a written questionnaire. The research group consisted of 63 patients who underwent renal transplantation in 1998 at the University Medical Center St Radboud Nijmegen. The control group consisted of 74 patients with nonurological complaints who visited an outpatient clinic at the same university.

Results: The most important finding was that patients who underwent renal transplantation needed to void more often than controls, both during the day and at night. After renal transplantation, almost 50% of the patients complained of frequency and 62% nocturia. Patients with a transplant had tended to perceive frequency and nocturia less as problems than those in the control group.

Conclusions: No relation was found between the functioning of the lower urinary tract before transplantation, and occurrence of frequency and nocturia after transplantation. The amount of fluid intake at the interview was not related to the occurrence of frequency and nocturia. No abnormalities were found regarding bladder evacuation.

Currently, renal transplantation is a common treatment of patients with end stage renal failure.[1] Unfortunately, the demand for kidney donors is larger than the supply. In The Netherlands the average waiting period for a kidney graft is 2 to 3 years. Therefore, these patients usually require renal replacement therapy and will have to undergo hemodialysis or peritoneal dialysis. In patients with end stage renal failure the amount of urine produced can still be normal but usually it is strongly reduced. Therefore, given the long waiting period, many patients will hardly if at all make use of the lower urinary tract at transplantation. It is a well-known fact that muscles that are not used for a long period tend to atrophy.

Muscle atrophy is characterized by a reduction in muscle volume and strength.[2] The bladder is a hollow muscular organ with reservoir and evacuation functions, and when the it becomes atrophic, this may have consequences for these functions.

After successful transplantation, urine production is restored. During the first days after surgery, the patient will still have an indwelling catheter, which is usually removed on postoperative day 8. The bladder should then begin to function normally again. It was assumed that this back to normal process might cause problems. The assumption was that more lower urinary tract symptoms would develop in patients with bladders that had either not functioned at all or only to a limited extent than those kept functioning normally.

It was also expected that the risk of lower urinary tract symptoms after transplantation would increase with longer periods of bladder dysfunction. In studies on lower urinary tract symptoms fluid intake is a major influential factor. This factor holds particularly for patients who have undergone renal transplantation, as they are advised to consume ample amounts of fluid. In the literature lower urinary tract symptoms after renal transplantation have gained only little attention. Serrano et al studied the effects of a dysfunctional bladder during a longer period (range 15 to 26 years).[3] They state that these patients may retain the ability to recover bladder function but often a bladder with little capacity and bad compliance develops.

Reinberg et al published an analytical survey on urological aspects related to renal transplantation.[4] They stated that resumption of bladder function does not always go smoothly and mentioned such complications as incontinence, frequency, including a voiding frequency of 7 times daily or more often, and hydronephrosis. Bladders that have become particularly thick walled as a result of an obstruction of the bladder outlet or urethra would not recover easily. This statement was based on research concerning bladder function in children with urethral valves.[5,6] However, detailed information on the prevalence and nature of lower urinary tract symptoms after renal transplantation is not available, and our study is meant to fill this gap. We have tried to find answers to the questions: What is the prevalence and nature of lower urinary tract symptoms after renal

transplantation? What is the impact of these symptoms on the quality of life? Is the incidence of lower urinary tract symptoms after transplantation influenced by urine production before transplantation and/or duration of renal replacement therapy? To what extent is the amount of fluid intake associated with lower urinary tract symptoms?

Materials and methods

The incidence and severity of lower urinary tract symptoms were examined in a group of patients who underwent renal transplantation as well as in a control group. In the 2 groups data were collected about lower urinary tract symptoms and the impact on daily life. These data were obtained by a written questionnaire. In addition, we collected some background information on patients in the research group that was obtained from medical records.

The research group consisted of all patients who underwent renal transplantation at University Medical Center St Radboud Nijmegen in 1998. The inclusion criteria were patient age older than 18 years, a good command of the Dutch language, functioning graft and reasonable-to-good general physical health. In 1998, 97 transplantations were performed.

There were 8 patients younger than 18 years, 2 died during the course of 1998, 4 were not masters of the Dutch language, 5 were considered too ill to participate in the study and in 1 the graft was rejected. Exclusion criteria were those patients having a bladder catheter (1) or urinary stoma (1). Ultimately, there remained 75 patients who satisfied the exclusion and inclusion criteria. With permission from the Medical Ethics Committee, we sent the questionnaires, together with a letter of recommendation from the nephrologist to the 75 people in the research group. A total of 63 completed questionnaires were returned, which is a response rate of 84%.

The control group consisted of patients with nononcological complaints who visited the Outpatient Clinic of Otorhinolaryngology during week 13 of 1999. Patients who registered at the reception desk were asked to participate in our research project for the benefit of those who underwent renal transplantation.

The patients who were willing to participate in our study were then asked to complete the questionnaire in the waiting room and hand it in at the reception desk. The control group completed a total of 74 questionnaires. It was assumed that these patients had neither more nor less lower urinary tract symptoms than the average Dutch person and, therefore, could be considered a cross section of the Dutch population. For patient selection for the control group we used the quota sampling method to ensure that composition of the control group matched that of the research group in regard to patient gender and age.[7] This method is important because there tends to be a natural increase in urgency, frequency and nocturia, including 2 or more voids at night, when people get older. There is also a

difference between the complaint patterns of men and women.[8,9] To collect data on symptoms of lower urinary tract dysfunction we used the International Continence Society male[10] and Bristol Female Lower Urinary Tract Symptoms questionnaires.[11] The Bristol questionnaire is based on the International Continence Society questionnaire. These questionnaires were developed to have an idea of the nature and severity of lower urinary tract symptoms and impact on the quality of life. The questionnaires were tested on content, construct and criterion validities, internal consistency and test-retest reliability.[10–12] Questions that are the same on the 2 questionnaires were used in this study. Questions on sexuality were omitted because it was not a research object and such questions might have a negative effect on the response rate. The items on the questionnaire can be divided into 2 categories, including symptoms of an insufficient bladder reservoir and evacuation functions. In regard to the bladder reservoir function we assessed the symptoms "frequency"— voiding 7 times or more per 24 hours, "nocturia"—twice or more nightly, "urgency"—a sudden, strong uncontrollable urge to void, "pain in the bladder" and "loss of urine." With bladder evacuation we measured the symptoms "hesitancy"— poor initial urinary flow, "needing to strain to urinate," "stop-and-go urinary flow" and "post-void residual urine sensation."

For each symptom we asked whether it had occurred in the previous 4 weeks. The optional answers were 1—never, 2—occasionally, 3—regularly, 4—often and 5—always.[10, 11] With these answers ordinal scales with 5 categories were obtained. Because the categories "regularly," "often" and "always" were used infrequently, they were combined. The variables were reduced to a 3-point scale with the categories "never," "occasionally" and "regularly to always." We also asked questions about the quality of life, by which we measured the impact of each symptom on daily life. For this purpose we asked "How much of a problem is this for you?" after the assessment of each symptom. The optional answers were 1—"No, it is no problem," 2—"Yes, it is a bit of a problem," 3—"Yes, it is quite a problem" and 4 "Yes, it is a serious problem." An alternative answer to these questions was "not applicable." The scores on "not applicable" were coded as "missing." Because the categories "Yes, it is quite a problem" and "Yes, it is a serious problem" were used rarely, the 4-point scale was reduced to 2 categories, including "no problem" versus "problem."

To be able to determine whether function of the lower urinary tract before transplantation does have any effect on the subsequent occurrence of lower urinary tract symptoms, data were collected about the extent of patient urine production before transplantation and duration of renal replacement therapy. From the interviews with the research group we also collected data on the underlying nephrological condition, type of renal replacement therapy and how many times the patients underwent transplantation previously. To evaluate whether the fluid intake of the research group is related to the

occurrence of lower urinary tract symptoms we asked the research group “Can you indicate how much fluid you drink per 24 hours?” Because patients with renal disease are required to keep a record of fluid intake, we assumed that they would not have any problem answering this question accurately. For those patients who might not be able to answer this question we inserted “Don’t know” as an alternative.

The data were processed with commercial software. To compare the research with the control group as well as subgroup comparisons, the chi-square test was used. For measuring the function of the lower urinary tract we used patient urine production and duration of renal replacement therapy before transplantation. In regard to the urine production before transplantation we have divided the research group into 2 categories, including “no urine production” versus “urine production.” For the duration of renal replacement therapy we made 3 categories that included “no renal replacement therapy,” “1 to 24 months of renal replacement therapy” and “25 months or more of renal replacement therapy.” To determine to what extent the fluid intake influenced the results of the study we divided the research group into 2 categories, “fluid intake up to two liters per 24 hours” and “fluid intake more than two liters per 24 hours.” The symptom frequency was reduced to 2 categories, including “1 to 6 micturitions per day” and “7 or more micturitions per day.” The symptom nocturia also was reduced to 2 categories, “0 to 1 micturition per night” and “2 or more micturitions per night.”

Results

Table 1 provides an overview of the research group characteristics.

The symptoms related to bladder reservoir function are compared between the 2 groups in table 2. The research and control groups did not differ in regard to patient age and gender distribution. There were marked differences regarding voiding frequency. Of the research group 49% voided 7 times or more often during the day as was the case in the control group with 23%. Of the research group 38% voided once every 2 hours or more often, the control group 22%.

Table 1. Characteristics of the renal transplant patients

Characteristics	Valid cases	Frequency	Percent
Underlying nephrologic condition	**63**		
Chronic Glomerulonephritis		19	30
Diabetes mellitus		2	3
Congenital cystic kidneys		8	13
Vesico-ureteral reflux		6	10
Chronic pyelonephritis		3	5
Neurogenic bladder		1	2
Chronic tubulo-interstitial nephritis		3	5
Other		5	8
Unknown		16	25
Type of renal replacement therapy	**62**		
No renal replacement therapy		6	10
Peritoneal dialysis		22	35.5
Peritoneal dialysis followed by haemodialysis or vice versa		12	19
Haemodialysis		22	35.5
Duration of renal replacement therapy in months	**62**		
0		6	10
1-24		24	39
≥ 25		32	51
Urineproduction before transplantation in ml per 24 hours	**59**		
0		17	29
1-499		12	20
500-1000		11	19
>1000		19	32
First or second transplant	**63**		
First transplant		51	81
Second transplant		12	19
Fluid intake in ml per 24 hours	**47**		
1500 – 1999		28	59
2000 – > 3000		19	41

These measurements showed the same results, specifically that patients who underwent renal transplantation needed to void more often than controls. An even larger difference was found between the research and control groups for the voiding frequency at night. Of the patients who had a transplant 62% needed to void 2 times or more during the night, whereas of the controls only 19% needed to do so. “Urgency”, “pain in the bladder” and “loss of urine” occurred to the same extent in the 2 groups.

Table 2. Reservoir function of the bladder, renal transplant patients versus control group

Dependent variables	Renal transplant patients	Control group	P value
Number of valid cases,	63	74	
Mean patient age (range)	47 (20–70)	44 (15–69)	NS
Gender			
Men	34 (54%)	37 (50%)	NS
Female	29 (46%)	37 (50%)	
Number of voids daily (%)			
1-4	13 (21.3%)	34 (46.6%)	
5-6	18 (29.5%)	22 (30.1%)	0.002
7-8	24 (39.3%)	10 (13.7%)	
9 or more	6 (9.8%)	7 (9.6%)	
Number of voids hourly (%)			
Once per 4 hours or less	13 (21.7%)	28 (37.8%)	
Once per 3 hours	24 (40.0%)	30 (40.5%)	0.075
Once per 2 hours	20 (33.3%)	12 (16.2%)	
Once per hour or more	3 (5.0%)	4 (5.4%)	
Number of voids nightly (%)			
0	6 (9.5%)	35 (47.3%)	
1	18 (28.6%)	25 (33.8%)	< 0.001
2	26 (41.3%)	10 (13.5%)	
3 or more	13 (20.6%)	4 (5.4%)	
Number of urgency (%)			
Never	37 (58.7%)	30 (40.5%)	NS
Occasionally to always	3 (4.8%)	6 (8.1%)	
Pain in the bladder			
Never	51 (81.0%)	62 (83.8%)	
Occasionally	11 (17.5%)	10 (13.5%)	NS
Regularly to always	1 (1.6%)	2 (2.7%)	
Number of urine loss			
Yes	9 (14.3%)	14 (18.9%)	NS
No	54 (85.7%)	60 (81.1%)	

NS=not significant

In regard to bladder evacuation the patients who had undergone renal transplantation did not have more symptoms than controls, and differences were not significant (table 3). Table 4 shows that there was no significant difference between the research and control groups regarding the impact of frequency and nocturia on the quality of life. However, we observed a certain trend. Patients who had transplants had tended to perceive frequency and nocturia less as a problem than controls. Table 5 shows that no significant relations were found between the presence or absence of urine production before transplantation, and frequency and nocturia after transplantation. In addition, the duration of renal replacement therapy was not significantly related to the occurrence of frequency and nocturia (table 6).

Because 40% of patients who underwent transplantation had a daily fluid intake greater than 2,000 ml., we considered the possibility that it was higher in the research than control group. To evaluate whether fluid intake in the patients with transplants was related to frequency and nocturia, we compared those with transplants who had a fluid intake of less

than 2,000 ml. to those who had greater than 2,000 ml. We found that the 2 groups were equal in regard to frequency and nocturia (table 7). When we compared the control with the research group after excluding the patients with transplants who had a fluid intake greater than 2,000 ml., we still found that those 28 with transplants voided significantly more often than controls during the day (p=0.003) and at night (p < 0.001, table 8).

Tabel 3. Bladder evacuation

Dependent variables	Renal transplant patients	Control group	P value
Number of valid cases	63	74	
Hesitancy			
Never	43 (69.4%)	47 (63.5%)	
Occasionally	18 (29.0%)	22 (29.7%)	NS
Regularly to always	1 (1.6%)	5 (6.8%)	
Straining			
Never	53 (84.1%)	52 (70.3%)	
Occasionally	8 (12.7%)	18 (24.3%)	NS
Regularly to always	2 (3.2%)	4 (5.4%)	
Intermittend flow			
Never	52 (82.5%)	60 (83.3%)	
Occasionally	11 (17.5%)	11 (15.3%)	NS
Regularly to always		1 (1.4%)	
Post-void residual urine			
Never	48 (77.4%)	46 (62.2%)	
Occasionally	13 (21.0%)	21 (28.4%)	NS
Regularly to always	1 (1.6%)	7 (9.5%)	

Table 4. Impact of the symptoms on the quality of life

Dependent variables	Renal transplant patients	Control group	P value
≥ 7 voids daily	N=28	N=17	
No problem	26 (93%)	13 (77%)	0.12
Problem	2 (7%)	4 (23%)	
≥ 1 void/2 hours	N=21	N=15	
No problem	21 (100%)	13 (87%)	0.09
Problem	0 (0%)	2 (13%)	
≥ 2 voids nightly	N=37	N=12	
No problem	31 (84%)	7 (58%)	0.07
Poblem	6 (16%)	5 (42%)	

Table 5. Urine production before transplantation and frequency and nocturia after transplantation

Dependent variables	Urine production before transplantation		Total	P value
	Present	**Absent**		
Voids daily				
1 – 6	21 (53%)	9 (53%)	30	0.98
≥ 7	19 (47%)	8 (47%)	27	
Total	40 (100%)	17 (100%)	57 (100%) (2 missings)	
Voids nightly				
0 – 1	15 (36%)	7 (41%)	22	0.69
≥ 2	27 (64%)	10 (59%)	37	
Total	42 (100%)	17 (100%)	59 (100%)	

Table 6. Duration of renal replacement therapy before transplantation and frequency and nocturia after transplantation

Dependent variables	Duration of renal replacement therapy in months			Total	P value
	0	**1 - 24**	**≥ 25**		
Voids daily					
1 – 6	3 (60%)	12 (50%)	16 (52%)	31	0.92
≥ 7	2 (40%)	12 (50%)	15 (48%)	29	
Total	5 (100%)	24 (100%)	31 (100%)	60 (2 missings)	
Voids nightly					
0 – 1	3 (50%)	10 (42%)	11 (34%)	34	0.72
≥ 2	3 (50%)	14 (58%)	21 (66%)	38	
Total	6 (100%)	24 (100%)	32 (100%)	62	

Table 7. Fluid intake at interview and frequency in renal transplant patients

Dependent variables	Fluid intake in ml per 24 hours		Total	P value
	0 - 2000	**≥ 2001**		
Voids daily				
1 – 6	13 (46%)	9 (47%)	22	0.95
≥ 7	15 (54%)	10 (53%)	25	
Total	28 (100%)	19 (100%)	47	
Voids nightly				
0 – 1	12 (43%)	8 (42%)	20	0.96
≥ 2	16 (57%)	11 (58%)	27	
Total	28 (100%)	19 (100%)	47	

Table 8. Fluid intake at interview and occurrence of frequency, renal transplant patients versus control group

Dependent variables	Renal transplant patients with fluid intake 0–2000 mL per 24 hours	Control group	Total	P value
Voids daily				
1 – 6	13 (46%)	56 (77%)	69	0.003
≥ 7	15 (54%)	17 (23%)	32	
Total	28 (100%)	73 (100%)	101	
Voids nightly				
0 – 1	12 (43%)	60 (81%)	72	< 0.001
≥ 2	16 (57%)	14 (19%)	30	
Total	28 (100%)	74 (100%)	102	

Discussion

The results obtained from our study show that patients with transplants needed to void significantly more often than controls both during the day and at night. In half of the patients we found a daytime voiding frequency of 7 times or more often. At night approximately 62% of the patients with transplants needed to void 2 times or more often. Based on these results we conclude that the reservoir function of the bladder is impaired after renal transplantation. However, the urge to void was perceived as normal. Therefore, we suspect that frequency is solely caused by a decrease in bladder capacity.

More information about bladder capacity may be acquired by giving patients with transplants frequency volume charts to complete.

Bladder evacuation appears to be normal after renal transplantation.

However, it is noteworthy that this function cannot be assessed well by a questionnaire. Better methods to evaluate voiding and post-voiding residue are flow measurement and ultrasonography. However, this evaluation was beyond the scope of our study.

To our surprise, the occurrence of frequency and nocturia after transplantation was neither related to the amount of urine production nor the duration of renal replacement therapy before transplantation. A number of studies emphasize that a dysfunctional bladder may retain the ability to recover function.[3, 4] However, if the bladder is scarred or thick walled it can limit recovery. Therefore, we suspect that patients who have undergone renal transplantation, and have frequency and nocturia possibly have a scarred or thick bladder wall. We suggest evaluation of the bladder wall with ultrasonography in patients with persistent frequency and nocturia after renal transplantation, as they run the risk of a high pressure bladder and, therefore, renal failure may develop.

We realize that in studies on lower urinary tract symptoms, fluid intake is an influential factor. Because patients with renal disease are required to keep a record of fluid intake, we assumed that they would not have any problem answering a question about it accurately. However, it is difficult to evaluate fluid intake in the general population. It is noteworthy that the fluid intake of subjects in the control group cannot be assessed by a questionnaire because they were not able to indicate accurately how much fluid they drink per 24 hours. A method to evaluate fluid intake is to give them frequency volume charts to complete but this was beyond the scope of our study. However, we found that patients with transplants who had a fluid intake of less than 2,000 ml., and those who had greater than 2,000 ml. were equal in regard to frequency and nocturia. In addition, if we compared the control with the research group after excluding the patients with transplants who had a fluid intake greater than 2,000 ml. we still found that those 28 with transplants voided significantly more often than controls during the day ($p=0.003$) and at night ($p=0.001$). Therefore, we conclude that the actual fluid intake to a large extent did not contribute to the occurrence of frequency and nocturia in our patients. Patients who underwent renal transplantation did not differ from controls regarding satisfaction about the voiding pattern. The patients with transplants even tended to accept a high voiding frequency and nocturia more readily. Apparently, we are dealing with a group of grateful patients who do not tend to complain about having to void more often. This result may be because the patients with transplants are so relieved to be free of renal replacement therapy that the presence of lower urinary tract symptoms seems a small price to pay. Possibly, these patients perceived the change in the voiding pattern after transplantation as positive. In this context it may be that a higher frequency is recognized as more normal than no voiding at all. Moreover, it is possible that the patients regard each voiding as a positive sign, that is an indication that the kidney is

still functioning properly. Nevertheless, the question occurs as to whether patients with transplants would prefer treatment, for example bladder training, if they knew that this might lead to a reduction in voiding frequency. Bladder training consists of a rehabilitation program for the lower urinary tract that teaches the patient to suppress and postpone the urge to void and, thus, increase bladder capacity.[13–15] It may prove useful to ask the patients who underwent renal transplantation specific questions about frequency, nocturia and the impact of these so that they can be referred for bladder training. Another option is to prepare guidelines that may help patients reduce voiding frequency themselves.

Conclusions

It would be interesting to examine if symptoms develop in these patients with time. Will frequency disappear with time, and if not how will patients perceive it longer after transplantation?

To answer these questions a longitudinal study of kidney transplant recipients is required. This study would serially document the recovery of bladder function after successful kidney transplantation.

References

1. Morris PJ. Kidney transplantation, principles and practice, 4th ed. Philadelphia: W. B. Saunders Co., p. xv, 1994.
2. Bernards JA, Bouwman LN. Fysiologie van de mens. Utrecht: Bohn, Scheltema & Holkema, 1988.
3. Serrano DP, Flechner SM, Modlin CS, et al. Transplantation into the long-term defunctionalized bladder. J Urol 1996; 156: 885-888.
4. Reinberg Y, Bumgardner GL, Aliabadi H. Urological aspects of renal transplantation. J Urol 1990; 143: 1087.
5. Reinberg Y, Gonzalez R, Fryd D, et al. The outcome of renal transplantation in children with posterior urethral valves. J Urol 1988; 140: 1491.
6. Campaiola JM, Perlmutter AD, Steinhardt GF. Noncompliant bladder resulting from posterior urethral valves. J Urol 1985; 134: 709.
7. Polit DF, Hungler BP. Nursing research: Principles and Methods, 6th ed. Philadelphia: J. B. Lippincott Co., 1999
8. Arrighi HM, Guess HA, Metter EJ, et al. Symptoms and signs of prostatism as risk factors for prostatectomy. Prostate 1990; 16: 253.
9. Guess HA, Chute CG, Garraway WM, et al. Similar levels of urological symptoms have similar impact on Scottish and American men, although Scots report less symptoms. J Urol 1993; 150: 1701.
10. Donovan JL, Abrams P, Peters TJ, et al. The ICS-'BPH'study: the psychometric validity and reliability of the ICS male questionnaire. Br J Urol 1996; 77: 554-562.
11. Jackson S, Donovan J, Brookes S, et al. The Bristol Female Urinary Tract Symptoms questionnaire: developement and psychometric testing. Br J Urol 1996; 77: 805-812.
12. Jolleys JV, Donovan JL, Nanchahal K, et al. Urinary symptoms in the community: how bothersome are they? Br J Urol 1994; 74: 551.
13. Frewen WK. Urge and stress incontinence; fact and fiction. J Obstet Gynaecol Br Commonw 1970; 77: 932.
14. Cardozo LD. Detrusor instability current management. Br J Obstet Gynaecol 1990; 97: 463.
15. McFarland GK, McFarlane EA. Nursing Diagnosis & Intervention: Planning for Patient Care. St. Louis: Mosby, 1993.

Chapter 3

Lower urinary tract symptoms after renal transplantation: are there changes over time?

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Abstract

Objectives. To examine the changes in bladder function after renal transplantation by comparing lower urinary tract symptoms in the first and third years after transplantation in a group of renal transplant recipients.

Methods. The long-term changes in bladder function after transplantation were studied using a longitudinal study design. The study group consisted of 53 patients who underwent renal transplantation in 1998 at the University Medical Centre Nijmegen and who returned a completed questionnaire about their micturition pattern in the first and third year after transplantation. The data on symptoms of lower urinary tract dysfunction were collected using the International Continence Society (male) and Bristol Female Lower Urinary Tract Symptoms questionnaires. The control group consisted of 74 patients who visited the Outpatient Clinic of Otorhinolaryngology at year 1. In our analyses, we compared the micturition behavior of the transplant group at year 3 with the control group and with their own micturition behavior at year 1

Results. The results of our study showed that 3 to 4 years after transplantation, the renal transplant group still urinated significantly more often during the day and during the night than did the control patients. Furthermore, among most (63% to 68%) of the patients who showed these symptoms in the first year after transplantation, the symptoms were still present 2 to 3 years later.

Conclusions. The frequency and incidence of nocturia among renal transplant patients are fairly persistent phenomena.

Introduction

In published reports, the recovery of bladder function in renal transplant patients has gained some attention.[1–3] Serrano et al.[1] reported the results of bladder rehabilitation by bladder cycling in 5 patients. A progressive increase in bladder capacity was noted in all patients (median 300 mL) within the first 3 months after transplantation. Al Khudair and Mansi[2] reported a case of a 17-year old boy who had been receiving hemodialysis for 9 years whose bladder capacity increased with 240 mL in 3 months (from 80 to 320 mL) as a result of bladder cycling. However, Errando et al.,[3] who performed bladder cycling in 9 patients with low compliance, found the urodynamic studies to be normalized in only 3 cases, improved in 2 cases, and remained unchanged in 4 patients with extremely low compliance. These studies demonstrated that after transplantation a rapid recovery of the bladder could be achieved in some cases, but that in other cases, the bladder condition remains unchanged. In an earlier study, we found that in the first year after renal transplantation, recipients (n=63) needed to void more often than controls (n=74) during both daytime and nighttime.[4] We concluded that these symptoms might have been a result of a decrease in bladder capacity. The foregoing raised the question of whether the excessive voiding of renal recipients decreases with time. In this study, we sought to answer this question by studying the changes in lower urinary tract symptoms (LUTS) after renal transplantation over a longer period. We approached a group of patients in the first (T1) and the third (T2) year after transplantation and determined their micturition pattern.

Material and methods

The research group consisted of all 97 patients who underwent renal transplantation at the University Medical Centre Nijmegen in 1998. The inclusion criteria were age older than 18 years, a good command of the Dutch language, a functioning graft, and reasonable to good general physical health. The exclusion criteria were the presence of a bladder catheter or urinary diversion. To guarantee that our research group consisted of patients with at least a reasonably functioning bladder, we excluded patients who performed clean intermittent catheterization, with an indwelling bladder catheter or a urinary diversion from our study. Of the 97 patients, 75 satisfied the inclusion criteria. With permission from the Medical Ethics Committee, we sent the first questionnaires to these 75 patients in February 1999. The interval between the transplantation and the first interview (T1) was 2 to 13 months (mean interval 8). A total of 63 completed questionnaires (84%) were returned.[4]

The second questionnaire was sent in September 2001. From the 63 patients who completed the first questionnaire, 58 transplant patients were assessable at T2. Three patients had died, one patient's graft was lost, and one letter came back as undeliverable. A total of 53 completed questionnaires were returned (91%). The interval between

transplantation and the second moment of interview (T2) was 33 to 44 months (mean interval 38). The mean interval between T1 and T2 was 30 months. After treatment, all patients had to take medication for immunosuppression, and many of them also took medication because of hypertension. However, these medicines do not influence bladder function. Between T1 and T2, only 6 patients used medication because of temporary LUTS. Five of them used antibiotics because of urinary tract infection and the other patient used anticholinergics temporarily because of urge incontinence. Because this medication is used to reduce LUTS, this may have led to an underestimation of the LUTS.

To find out whether the loss of 10 patients between T1 and T2 was selective, we compared the proportion of the frequency of urination and nocturia of the 53 patients available at T2 with those of all 63 patients at T1. Of the 63 transplant patients at T1, 49% said they had frequency and 62% nocturia. For the same group of transplant patients minus the 10 patients lost between T1 and T2, we found almost the same values: frequency of 46% and nocturia of 64%. This indicates that the loss of patients between T1 and T2 was not selective in this regard.

The control group consisted of 74 nononcologic patients who visited the Outpatient Clinic of Otorhinolaryngology in week 13 of 1999. In the selection of patients for the control group, we used the quota sampling method to ensure that the composition of the control group matched that of the research group for sex and age.[5]

To collect data on the symptoms of lower urinary tract dysfunction, we used a composite of the International Continence Society male questionnaire and the Bristol Female Lower Urinary Tract Symptoms questionnaire.[6,7] With regard to the bladder's reservoir function, we assessed the symptoms "frequency" (a micturition frequency of seven times per day or more), "nocturia" (a micturition frequency of two times per night or more), "urgency" (a sudden, strong, uncontrollable urge to void), "pain in the bladder," and "loss of urine." With regard to the bladder's evacuation function, we measured the symptoms of "hesitancy" (poor initial urinary flow), "needing to strain to urinate," "stop-and-go urinary flow," and "postvoid residual urine sensation." The micturition frequency per day and night was measured with a precise scale and afterward reduced to two categories: one to six micturitions per day and seven or more micturitions per day and zero to one micturition per night and two or more micturitions per night. For all other symptoms, we asked whether it had occurred in the previous 4 weeks. The answers were 1, never; 2, occasionally; 3, regularly; 4, often; and 5, always. In this way, ordinal scales with five categories were obtained. Because the categories occasionally, regularly, often, and always were seldom used, these categories were combined, so that the variables were reduced to two categories: never and occasionally to always. For the patients in the

research group, some background information was obtained from the patients' medical records.

The data were processed with commercial software. Pearson chi-square tests were used to compare the results from the first and the second moment of interview with the results of the control group.

Results

Table 1 provides an overview of the characteristics of the transplant patients. At T2, the mean age of the patients was 49 years (range 23 to 71). In the control group, the mean age was 44 years (range 15 to 69), and 50% of the control persons were male.

Table 1. Characteristics of the renal transplant patients T2

Characteristics of the renal transplant patients	No. cases	No.	(%)
Age	53		
Range		23 - 71	
Mean		49	
Gender	53		
Male		29	(55)
Female		24	(45)
Underlying nephrological condition	53		
Chronic Glomerulonephritis		18	(34)
Diabetes mellitus		1	(2)
Congenital cystic kidneys		6	(11)
Vesicoureteral reflux		3	(6)
Chronic pyelonephritis		2	(4)
Chronic tubulointerstitial nephritis		3	(6)
Other		6	(11)
Unknown		14	(26)
Renal replacement therapy	52		
None		5	(10)
Peritoneal dialysis		19	(36)
Peritoneal dialysis followed by haemodialysis or vice versa		12	(23)
Haemodialysis		16	(31)
Months of renal replacement therapy	52		
0		5	(9)
1-18		14	(27)
19-36		18	(35)
> 36		15	(29)
Urine production before Tx (ml/ 24 hrs)	49		
0-300 Defunctionalized bladder		23	(47)
301 – 1500		21	(43)
> 1501 Polyuria		5	(10)
Transplant	53		
First		41	(77)
Second		12	(23)

Bladder function

In Table 2, the symptoms related to the bladder's function at T1 and T2 are compared between the research and control groups. With regard to daytime micturition frequency, we found that at both T1 and T2, the transplant patients had frequency about twice as often as the control patients. The micturition frequency at night showed the findings. At both T1 and T2, the transplant patients had nocturia significantly more often than did the control patients.

Table 2. Bladder function, Renal transplant patients at T1 and T2 versus control group

	Renal transplant patients		Control group
	T1	T2	
Cases, N	53	53	74
Micturitions per day			
1-6	28 (54%)	31 (58%)	56 (77%)
7 or more	24 (46%)	22 (42%)	17 (23%)
P (compared with controls)	0.007	0.03	
Micturitions per night			
0 – 1	19 (36%)	27 (51%)	60 (81%)
2 or more	34 (64%)	26 (49%)	14 (19%)
P (compared with controls)	< 0.001	< 0.001	
Urgency			
Never	31 (58%)	39 (74%)	30 (41%)
Occasionally to always	22 (42%)	14 (26%)	44 (59%)
P (compared with controls)	0.05	< 0.001	
Pain in the bladder			
Never	42 (79%)	42 (79%)	62 (84%)
Occasionally to always	11 (21%)	11 (21%)	12 (16%)
P (compared with controls)	NS	NS	
Loss of urine			
Yes	8 (15%)	8 (15%)	14 (19%)
No	45 (85%)	45 (85%)	60 (81%)
P (compared with controls)	NS	NS	
Hesitancy			
Never	35 (67%)	33 (62%)	47 (64%)
Occasionally to always	17 (33%)	20 (38%)	27 (36%)
P (compared with controls)	NS	NS	
Straining			
Never	44 (83%)	40 (75%)	52 (70%)
Occasionally to always	9 (17%)	13 (25%)	22 (30%)
P (compared with controls)	NS	NS	
Intermittent flow			
Never	42 (79%)	40 (75%)	60 (83%)
Occasionally to always	11 (21%)	13 (25%)	12 (17%)
P (compared with controls)	NS	NS	
Post-void residual urine			
Never	41 (79%)	33 (62%)	46 (62%)
Occasionally to always	11 (21%)	20 (38%)	28 (38%)
P (compared with controls)	0.05	NS	

Although the incidence of nocturia and frequency tended to wane between T1 and T2, no statistically significant changes occurred over time. At both points, the transplant patients

had significantly less urgency than those in the control group. For the symptoms pain in the bladder, loss of urine, hesitancy, straining, and intermittent flow, no statistically significant differences were found between the transplant group and control group. However, at T1, the postvoid residual urine symptom tended to be less frequent among the transplant patients than in the control group. At T2, this difference had disappeared.

Transplant patients at t1 versus t2

The question arises of whether the patients who have frequency, urgency, and nocturia at T2 were the same patients who already had these symptoms at T1. In Table 3, the daytime micturition frequency of the transplant patients at T1 was cross-classified against their micturition frequency at T2. Of the 24 patients who showed a daytime micturition frequency of more than seven at T1, 15 (63%) still showed such a high micturition frequency at T2. Of the 34 patients who showed a nighttime voiding frequency of two times or more at T1, 23 (68%) still showed this pattern at T2. Of the 31 patients who showed no sensation of urgency at T1, 29 (93.5%) still showed no sensation of urgency at T2.

Table 3. Frequency, nocturia and urgency T1 versus T2

	Frequency at T2		
Frequency at T1	1 - 6	≥ 7	Total
1 – 6	21 (75%)	7 (25%)	28 (100%)
≥ 7	9 (37.5%)	15 (62.5%)	24 (100%)
Total	30 (57.7%)	22 (42.3%)	52 (100%)
P = 0.006			
	Nocturia at T2		
Nocturia at T1	0 - 1	≥ 2	Total
0 – 1	16 (84.2%)	3 (15.8%)	19 (100%)
≥ 2	11 (32.4%)	23 (67.6%)	34 (100%)
Total	27 (50.9%)	26 (49.1%)	53 (100%)
P < 0.001			
	Urgency at T2		
Urgency at T1	Never	Occasionally/always	Total
Never	29 (93.5%)	2 (6.5%)	31 (100%)
Occasionally/always	10 (45.5%)	12 (54.6%)	22 (100%)
Total	39 (73.6%)	14 (26.4)	53 (100%)
P < 0.001			

Comment

The patients who had frequency and nocturia at T2 were mainly the same patients who already had these symptoms at T1. This finding might mean that the bladder's ability for additional recovery is limited. This is in line with findings of previous research.[1–3]

Both at T1 and T2, transplant patients showed less sensation of urgency. Moreover, most of those who had no sensation of urgency at T1 still had no sensation of urgency at

T2 (93.5%). This finding could mean that transplant patients are less sensitive with regard to their bladder than normal people.

With respect to the evacuation function of the bladder, one statistically significant difference was found between the transplant group and the control group. At T1, the postvoid residual urine symptom was significantly less frequent among the transplant patients than in the control group. At T2, this difference had disappeared. However, the tendency for a decreased incidence of postvoid residual urine sensation in the transplant patients at T1 also indicated a decrease in bladder awareness after transplantation.

The interesting finding of, on the one hand, an increased micturition frequency and, on the other hand, indications of decreased bladder sensitivity can be explained in different ways. The transplant patients may have an increased urinary output, they may have a small bladder capacity, or psychological reasons may be present (ie, out of habit or the need to reassure oneself that the kidney is still functioning). The first explanation, an increased urinary output is not very likely, because in our earlier study, we found that the actual fluid intake did not contribute much to the occurrence of frequency and nocturia in our patients. Therefore, we assume that frequency and nocturia are caused by a small bladder capacity, perhaps in combination with psychological factors.

For the symptoms of hesitancy, straining, and intermittent flow, no statistically significant differences were found between the transplant group and the control group or between T1 and T2.

Because of the interval between T1 and T2, the research group at T2 was, on average, 2.5 years older compared with the research group at T1 and the control group (which was also selected at T1). This may be a problem because a natural increase tends to occur in urgency, frequency, and nocturia hen people are aging. However, a period of 2.5 years is rather short compared with a lifetime, and the people in our research and control groups were relatively young. Therefore, we do not expect that the effects of this age difference distorted our results seriously.

Conclusions

The objective of the present study was to determine whether LUTS after renal transplantation change over time. Our results showed that 3 years after transplantation, the LUTS were still present in most patients. Regarding the reservoir function of the bladder, we found that the incidence of frequency and nocturia remained greater in transplant patients than in controls. Furthermore, most of those who showed an increased micturition frequency shortly after transplantation still showed these symptoms 2 to 3 years later. We, therefore, concluded that frequency and nocturia in renal transplant patients are rather persistent phenomena.

References

1. Serrano DP, Flechner SM, Modlin CS, et al. Transplantation into the long-term defunctionalized bladder. J Urol 1996; 156: 885–888.
2. Al Khudair WK, Mansi MK: Rehabilitation of longterm defunctionalized bladder for renal transplantation. Transpl Int 1998; 11: 452–454.
3. Errando C, Batista JE, Caparros J, et al. Urodynamic evaluation and management prior to renal transplantation. Eur Urol 2000; 38: 415–418.
4. van der Weide MJA, Hilbrands LB, Bemelmans BLH, et al. Lower urinary tract symptoms after renal transplantation. J Urol 2001; 166: 1237–1241.
5. Polit DF, Hungler BP. Nursing research: principles and methods. Philadelphia, JB Lippincott, 1995.
6. Donovan J, Abrams P, Peters TJ, et al. The ICS-'BPH' study: the psychometric validity and reliability of the ICS male questionnaire. Br J Urol 1996; 77: 554–562.
7. Jackson S, Donovan J, Brookes S, et al. The Bristol Female Urinary Tract Symptoms questionnaire: development and psychometric testing. Br J Urol 1996; 77: 805–812.

Chapter 4

Why do many renal transplant patients suffer from frequency and nocturia?

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Abstract

Background. Literature has shown that after renal transplantation more than half of adult renal recipients report frequency and nocturia. However, the causes of these high voiding frequencies are still largely unknown. The present study explores the role of bladder capacity, bladder pain, dysfunctional voiding, urgency, urinary tract infections, and fluid intake as potential causes of frequency and nocturia after renal transplantation.

Methods. Data were gathered from 52 adult renal transplant patients; 35 males and 17 females, mean age 49, using a written questionnaire, medical records, frequency/volume charts, and urinary cultures. Mean time between transplantation and data collection was five months. Structural Equations Modeling (SEM) was used for simultaneous assessment of direct and indirect relationships between explanatory variables and voiding frequency.

Results. Frequency and nocturia were found in 54% and 60% of the study population, respectively. Frequency was associated with daytime urine volume, bladder capacity, bladder pain, and urgency and indirectly with urinary tract infections. Nocturia was associated with nocturnal urine volume, bladder capacity, bladder pain, and dysfunctional voiding.

Conclusion. Our results indicate that frequency after renal transplantation may be caused directly by small bladder capacity, bladder pain, urgency, and a high fluid intake, and indirectly by urinary tract infections (via urgency and bladder pain). Nocturia may be caused by high nocturnal urine volume, small bladder capacity, and dysfunctional voiding. A quarter of our patients had small bladders and another quarter had large bladders, the latter being associated with nocturnal polyuria. Bladder rehabilitation programs may be beneficial in these patients.

Introduction

In previous research on lower urinary tract function after renal transplantation we showed that during the first year following transplantation, renal recipients reported significantly more frequency (≥7 voids per day) and nocturia (awaken at night ≥ 2 times to void) than a control group.[1] Frequency was observed in 49% of the transplant patients and nocturia in 62%.[1] In about two thirds of the patients with frequency and nocturia shortly after transplantation, the symptoms were still present two to three years later.[2] More recently, these finding were confirmed by Zermann et al. who studied 150 renal transplant patients and found frequency in 87% and nocturia in 93% of patients.[3]

The consistent finding of frequency and nocturia in transplant patients raises the question of what the causes of these symptoms are. To answer this question, we studied the role of five potential causes of frequency and nocturia after transplantation: bladder capacity, bladder pain, urgency, dysfunctional voiding and fluid intake. These five potential causes may occur separately, but also in various combinations, because they are not completely independent of each other.

The interrelationships among these five factors and their expected effects on frequency and nocturia, as they can be derived from the literature, are depicted schematically in Figure 1. Each arrow in this model represents a hypothesized relationship and the sign indicates whether the relationship is expected to be positive or negative. The central aim of this paper is to test for the presence, and strength of these hypothesized relationships. This is done with structural equations modeling, a technique that makes it possible to test all relationships in the model simultaneously. The reasoning behind the hypothesized relationships in Figure 1 is as follows.

Bladder capacity is included in the model because results from the present and earlier research show that before transplantation almost half (between 40% and 50%) of the patients had a urine production of ≤150 mL/24 hrs. About one third (between 29% and 39%) of the patients even had a complete anuria.[1,2] After renal transplantation, normal bladder function is assumed to recover within 12 weeks.[4] Several studies have shown that recovery of the bladder capacity may be limited in bladders that are scarred due to urinary tract infections (UTI's) or previous surgery, in bladders that are thick walled due to outlet obstruction, and in bladders that are defunctionalized due to longstanding anuria.[5] These conditions may result in a small, thick-walled, low compliance bladder, which is known to be a major cause of frequency and nocturia.[5] It is important to know whether frequency and nocturia are caused by small thick-walled low compliance bladders, because such bladders might cause renal transplant deterioration, due to high pressure in the lower urinary tract.[6]

An increased incidence of *bladder pain* may be expected after transplantation, because the extension of scarred, thick walled and defunctionalized bladders can lead to unpleasant feelings and pain. When bladder filling causes pain, this may lead to more frequent emptying of the bladder. We previously observed bladder pain after renal transplantation in 19% of the patients.[1] From literature about interstitial cystitis it is known that painful bladder syndrome is typically characterized by urgency and frequency.[7]

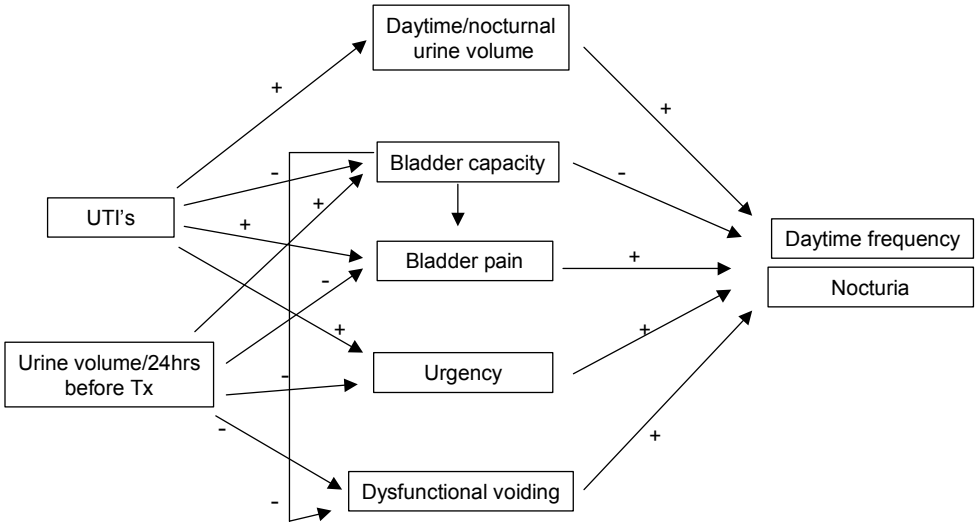
Urgency may be expected after renal transplantation, especially after long periods of anuria, because the bladder wall is not used anymore to stretching due to bladder filling. Urgency is also known to be associated with frequency, nocturia, and possibly urinary incontinence in a syndrome known as "overactive bladder".[8] Underlying conditions may be urological, like irritability of the bladder due to UTI's or obstruction, but mostly the underlying condition is unknown. Neurological diseases also can cause urgency, however their presence is not particularly expected in our study population.

Dysfunctional voiding. The lower urinary tract has two functions; storage of urine and evacuation of urine. Frequency and nocturia are both symptoms of impaired urine storage. However, it is imaginable that disturbances in bladder storage are accompanied by an impaired evacuation function. Indeed, pathological bladder conditions have been shown to be characterized by the simultaneous presence of reduced bladder capacity, thickened bladder wall, and voiding dysfunction[9].

A rather obvious (potential) cause of frequency is a *high fluid intake*. Renal recipients are advised to consume ample amounts of fluid. With respect to nocturia, there are indications that the diurnal rhythm in the excretion of urine may be altered after renal transplantation[10]. Nocturnal polyuria is also a well-known symptom of renal insufficiency.[11,12]

Besides these five potential causes, Figure 1 also contains two factors that may indirectly affect frequency and nocturia. Oliguria before transplantation may influence bladder capacity, and add to bladder pain, urgency, and dysfunctional voiding after transplantation, and hence should be taken into account. As discussed above, also UTI's, that are very common after renal transplantation[13], may increase the risk of frequency and nocturia via their effects on other factors.

Figure 1. Hypothesized relationships among explanatory variables and their effects on daytime frequency and nocturia



Materials and methods

The Medical Ethics Committee approved the study and all patients gave informed consent. The study population consisted of patients who received a renal transplant between July 2003 and August 2004 at one University Medical Centre. Standard immunosuppressive therapy consisted of a combination of tacrolimus, corticosteroids, and mycophenolate mofetil. Patients received antibiotic prophylaxis (cotrimoxazol 480 mg/d) during the first three months after transplantation. Inclusion criteria were: being able to understand the questionnaire, a functioning renal graft, and regular visits to the outpatient clinic. Excluded were patients younger than 18 years, patients who performed clean intermittent catheterization, and patients with a urinary diversion or indwelling catheter. During the study period, 127 patients received a renal transplant, of whom 13 were under the age of 18, 13 did not master the Dutch language, 13 went to another hospital for follow-up care, 6 had a nephrostomy because of ureteral obstruction, 5 died shortly after transplantation, 2 had a urinary diversion, and one had an indwelling catheter. A group of 74 patients met the inclusion and exclusion criteria, and 52 (70%) of them agreed to participate in the study. Table 1 presents the characteristics of this study group.

Data collection

Data were gathered using an adapted version of the Bristol Female Lower Urinary Tract Symptoms (BFLUTS)[1,14] questionnaire, medical records, 24 hours frequency/volume charts[13], and urinary cultures. Patients were verbally informed about the study and given an information package, consisting of written study information, an informed consent form, a questionnaire, a frequency/volume chart, and a measuring cup. Patients who participated

filled out the questionnaire and frequency/volume charts at home and returned them in a prepaid envelope. Between transplantation and data collection, urinary dipstick analyses for leucocytes and nitrite were performed at each visit of the outpatient clinic. A urinary culture was done when a positive leukocyte reaction was accompanied by positive nitrite test, and in case the patient reported symptoms of a UTI. In addition an urinary culture was obtained in all patients at the time of collecting the questionnaire and frequency/volume chart. Infections were treated, except cases of chronic asymptomatic bacteriuria. Information about the use of diuretics at the moment of study was gathered from the patient's medical records.

Table 1. Characteristics of the study group

	N=52
Age (years)	
Range	21 - 76
Mean	49
Gender	
Male (%)	35 (67)
Female (%)	17 (33)
Diuretics	
None	44 (88%)
Yes	6 (12%)
Time between Tx and data collection (months)	
Range	3 - 9
Mean	5
Underlying nephrological condition	
Chronic glomerulonephritis (%)	14 (27)
Diabetes mellitus (%)	1 (2)
Congenital cystic kidneys (%)	12 (23)
Vesicoureteral reflux (%)	2 (4)
Chronic pyelonephritis(%)	2 (4)
Neurogenic bladder (%)	-
Chronic tubulointerstitial nephritis (%)	3 (6)
Other (%)	4 (7)
Unknown (%)	14 (27)
Urinary volume before Tx (ml/ 24 hrs)	
Mean	788
Range	0 - 3500
0 (%)	16 (31)
1 – 150 (%)	5 (10)
151 – 500 (%)	5 (10)
$\geq$ 501 (%)	26 (49)

Tx: transplantation

Outcome measures

The following items were abstracted from the frequency/volume chart: daytime frequency, nocturia, maximum voided volume, daytime urine volume, and nocturnal urine volume. Daytime frequency was defined as $\geq$ 7 voids recorded during waking hours (including the last void before sleep and the first void after rising in the morning). Nocturia was defined

as ≥ 2 voids recorded during a night's sleep. Bladder capacity was estimated by looking for the largest volume of urine voided during a single micturition.[15] Normal bladder capacity in adults is between 400 and 500 mL.[16] Daytime urine volume was defined as the total volume of urine passed during waking hours (excluding the first void after rising in the morning but including the last void before going to sleep). Nocturnal urine volume was defined as the total volume of urine produced during sleeping, including the first void after rising.[15] A measured urine production of more than 2.8 liters/24 hours was classified as polyuria. Nocturnal polyuria was defined as a urinary output at night of more than 20% (young adults) to 33% (over 65 years) of the urinary output/24 hrs.[15]

The symptoms urgency, bladder pain, hesitancy, straining, intermittent stream, and sensation of incomplete emptying, derived from the BFLUTS questionnaire were measured with categories 'never', 'occasionally', 'regularly to always' and slow stream with categories 'same as before', 'weaker', 'much weaker'. Dysfunctional voiding is measured by a scale combining 5 of these symptoms: slow stream, hesitancy, straining, intermittent stream and sensation of incomplete emptying. To construct the dysfunctional voiding scale, a symptom score ranging from 0 to 5 was used. One point was added for each of the 5 symptoms the patient reported.

A UTI was defined as $> 10^5$ colony forming units per ml clean voided midstream specimen. Positive urinary cultures from mixed flora were not taken into account. The explanatory factor UTI was defined to be present, when there was at least one UTI between the time points of transplantation and data collection. Control factors in our analyses were age, sex and use of diuretics.

Statistical analysis

Structural equations modeling (SEM) was used to study the relationships among the explanatory variables and between these variables and voiding frequency in our theoretical model of Figure 1. SEM analysis is an extension of the multiple regression model which allows for the simultaneous estimation of hypothesized relationships (paths) among a set of variables. In a SEM analysis, both direct, indirect and total path coefficients are estimated.[17,18] We used a stepwise modeling strategy, in which we started with a model including all relationships presented in Figure 1, plus the direct effects of the factors UTI's and urine volume before transplantation on frequency and nocturia. In each following step we removed the non-significant path coefficient with the lowest t-value, until only coefficients that were significant at $p < 0.1$ were left in the model. This procedure was done separately for frequency and nocturia.

Results

Characteristics of the study group are presented in Table 1 and the incidence of LUTS in the patients in Table 2.

Symptoms of lower urinary tract dysfunction

Table 2 shows that frequency and nocturia occurred in 54% and 60% of the patients respectively. Although in 19 patients (38%) both symptoms were present together, no significant association between frequency and nocturia was found. Small bladder capacity was found in 13 (25%) patients and large bladder capacity was found in 14 (27%) patients. Median daytime urine volume was 1345 mL and median nocturnal urine volume was 742 mL. Polyuria was found in 12 (23%) patients and nocturnal polyuria in 33 (64%) patients. UTI's were diagnosed in 10 patients.

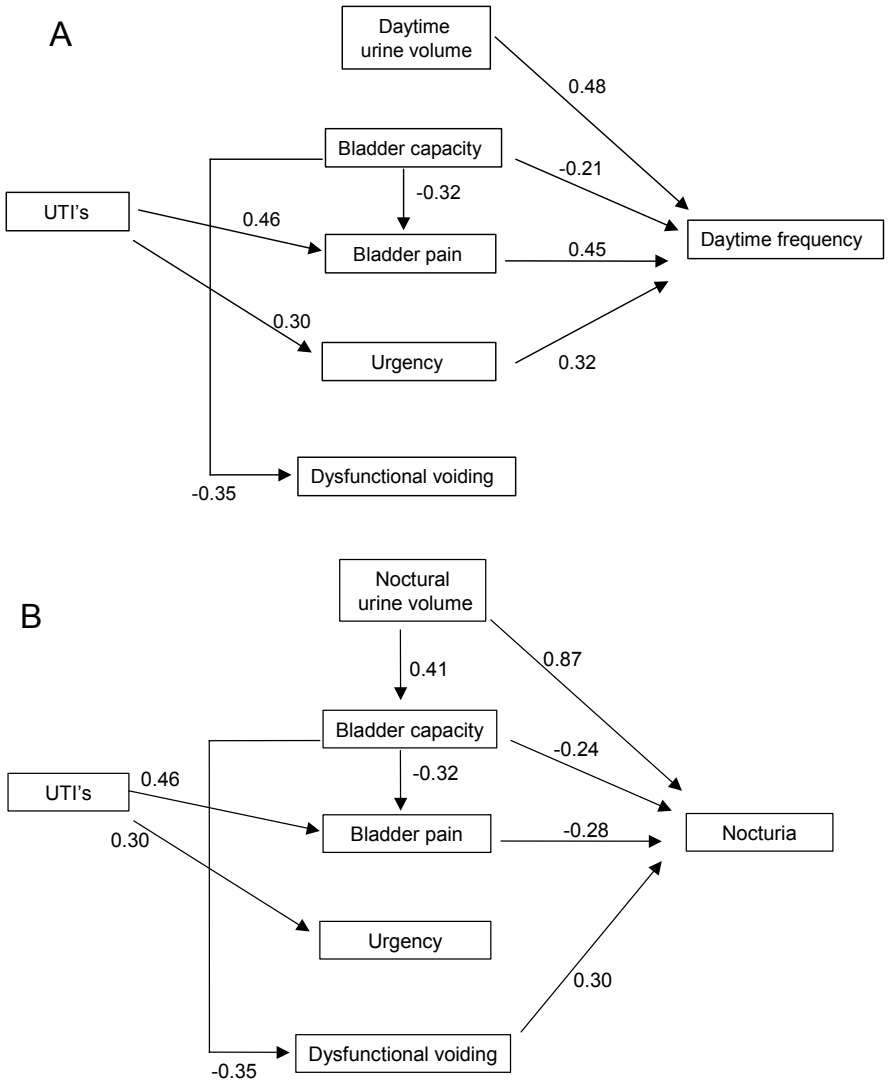
Table 2. Symptoms of dysfunction of the lower urinary tract

	N=52
BFLUTS questionnaire	
Urgency	
Occasionally to always	34 (65%)
Bladder pain	
Occasionally to always	7 (13%)
Dysfunctional voiding Symptom Score	
0	12 (23%)
1	14 (27%)
2	5 (10%)
3	10 (19%)
4	10 (19%)
5	1 (2%)
Frequency / volume charts	
Daytime frequency	
≥ 7	28 (54%)
Nocturia	
≥ 2	31 (60%)
Both daytime frequency and nocturia	19 (38%)
Bladder capacity (mL)	
Mean (range)	468 (90 – 920)
Small (≤ 399 mL)	13 (25%)
Normal (≥ 400 mL and ≤ 500 mL)	25 (48%)
Large (≥ 501 mL)	14 (27%)
Polyuria (≥ 2.8 liters/24 hours)	12 (23%)
Nocturnal polyuria (≥ 33% at night of total/24hrs)	33 (64%)
Daytime urine volume ml	
Mean (range)	1394 (505 – 2895)
Nocturnal urine volume ml	
Mean (range)	788 (200 – 1680)
Urinary cultures	
Urinary tract infections	
None	42 (81%)
Yes	10 (19%)

Causes of frequency and nocturia

The results of the SEM analyses are presented in Table 3 and in Figures 2A and 2B. All presented path coefficients are significant at $p < 0.05$.

Figure 2. Selected SEM model explaining daytime frequency and nocturia



* All presented path coefficients are significant at p<0.05

As expected, daytime urine volume, bladder pain, and urgency were positively related to daytime frequency, while bladder capacity had the expected negative effect. The negative effect of bladder capacity on frequency not only ran directly, but also indirectly via its negative effect on bladder pain. Bladder capacity was also negatively associated with

dysfunctional voiding, but this had no further effect on frequency. UTI's and bladder defunction before transplantation had no significant direct effect on daytime frequency. However, there were significant positive indirect effects of UTI's via urgency and bladder pain.

Nocturia was directly affected by bladder capacity, bladder pain, dysfunctional voiding, and nocturnal urine volume. Because nocturnal urine volume negatively affected nocturia in an indirect way through bladder capacity, the total effect of nocturnal urine volume on nocturia was less than the direct effect, but still substantial. Bladder capacity also affected nocturia indirectly through its negative effect on dysfunctional voiding.

Not surprisingly, daytime and nocturnal urine volume, reflecting fluid intake and the diurnal rhythm of urine excretion, had the largest effects on frequency and nocturia (Table 3). But also the total effects of bladder capacity, bladder pain, dysfunctional voiding (only for nocturia), urgency (only for frequency) and UTI's (indirectly via urgency and bladder pain) were quite substantial. Anuria before transplantation had no significant effects and none of the control factors (age, sex, use of diuretics) was significantly related to frequency or nocturia.

Table 3. Results of SEM analyses of frequency and nocturia: Standardized direct, indirect and total effects of selected symptoms on daytime frequency and nocturia

	Daytime frequency			Nocturia		
	Direct	**Indirect**	**Total**	**Direct**	**Indirect**	**Total**
Bladder capacity	-.208	-.142	-.350	-.242	-.018	-.260
Bladder pain	.449	-	.449	-.275		-.275
Urgency	.317	-	.317	-		-
Dysfunctional voiding	-	-	-	.304		.304
UTI's	-	.301	.301	-	-.125	-.125
Daytime urine volume	.479	-	.479	-	-	-
Nocturnal urine volume	-	-	-	.866	-.106	.760

UTI's: urinary tract infections; Tx: transplantation

Discussion

Literature on lower urinary tract function after renal transplantation, including this study, showed that the majority of renal recipients suffer from frequency and nocturia.[1-3] The precise causes of frequency and nocturia in this population are not known. Based on the literature, we designed a theoretical model in which several factors that might explain the occurrence of frequency and nocturia were included. The presence and strength of the hypothesized relationships among these factors and between these factors and frequency and nocturia were statistically analyzed with structural equations modeling (SEM).

Our findings indicate that there are several major causes of frequency after renal transplantation. Firstly, we found a strong positive association with a high daytime urine volume. A likely explanation of this finding is a high fluid intake, since transplant patients

are generally advised to drink much. Secondly, we found positive associations with urgency and bladder pain, which were related to the occurrence of UTI's. Thirdly, we found that frequency after renal transplantation is associated with a small bladder capacity, which may be accompanied by dysfunctional voiding and bladder pain, of which the latter makes the effect from bladder capacity on frequency even stronger. Our results show that 13 (25%) patients of the study group had a small bladder capacity. The interrelationships between small bladder capacity, bladder pain and dysfunctional voiding, suggest that these patients have thick walled non-compliant high-pressure bladders. This finding is important, because such thick walled bladders can have a deleterious effect on the kidney.[6,19] Thus, the presence of frequency may aid the physician to identify patients with small, high-pressure bladders.

Nocturia was most strongly affected by nocturnal urine volume. As 64% of patients suffered from nocturnal polyuria, this obviously is a major cause of nocturia. The high prevalence of nocturnal polyuria in our patients fits with previous observations of a disturbed diurnal rhythm in urine production after renal transplantation.[3,10] Whether there is a connection with the well-known prevalence of nocturnal polyuria in patients with renal insufficiency remains an open question.[11,12] The relationship found between small bladder capacity, dysfunctional voiding and nocturia parallels the relationship we found between small bladder capacity, dysfunctional voiding and daytime frequency. The negative effect of bladder pain on nocturia is in contrast with the positive effect we found on daytime frequency. We do not have a clear explanation for this apparent discrepancy.

In previous pediatric studies we found that a large majority (78%) of renal transplant children suffered from increased bladder capacity. This group on average had a bladder capacity of 175% (75% more than normal bladder capacity for age).[20,21] Post void residual urine was found in 50% and UTI's in 48% of these children.[20] Both UTI's and post void residual urine were independently associated with renal graft function deterioration.[21] The positive relation between nocturnal urine volume and bladder capacity found in the current study suggests that bladder enlargement may also take place in adults. A high nocturnal urine volume can stretch out the bladder wall, resulting in a gradual increase of bladder capacity. In the present study, 14 (27%) patients had a large bladder capacity. Taken together, in adult renal recipients both too small and too large bladders can be found.

Study limitations include possible selection bias, because all patients were from the same transplantation center and because 30% of the included patients refused to participate. As patients who refuse to participate probably are the least healthy, their exclusion may have led to an underestimation of the symptoms in our study. The higher prevalence of frequency and nocturia found by Zermann et al., points in this direction.[3] Another limitation is that, strictly spoken, no definite causal conclusions can be drawn on

the basis of largely cross-sectional data. Our findings regarding the causes of frequency and nocturia therefore should be considered as preliminary evidence, to be confirmed in further studies using preferably a broader study population and a longitudinal design.

Our results suggest that daytime frequency after renal transplantation is associated with a small bladder capacity, which may be accompanied by bladder pain and dysfunctional voiding. Daytime frequency is also caused by high fluid intake. The presence of UTI's may indirectly lead to frequency by causing urgency and bladder pain. Nocturia is related to a high nocturnal urine volume, and to small bladder capacity, which may be accompanied by dysfunctional voiding. About a quarter of patients has small bladders and another quarter has large bladders, the latter being associated with nocturnal polyuria. Because, previous literature[6,20] shows that both abnormal bladder conditions may impair long-term graft function, we recommend urological follow-up after renal transplantation using frequency/volume charts, especially in patients with daytime frequency and/or nocturia.

References

1. van der Weide MJA, Hilbrands LB, Bemelmans BLH, et al. Lower urinary tract symptoms after renal transplantation. J Urol 2001; 166: 1237-1241.
2. van der Weide MJA, Hilbrands LB, Bemelmans BLH, Kiemeney ALM. Lower urinary tract symptoms after renal transplantation: are there changes over time. Urology 2004; 63: 442-446.
3. Zermann D, Janitzky A, Hohne M, Schubert J. Frequency and nocturia after successful renal transpantation: a normal situation? BJU Int 2005; 97: 555-558.
4. Mizerski A, Ostrowska Clark K, et al. Postoperative adaptation of urinary bladder to variable volume of urine in the initial period following kidney transplantation. Transplant Proc 2003; 35: 2174-2175.
5. Serrano DP, Flechner SM, Modlin CS, et al. Transplantation into the long-term defunctionalized bladder. J Urol 1996; 156: 885-888.
6. Vega PJM, Pascual LA. High-pressure bladder: an underlying factor mediating renal damage in the absence of reflux? BJU Int 2001; 87: 581-584.
7. Mukerji G, Yiangou Y, Agarwal SK, Anand P. Transient receptor potential vanilloid receptor subtype 1 in painful bladder syndrome and its correlation with pain. J Urol 2006; 176: 797-801.
8. Homma Y, Yoshida M, Seki N, et al. Symptom assessment tool for overactive bladder syndrome-overactive bladder symptom score. Urology 2006; 68: 318-323.
9. Yeung CK, Sreedhar B, Leung VT, Metreweli C. Ultrasound bladder measurement in patients with primary nocturnal enuresis: a urodynamic and treatment outcome correlation. J Urol 2004; 171: 2589-2594.
10. McMillan R, Evans DB, Lines JG. Reversed rhythm of kidney transplants. N Engl J Med 1969; 280: 166.
11. Fukuda M, Motokawa M, Miyagi S, et al. Polynocturia in Chronic Kidney Disease is Related to Natriuresis Rather than to Water Diuresis. Nephrol Dial Transplant 2006; 21: 2172-2177.
12. Feinfeld DA, Danovitch GM. Factors affecting urine volume in chronic renal failure. Am J Kidney Dis 1987;10: 231-235.
13. Chuang P, Parikh CR, Langone A. Urinary tract infections after renal transplantation: a retrospective review at two US transplant centers. Clin Transplant 2005; 19: 230–235.
14. Jackson S, Donovan J, Brookes S, Eckford L, Swithinbank L, Abrams P. The Bristol Female Urinary Tract Symptoms questionnaire: development and psychometric testing. Brit J Urol 1996; 77: 805-812.
15. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, Van Kerrebroeck P, Victor A, Wein A. The standardisation of terminology in lower urinary tract function: Report from the standardisation sub-committee of the International Continence Society. Neurourol Urodyn 2002; 21: 167-178.
16. Tanago AE. Urodynamic studies: In: Tanago AE, McAninch JW. Smith's General Urology. New York: Lange Medical Books, 2004: 453-471.
17. Hoyle R. Structural equations modeling. Sage: Thousand Oaks, 1995.
18. Maruyama G. Basics of structural equations modeling. Sage: Thousand Oaks, 1998
19. Kalble T, Lucan M, Nicita G, Sells R, Burgos Revilla FJ, Wiesel M. EAU Guideline on Renal Transplantation. Eur Urol 2005; 47: 156–166.
20. van der Weide MJA, Cornelissen EAM, van Achterberg T, de Gier RPE, Feitz WFJ. Lower urinary tract symptoms after renal transplantation in children. J Urol 2006; 175: 297-302.
21. van der Weide MJA, Cornelissen EAM, van Achterberg T, Smits JPJM, Feitz WFJ. Dysfunction of the lower urinary tract in renal transplant children with nephrological disease. Urology 2006; 67:1060-1065.

Part 2:

Lower Urinary Tract Symptoms after renal transplantation in children

Chapter 5

Lower urinary tract symptoms after renal transplantation in children

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Abstract

Purpose: We investigated the prevalence and nature of LUTS after renal Tx in children. The focus of the study was the presence of LUTS in children without a history of urological symptoms. We also studied the relationship between the characteristics of these patients and the occurrence of LUTS.

Materials and Methods: Data were gathered using a written questionnaire, frequency volume chart, free uroflowmetry, transabdominal ultrasonography and medical records. The study group (30 patients) consisted of 9 children (30%) undergoing renal transplantation with an underlying urological disease and 21 (70%) with an underlying nephrological disease.

Results: In the nephrological group the incidence of high capacity bladder was 75%, residual urine 50%, UTI 43%, hesitancy 38%, intermittent flow 33%, bladder pain 33%, nighttime incontinence 29%, nocturia 24%, feeling of incomplete emptying 15%, daytime incontinence 14%, straining 14%, urgency 10%, burning sensation 10% and intermittency 5%. No substantial difference in the occurrence of LUTS, UTI or high bladder capacity after Tx was found between children with an underlying urological disease and those with an underlying nephrological disease. On average, patients in both groups suffered from 3 different LUTS.

Conclusions: After renal Tx children with a nephrological disease demonstrated a high incidence of LUTS. The occurrence of LUTS combined with UTI and increased bladder capacity indicates that these children are at risk for development of myogenic failure. This finding emphasizes the importance of close urological followup after Tx in children with urological and nephrological disease.

Introduction

Renal transplantation is a common treatment in children with end stage renal disease (ESRD).[1] After transplantation (Tx) it is important that the bladder function normally, because bladder dysfunction may harm the transplanted kidney.[1,2] Research into bladder dysfunction after Tx has concentrated on high risk populations, such as children with posterior urethral valves. Approximately 15% to 25% of children with ESRD have associated structural urological abnormalities that may lead to lower urinary tract dysfunction,[2] including a thick walled bladder as a result of outlet obstruction and a bladder scarred by chronic infection.[3] The affected bladder may lose contractile strength and compliance, and could develop high filling pressures.[4] Therefore, most clinicians assume that children with preexisting urological disease require close care after Tx.

Little information is available about the prevalence of lower urinary tract symptoms (LUTS) after Tx in children without urological disease. However, in adult renal Tx recipients resumption of bladder function after Tx does not always go smoothly.[5,6] In the first year after Tx 49% of patients suffer from frequency and 62% suffer from nocturia. In about two thirds of the patients these symptoms are still present 2 to 3 years later.[5,6] Whether these symptoms also occur in children is unknown. A reason to expect LUTS after Tx in children is that ESRD may lead to polyuria.[7] Because of the high amount of urine produced, these children run the risk of development of a high capacity bladder with little or no sensation of distention and/or over distention of the bladder.[7] Conversely, they may have development of a low capacity bladder.

Before Tx most children require renal replacement therapy (RRT) because the average waiting time for a kidney graft in The Netherlands is 2 years and Tx is not performed until the child weighs at least 12 kg. During RRT the amount of urine produced can still be normal but it can also be strongly decreased, which may result in the development of a low capacity bladder. Polyuria and anuria increase the risk of LUTS after Tx.[8]

To gain more insight into the presence of LUTS after renal Tx in children with nephrological disease, we studied 30 children who received a transplant kidney at our medical center. We sought to answer the questions, What are the prevalence and nature of LUTS after renal Tx in children? Does the occurrence of LUTS after renal Tx differ between children with an underlying urological disease and those with an underlying nephrological disease? Which characteristics in patients with an underlying nephrological disease are related to the occurrence of LUTS after renal Tx?

Methods

Data were gathered from January to May 2003 using a written questionnaire, free uroflowmetry, transabdominal ultrasonography, frequency volume chart and medical records. All 59 pediatric renal recipients who regularly visited our outpatient clinic were asked to participate in the study. Inclusion criteria were the ability to understand the questionnaire, a functioning renal graft and regular visits to the outpatient clinic. One child did not speak Dutch. The remaining 58 children were given information about the project, an informed consent form and a questionnaire. For children younger than 13 years the parents completed the questionnaire. Older children filled out the questionnaire themselves, with the help of the parents if necessary.

Completed questionnaires were returned for 34 children (response rate 59%). Four questionnaires could not be used in the study, of which 2 were from mentally retarded children, 1 was from a child who was not toilet trained and 1 was from a child with a urinary diversion. Of the remaining 30 children 9 had an underlying urological disease and 21 had an underlying nephrological disease.

Free uroflowmetry and post-void residual urine measurements were obtained from 24 children. Of the remaining 6 children 4 refused to complete uroflowmetry and 2 were receiving clean intermittent catheterization. Before flow measurement children were asked to hold the urine for at least 2 hours. When voiding was experienced as unusual, or the amount of voided volume was too low, the flow measurement was repeated. We distinguished 2 flow patterns, namely “continuous flow” and “intermittent flow.”[9] Residual volumes 20 ml or greater were considered abnormal.[10-12]

A completed frequency volume chart was returned for 23 children. Bladder capacity was expressed in relation to normal bladder capacity (NBC) for age,[11] volume = ([age/2] + 6) × 28.35 ± 20%. Because children with renal transplants often have growth retardation,[13,14] we used a standard Dutch growth diagram to determine age corresponding with height to correct for growth retardation. This age was used in the NBC computation. From the medical records we obtained information about patient characteristics and medication.

To determine which characteristics of patients with nephrological disease were related to LUTS, we charted gender, type of RRT, transplant donor, number of transplants, age at Tx, age at data collection, duration of RRT, graft age, nephrectomy and growth retardation. Depending on the measures of the variables involved, Pearson correlations (both continuous), phi coefficients (both dichotomous) and differences among means (1 continuous, 1 dichotomous) were used.

To collect data on LUTS, we used the Bristol Female Lower Urinary Tract Symptoms questionnaire.[15] In this instrument LUTS are defined from the perspective of the patient. Symptoms can be described by either the patient or the caregiver. The definitions of

symptoms associated with lower urinary tract dysfunction used in this instrument can be used in all patient groups, including children.[16] The items in the questionnaire can be divided into 3 categories of storage symptoms, voiding symptoms and post-void symptoms.[16]

We assessed the storage symptoms "daytime frequency" (number of voids during waking hours), "nocturia" (waking up to void 2 or more times), "urgency" (rushing to the toilet to pass urine), "pain in the bladder" and "involuntary leakage of urine during the day and/or night." With regard to voiding symptoms, we assessed "hesitancy" (difficulty initiating voiding resulting in a delay in the onset of voiding after the individual is ready to pass urine), "straining" (the need to use muscular effort to initiate the urinary stream) and "intermittency" (urine flow that stops and starts during voiding). Finally, we assessed the post-void symptoms "feeling of incomplete emptying" and "burning sensation." Questions on sexuality were omitted. For each symptom we asked whether and how often it had occurred in the previous 4 weeks. The answers were 1—never, 2—occasionally, 3—regularly, 4—often and 5—always.15 Since the categories "regularly," "often" and "always" were used infrequently, these categories were combined. In this way the variables were reduced to a 3-point scale with the categories "never," "occasionally" and "regularly to always." We added some items to the questionnaire about the occurrence of urinary tract infection (UTI) since Tx, and about patiënt intellectual faculties.

Results

We gathered information about medical history and demographic characteristics for the 58 children participating in the study. No significant differences were found between the study group and the nonresponse group, indicating the absence of selection bias. Therefore, we considered the study group of 30 children as representative of the population of children with a transplanted kidney at our medical center.

Patient characteristics. Table 1 outlines the characteristics of the total study group (30 patients), and the nephrological (21) and urological (9) subgroups. The total study group consisted of 16 boys and 14 girls. Mean age at data collection was 14 years (range 6 to 19). Of 30 children 9 underwent bilateral nephrectomy and 3 underwent unilateral nephrectomy. Almost all children suffered from growth retardation. Both groups were similar with respect to patient characteristics. In the urological group only 1 child was receiving oxybutynin.

Table 1. The children's characteristics

	Total	Nephrological	Urological
No. gender(%)			
Males	16 (53)	9 (43)	7 (78)
Females	14 (47)	12 (57)	2 (22)
No. Underlying disease (%)			
Haemolytic uremic syndrome	1 (3)	1 (5)	
Glomerulonephritis	8 (27)	8 (38)	
Aplastic and dysplastic kidney	4 (13)	4 (19)	
Hereditary nephropathy	8 (27)	8 (38)	
Pyelonephritis & reflux nephrp.	2 (7)	-	2 (22)
Obstructive uropathy	7 (23)	-	7 (78)
No. Nephrectomy (%)			
No nephrectomy	18 (60)	12 (57)	6 (67)
Unilateral nephrectomy	3 (10)	1 (5)	2 (22)
Bilateral nephrectomy	9 (30)	8 (38)	1 (11)
No. Type of RRT (%)			
None	4 (14)	3 (14)	1 (11)
Peritoneal dialysis	13 (43)	8 (38)	5 (56)
Haemodialysis	13 (43)	10 (48)	3 (33)
No. Transplant donor (%)			
Living related	7 (23)	5 (24)	2 (22)
Post mortal	23 (77)	16 (76)	7 (78)
No. Transplant (%)			
First	25 (83)	18 (86)	7 (78)
Second	3 (10)	2 (9)	1 (11)
Third	2 (7)	1 (5)	1 (11)
Age at Tx (years)			
Range	4 – 16	4 - 16	4 - 14
Mean	10	11	9
Age at study (years)			
Range	6 - 19	6 - 18	9 - 19
Mean	14	13	14
RRT duration (months)[a]			
Range	5 - 47	5 - 47	9 - 42
Mean	19	19	21
Graft age (months)			
Range	5 - 105	5 - 85	11 - 105
Mean	42	34	61
Growth retardation (SD)			
Range	-3.74 +1.36	- 3.74 + 1.36	-2.31 -1.13
Mean	- 1.58	-1.48	-1.80
No. Educational level			
Specialized primary school	6 (20)	5 (24)	1 (11)
General primary school	10 (33)	6 (29)	4 (45)
Secondary school	10 (33)	7 (33)	3 (33)
High school	4 (14)	3 (14)	1 (11)
N	30	21	9

[a] Based on 26 children (18 nephrological and 8 urological) because 4 children had no RRT

The only characteristic that differed significantly was graft age. This finding could be due to a higher graft loss, and, thus, a shorter graft life because of the recurrence of underlying disease in the allograft.

LUTS in nephrological cases. The data obtained from the questionnaire are presented in table 2. Because 2 children performed clean intermittent catheterization after voiding, not all 30 children could answer all questions.

Table 2. LUTS after Tx, BFLUTS questionnaire

Dependent variables	Total	Nephrological	Urological
Urgency			
Never	15 (50)	11 (52)	4 (44.5)
Occasionally	12 (40)	8 (38)	4 (44.5)
Regular to always	3 (10)	2 (10)	1 (11)
Total	30 (100)	21 (100)	9 (100)
Number of voids at day-time			
1 - 3	1 (3)	1 (5)	-
4 - 6	19 (66)	11 (52)	8 (100)
7 - 8	5 (17)	5 (23)	
9 – 10	2 (7)	2 (10)	
≥ 11	2 (7)	2 (10)	
Total	29 (100)	21 (100)	8 (100)
Nocturia			
Never	14 (47)	7 (33)	7 (78)
Once a night	11 (37)	9 (43)	2 (22)
Twice or more often	5 (16)	5 (24)	
Total	30 (100)	21 (100)	9 (100)
Bladder pain			
Never	21 (70)	14 (67)	7 (78)
Occasionally	8 (27)	6 (28)	2 (22)
Regularly to always	1 (3)	1 (5)	
Total	30 (100)	21 (100)	9 (100)
Urinary incontinence daytime			
Yes	4 (13)	3 (14)	1 (11)
No	26 (87)	18 (86)	8 (89)
Total	30 (100)	21 (100)	9 (100)
Urinary incontinence night-time			
Yes	8 (28)	6 (29)	2 (25)
No	21 (72)	15 (71)	6 (75)
Total	29 (100)	21 (100)	8 (100)
No. UTI since Tx			
Never	17 (56)	12 (57)	5 (56)
1	6 (20)	6 (28)	-
2	2 (7)	1 (5)	1 (11)
3 or more	5 (17)	2(10)	3 (33)
Total	30 (100)	21 (100)	9 (100)
Hesitancy			
Never	17 (59)	13 (62)	4 (50)
Occasionally	10 (34)	7 (33)	3 (38)
Regularly to always	2 (7)	1 (5)	1 (12)
Total	29 (100)	21 (100)	8 (100)
Straining			
Never	23 (79)	18 (86)	5 (63)
Occasionally	4 (14)	3 (14)	1 (12)
Regularly to always	2 (7)		2 (25)
Total	29 (100)	21 (100)	8 (100)

Dependent variables	Total	Nephrological	Urological
Intermittency			
Never	25 (89)	20 (95)	5 (71)
Occasionally	2 (7)		2 (29)
Regularly to always	1 (4)	1 (5)	
Total	28 (100)	21 (100)	7 (100)
Sensation of inc. emptying			
Never	24 (80)	18 (85)	6 (67)
Occasionally	5 (17)	2 (10)	3 (33)
Regularly to always	1 (3)	1 (5)	-
Total	30 (100)	21 (100)	9 (100)
Burning feeling after micturition			
Never	26 (90)	19 (90)	7 (88)
Occasionally	3 (10)	2 (10)	1 (12)
Total	29 (100)	21 (100)	8 (100)

Free uroflowmetry and ultrasonography. From the free uroflowmetry and ultrasonography measurements we learned that 9 children (43%) in the nephrological group and 3 (33%) in the urological group had residual urine after voiding 20 ml or more (table 3). Six children (29%) in the nephrological group and 1 (11%) in the urological group had intermittent flow.

Table 3. Free uroflowmetry and ultrasonography

Dependent variable	Total	Nephrological	Urological
Voided vol. + residual urine (ml)	N=24	N=18	N=6
Mean	230	218	264
Range	74 - 457	74 - 457	162 - 361
Residual urine (ml)	N=24	N=18	N=6
Mean	21	22	19
Range	0 - 55	0 - 55	0 - 37
No. of children with res. urine $\geq$ 20 ml.	12 (50%)	9 (50%)	3 (50%)
Flow curve	N=24	N=18	N=6
Continuous	17 (71%)	12 (67%)	5 (83%)
Intermittent	7 (29%)	6 (33%)	1 (17%)

Residual volumes of $\geq$ 20 ml are considered to be clinically significant

Frequency-volume. On average, the children with nephrological disease drank about 2 l fluid and visited the bathroom 7 times per 24 hours (table 4). Urine output per 24 hours varied from 850 to 3,350 ml. Since impaired renal function can result in decreased renal concentrating ability, we analyzed whether urinary output was related to the specific gravity of the urine. No relation was found between urine output and urine specific gravity. The most surprising finding was patient bladder capacity. The maximum voided volume ranged from 300 to 850 ml, with a mean of 528 ml. Of 16 children with nephrological disease 12 (75%) had increased bladder capacity for age. The average bladder capacity, calculated for age with correction for growth retardation, in these 12 children was 175%

(range 135% to 230%). In the urological group 6 of 7 children (86%) had increased bladder capacity, with a mean volume of 207% (range 141% to 285%).

Table 4. Frequency volume charts

Dependent variable	Total	Nephrological	Urological
Maximum voided volumes			
Mean	561	528	636
Range	300 - 950	300 - 850	300 - 950
Fluid intake ml/24 hrs			
Mean	2031	2084	1908
Range	1025 - 3250	1025 - 3250	1300 - 2278
Urinary output ml/24 hrs			
Mean	1820	1811	1841
Range	850 - 3350	850 - 3350	1275 - 2525
No voids /24 hrs** Sig. 0.059			
Mean	7	7	5
Range	3 - 15	3 - 15	4 - 7
No. of children with abnormal frequency ≤ 3 or ≥ 9	6 (26%)	6 (38%)	0 (0)
% Difference from NBC[ab]			
Mean[c]	165%	155%	183%
Range[c]	125% - 260%	126% - 204%	141% - 285%
Number of children with increased BC (>120)	18 (78%)	12 (75%)	6 (86%)
% Difference from NBC[ab] (corr. for growth retardation)			
Mean[c]	185%	175%	207%
Range[c]	135% - 285%	135% - 230%	125% - 260%
Number of children with increased BC (>120)	18 (78%)	12 (75%)	6 (86%)
N	23	16	7

[a] Normal Bladder Capacity (NBC) for age: $V = ((age/2) + 6) * 28.35 \pm 20\%$

[b] Percentage differences from NBC for age: $(BC_{observed} / BC_{for\ age}) * 100\%$

[c] Computed only for children with BC>120

Presence of LUTS. Apart from the mean number of LUTS, the number of LUTS in each individual child is also important. Were the LUTS concentrated in a small group of children who suffered from many symptoms, or did most children suffer from at least some LUTS? Table 5 shows the latter to be the case. The maximum score was 11 symptoms (urgency, daytime frequency 3 voids or less, or 9 or more, nocturia, bladder pain, daytime urinary incontinence, nighttime urinary incontinence, hesitancy, straining, intermittent flow, residual urine and burning feeling). In the nephrological disease group 11 children (52%) had 1 or 2 symptoms, 5 (24%) had 3 or 4 symptoms and 5 (24%) had 5 to 7 symptoms. On average, these patients had 3.0 different symptoms. This rate is about the same as in the urological disease group, where the average patient had 2.6 symptoms.

Relation between LUTS and nephrological disease group characteristics. To identify characteristics that indicate an increased risk of LUTS, the relationship between LUTS and patient characteristics in the nephrological disease group were analyzed. For reasons of clarity only significant effects are presented. Given the exploratory nature of this study,

these significance coefficients are considered indications that the effects are worthy of in-depth study in the future.

Table 5 Presence of symptoms in the children

Number of LUTS	Total	Nephrological	Urological
0	1 (3)	-	1 (11)
1	7 (23)	6 (29)	1 (11)
2	9 (30)	5 (24)	4 (44)
3	3 (10)	3 (14)	-
4	3 (10)	2 (10)	1 (11)
5	4 (13)	2 (10)	2 (22)
6	2 (7)	2 (10)	-
7	1 (3)	1 (5)	-
Total	30 (100)	21 (100)	9 (100)
Mean	2.83	2.95	2.56

Hemodialysis positively correlated with intermittent flow (table 6). Duration of RRT positively related to UTI. Age at Tx negatively correlated with frequency, daytime urinary incontinence, nighttime incontinence and residual urine, and positively correlated with bladder capacity. Age at data collection negatively correlated with urgency, bladder pain, daytime incontinence and nighttime incontinence, and positively correlated with bladder capacity. Graft age negatively correlated with urgency and bladder pain. Nephrectomy negatively correlated with hesitancy and positively correlated with intermittent flow curve.

Table 6. Association between childrens characteristics and LUTS for the Nephrological group (P-value between bracelets)[a]

	Children's characteristics					
	RRT = Haemodialysis	Duration of RRT	Age at Tx	Age at data collection	Graft age	Nephrectomy
Urgency	-	-	-	-.487[b] (0.025)	-.471[b] (0.031)	
Frequency/24 hrs	-	-	-.529[b] (0.035)	-		
Bladder pain	-	-	-	-.512[b] (0.018)	-.531[b] (0.013)	
Urinary Inc. daytime	-	-	- 4.56[d] (0.030)	-5.70[d] (0.003)		
Urinary Inc. night-time	-	-	-3.73[d] (0.021)	-3.62[d] (0.020)		
Hesitancy	-	-	-	-	-	-.533[c] 0.017
UTI	-	.793[b] (0.000)	-	-		
Residual urine	-	-	-.528[b] (0.020)	-		
Intermittent flow curve	.553[c] (0.019)	-	-	-		.485[c] 0.046
Bladder capacity	-	-	.553[b] (0.026)	.591[b] (0.016)		

[a] Only significant coefficients are presented
[b] Pearson coefficient
[c] Phi coefficient
[d] Differences among means

Discussion

We studied 30 cases of ESRD, of which 21 were due to nephrological disease. After renal Tx children with nephrological disease exhibited a high incidence of LUTS and UTI. Similar to the children with urological disease, these patients suffered from dysfunction of the lower urinary tract. Several studies have revealed that in boys with posterior urethral valves bladder capacity tends to increase, which may lead to myogenic failure.[4,9,17] This result is in line with our finding that 86% of the children with urological disease suffered from increased bladder capacity (mean 207%). More surprisingly, our results make clear that the large majority of children with nephrological disease (75%) also have increased bladder capacity (mean 175%). This finding suggests that, similar to the urological group, children with nephrological disease run the risk of myogenic failure developing.

With respect to the relationship between patient characteristics and LUTS, we found that the longer the graft is in situ, the less urgency and bladder pain are experienced. This finding might mean that bladder sensation decreases with time, which is in line with the finding that bladder overcapacity increases with age.

We also found that children who underwent hemodialysis had a higher incidence of intermittent flow, and those who underwent prolonged RRT had a higher incidence of UTI. Children who underwent bilateral nephrectomy had a higher rate of intermittent flow but less hesitancy. These findings indicate that LUTS might be related to circumstances existing before Tx, such as polyuria or anuria due to damaged renal function.[4]

Given the exploratory nature of this study, no definite conclusions can be drawn regarding the relationship between patient characteristics and LUTS. The causes of LUTS after Tx in children with nephrological disease remain unclear. Still, our findings suggest that it might be worthwhile to study the usefulness of these characteristics as predictive indicators for bladder dysfunction after Tx in a larger series.

Conclusions

After Tx most children with nephrological disease have a dysfunctional lower urinary tract along with a substantially increased bladder capacity and UTI. This finding indicates that nephrological cases require urological followup similar to cases involving urological disease. After Tx when the indwelling catheter is removed the child should begin to void normally again. However, since the urethra is often irritated, passing urine can be painful, which is a bad start to restoring normal voiding habits. To prevent dysfunctional voiding and increase bladder capacity, therapy should consist of restoring normal voiding habits and voiding training. Training should start immediately after Tx when the indwelling catheter is removed.

References

1. Morris PJ. Kidney transplantation, principles and practice. 4th ed. Philadelphia: W. B. Saunders Co., p. xv, 1994.
2. Koo HP, Bunchman TE, Flynn JT, Punch JD, Schwartz AC, Bloom DA. Renal transplantation in children with severe lower urinary tract dysfunction. J Urol 1999; 161: 240.
3. Rudge CJ. Transplantation and the abnormal bladder. In: Kidney Transplantation, Principles and Practice. Edited by PJ Morris. Philadelphia: W. B. Saunders Co., 1994: 138–148.
4. Lopez Pereira P, Martinez Urrutia MJ, Espinosa L, Lobato R, Navarro M, Jaureguizar E. Bladder dysfunction as a prognostic factor in patients with posterior urethral valves. BJU Int 2002; 90: 308.
5. van der Weide MJA, Hilbrands LB, Bemelmans BLH, Meuleman EJH, Frederiks CMA. Lower urinary tract symptoms after renal transplantation. J Urol 2001; 166: 1237-1241.
6. van der Weide MJ, Hilbrands LB, Bemelmans BL, Kiemeney LA. Lower urinary tract symptoms after renal transplantation: are there changes over time. Urology 2004; 63: 442-446.
7. Montane B, Abitbol C, Seeherunvong W, Chandar J, Strauss J, Gonzalez R, et al. Beneficial effects of continuous overnight catheter drainage in children with polyuric renal failure. BJU Int 2003; 92: 447.
8. Errando C, Batista JE, Caparros J, Vicente J, Arano P. Urodynamic evaluation and management prior to renal transplantation. Eur Urol 2000; 38: 415-418.
9. Misseri R, Combs AJ, Horowitz M, Donohoe JM, Glassberg KI. Myogenic failure in posterior urethral valve disease: real or imagined? J Urol 2002; 168: 1844-1848.
10. Hellstrom AL, Hanson E, Hansson S, Hjalmas K, Jodal U. Micturition habits and incontinence in 7-year-old Swedish school entrants. Eur J Pediatr 1990; 149: 434-437.
11. Norgaard JP, van Gool JD, Hjalmas K, Djurhuus JC, Hellstrom AL. Standardization and definitions in lower urinary tract dysfunction in children. International Children's Continence Society. Br J Urol 1998; 81(suppl. 3): 1-16.
12. Wen JG, Tong EC. Cystometry in infants and children with no apparent voiding symptoms. Br J Urol 1998; 81: 468-473.
13. Aschendorff C, Offner G, Winkler L, Schirg E, Hoyer PE, Brodehl J. Adult height achieved in children after kidney transplantation. Am J Dis Child 1990; 144: 1138-1141.
14. Kaefer M, Zurakowski D, Bauer SB, Retik AB, Peters CA, Atala A, et al. Estimating normal bladder capacity in children. J Urol 1997; 158: 2261-2264.
15. Jackson S, Donovan J, Brookes S, Eckford L, Swithinbank L, Abrams P. The Bristol Female Lower Urinary Tract Symptoms questionnaire: development and psychometric testing. Br J Urol 1996; 77: 805-812.
16. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Subcommittee of the International Continence Society. Neurourol Urodyn 2002; 21: 167-178.
17. De Gennaro M, Capitanucci ML, Mosiello G, Caione P, Silveri M. The changing urodynamic pattern from infancy to adolescence in boys with posterior urethral valves. BJU Int 2000; 85: 1104.

Chapter 6

Dysfunction of lower urinary tract in renal transplant children with nephrologic disease

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Abstract

Objectives. To investigate the relationship between dysfunction of the lower urinary tract after renal transplantation and renal transplant function in children with an underlying nephrologic disease.

Methods. The research group consisted of 21 renal transplant children (12 girls and 9 boys, mean age 13.5 years, range 6 to 18) with an underlying nephrologic disease. To indicate renal transplant function, the calculated creatinine clearance rate (Ccr) according to Schwartz was used. The Ccr was measured at two points, 2 months after transplantation and at the moment of study. The average graft age was 34 months (range 5 to 85). The data on dysfunction of the lower urinary tract were gathered using a written questionnaire, frequency volume chart, free uroflowmetry, transabdominal ultrasonography, and medical records. To determine the relationship between the symptoms of dysfunction of the lower urinary tract and Ccr at the moment of study, we computed bivariate correlations and performed multivariate regression analyses in which the associations were studied while controlling for the Ccr 2 months after transplantation and graft age.

Results. A sensation of incomplete emptying (P=0.03), postvoid residual urine volume (P=0.06), and urinary tract infection (P=0.004) correlated negatively with the Ccr at the moment of study. These effects remained present (P=0.07, P=0.03, and P=0.003, respectively) while controlling for graft age and the Ccr at 2 months after transplantation in the regression analysis.

Conclusions. The results of our study have shown that a postvoid residual urine volume and urinary tract infections after renal transplantation may result in renal transplant deterioration in children with an underlying nephrologic disease.

Several studies have indicated that bladder dysfunction after renal transplantation may have a negative effect onthe transplanted kidney.[1–5] Parkhouse et al.[1] reported a relation between continuing bladder dysfunction in boys (n=114) treated for posterior urethral valves and a poor long-term renal function outcome. Salomon et al.,[2] Groenewegen et al.,[3] and Ghanem et al.[4] also showed that boys with posterior urethral valves and a voiding disorder are at risk of renal function deterioration.

Luke et al.,[5] comparing the long-term outcomes of graft survival between children with a dysfunctional lower urinary tract (n=20) and children with a normal lower urinary tract (n=61), found that lower urinary tract pressure plays an important role in graft survival. Together, the results of these studies indicate that two deciding factors affect renal transplant deterioration in urologic high-risk populations such as children with posterior urethral valves: high pressure in the lower urinary tract and voiding disorder.

Concerning the effects of bladder dysfunction on renal transplant function in nonurologic populations much less is known. Some studies have been done on the effect of urinary tract infection (UTI) after renal transplantation on transplant deterioration in more extensive populations. However, the clinical relevance of UTI occurring after renal transplantation for transplant functioning is still under debate. Lyerova et al.,[6] Mueller et al.,[7] and Takai et al.[8] concluded that UTI after renal transplantation was a benign complication. Conversely, Abbot et al.[9] and Chuang et al.[10] found that UTIs after renal transplantation in a general population were significantly associated with an increased risk of death.

In an earlier study on lower urinary tract symptoms (LUTS) in pediatric renal transplant recipients, we found that not only children with an underlying urologic disease, but also children with an underlying nephrologic disease, may have a dysfunctional lower urinary tract, along with an increased bladder capacity and UTI.[11] The objective of the present study was to investigate to what extent such a dysfunctional lower urinary tract after renal transplantation in children with an underlying nephrologic disease could result in renal transplant deterioration. To reach this aim, we studied the relationship between symptoms of dysfunction of the lower urinary tract after transplantation and renal transplant function, as measured by the calculated creatinine clearance rate (Ccr), in 21 renal transplant children with an underlying nephrologic disease.[12]

Material and methods

With permission of the Medical Ethics Committee of Radboud University Nijmegen, data were gathered from January to May 2003 using a written questionnaire, free uroflowmetry, transabdominal ultrasonography, frequency volume chart, and the children's medical records. The questionnaire we used was based on the Bristol Female Lower Urinary Tract

Symptoms questionnaire.[11,13] In this instrument, LUTS are defined from the patient's perspective. The patient or the caregiver can describe the symptoms. The definitions of symptoms associated with lower urinary tract dysfunction, questioned in this instrument, can be used with all patient groups, including children.[14] The items in the questionnaire can be divided into three categories: storage, voiding, and postmicturition symptoms. The inclusion criteria for participants were being able to understand the questionnaire, a functioning renal graft, regular visits to our outpatient clinic, and being toilet trained.

Excluded were children with a urinary diversion. A group of 54 children at our center satisfied the inclusion and exclusion criteria. Completed questionnaires were returned for 30 children (56% response rate). Because the present study focused on transplant children with an underlying nephrologic disease, we excluded 9 children who had an underlying urologic disease. The study group therefore consisted of 21 children (9 boys and 12 girls). The mean age at data collection was 13.5 years (range 6 to 18). The children were given information about the project, an informed consent form, and a questionnaire.

For children younger than 13 years old, the parents completed the questionnaire. Older children filled out the questionnaire themselves, with the help of their parents if necessary. Free uroflowmetry and postvoid residual (PVR) urine volume measurements were obtained from 18 children; 3 refused to comply with uroflowmetry. Before the flow measurement, the children were asked to hold their urine for at least 2 hours. When the micturition was experienced as unusual, or the amount of voided volume was too small, the flow measurement was repeated. We distinguished two flow patterns: continuous flow and intermittent flow.[15] In the descriptive analysis, PVR volumes of 20 mL or greater were considered abnormal.[16–18]

A completed frequency volume chart was returned for 16 children. The bladder capacity was expressed in relation to the normal bladder capacity (NBC) for age.[17] The normal bladder capacity for age was determined as follows: $V = [(age/2)+6] \times 28.35$; $NBC = V \pm 20\%$. Because renal transplant children often have growth retardation,[19,20] we used a standard Dutch growth diagram to determine the age that would correspond with the child's height to correct for growth retardation. This age was used in the normal bladder capacity computation. From the medical records, we obtained information about the children's characteristics, medication, and the number of UTIs treated since transplantation. To indicate transplant function, the calculated creatinine clearance rate (Ccr) according to the Swartz formula was used.[12] The children's serum creatinine levels and body length were obtained at two points: 2 months after renal transplant and the time of study.

To determine whether the children were able to maintain a steady state of renal graft function, the Ccr tendency between these two points was calculated. Steady Ccr values in

children actually indicate that graft function does adapt to an increasing demand during growth.[21]

To determine the effects of the different LUTS on renal graft function, both bivariate and multivariate analyses were performed.

For the bivariate associations, depending on the measurement level of the variables involved, Pearson correlations (both variables continuous) and *t* tests for differences among mean values (one continuous and one dichotomous variable) were used. Correlations were only computed for symptoms found in a minimum of 3 children. Given the explorative nature of the study and the restricted number of respondents, all effects significant at P=0.1 were considered to be of potential interest. Thus, we reduced the risk of missing factors that might be potentially harmful for transplant functioning in children. Effects that are only significant at P=0.1 and not at P=0.05 are considered "marginally" significant. For the LUTS that showed significant effects in the bivariate analysis, multiple ordinary least squares (OLS) regression analyses were performed to test whether the effects remained intact when controlling for graft age and initial transplant function (Ccr 2 months after transplantation).

Results

Characteristics

Table 1 shows the characteristics of the study group (n=21). Eight children underwent bilateral nephrectomy and one unilateral nephrectomy. Three children underwent preemptive transplantation and therefore did not need renal replacement therapy. Eight children underwent peritoneal dialysis and 10 children hemodialysis before renal transplantation. Five children received their transplant from a living, related donor and 16 children from a postmortem donor. The mean age at transplantation was 10.6 years (range 4 to 16). The 18 children who needed renal replacement therapy before transplantation required it for an average of 19 months (range 5 to 47). At study, the graft age was on average 34 months (range 5 to 85). Almost all children had growth retardation; the mean standard deviation score was -1.48 (range -3.74 to +1.36). With respect to graft function, the mean Ccr 2 months after renal transplantation was 61 (range 32 to 83). At study, the mean Ccr was 64 (range 26 to 92). In 13 children, the Ccr was increasing and in 8 children, it was decreasing.

Table 1. Characteristics of the study group

	No children (%)
Sex	
Male	9 (43)
Female	12 (57)
Underlying disease	
Haemolytic uremic syndrome	1 (5)
Glomerulonephritis	8 (38)
Aplastic and dysplastic kidney	4 (19)
Hereditary nephropathy	8 (38)
Nephrectomy	
None	12 (57)
Unilateral	1(5)
Bilateral	8 (38)
RRT	
None	3 (14)
Peritoneal dialysis	8 (38)
Haemodialysis	10 (48)
RRT duration (months)[a]	
Range	5 - 47
Mean	19
Transplant	
First	18 (86)
Second	2 (9)
Third	1 (5)
Transplant donor	
Living related	5 (24)
Post mortem	16 (76)
Age at Transplant (years)	
Range	4 - 16
Mean	10.6
Age at measurement	
Range	6 - 18
Mean	13.5
Graft age (months)	
Range	5 - 85
Mean	34
Growth retardation (SDS)	
Range	-3.74 +1.36
Mean	-1.48
Calculated creatinine clearance rate (Ccr)	
2 months after transplantation	
Range	32 - 83
Mean	61
At study	
Range	26 - 92
Mean	64
Tendency after transplantation	
Increasing	13
Decreasing	8
Total (n)	21

LUTS and renal transplant function

The signs and symptoms of dysfunction of the lower urinary tract of the study group are shown in Table 2. Table 2 also shows the association between signs and symptoms of

dysfunction of the lower urinary tract and Ccr at measurement. Only 3 of the 16 symptoms had a significant association with renal transplant function. The presence of UTI after transplantation was strongly negatively correlated with the Ccr (P=0.004). Children who occasionally to always experienced a sensation of incomplete emptying had a lower Ccr (P=0.03). The presence of PVR urine volume as measured by ultrasonography showed a marginally significant negative correlation with Ccr (P=0.06).

To gain insight into the interrelationship among these three factors, we studied their bivariate associations. For UTI and PVR urine volume, a (marginally) significant positive correlation of 0.46 (P=0.06) was found. The other two associations among the three variables were not significant.

Table 2. Symptoms of dysfunction of the lower urinary tract and correlations of these symptoms with creatinine clearance rate at time of study (Ccr)

Symptoms of dysfunction	No of patients (%)	Correlation with Ccr (p-value)
Urgency		
Never	11 (52)	
Occasionally	8 (38)	-.032[a] (0.89)
Regularly to always	2 (10)	
Voids at day-time (n)		
1 - 3	1 (5)	
4 - 6	11 (52)	
7 - 8	5 (23)	.056[a] (0.81)
9 - 10	2 (10)	
≥ 11	2 (10)	
Nocturia		
Never	7 (33)	
Once a night	9 (43)	.008[a] (0.97)
Twice or more often	5 (24)	
Bladder pain		
Never	14 (67)	9.31[b] (0.30)
Occasionally to always	7 (33)	
Urinary incontinence daytime		
Yes	3 (14)	0.42[b] (0.97)
No	18 (86)	
Urinary incontinence night-time		
Yes	6 (29)	11.61[b] (0.22)
No	15 (71)	
Hesitancy		
Never	13 (62)	13.65[b] (0.11)
Occasionally to always	8 (38)	
Straining		
Never	18 (86)	
Occasionally	3 (14)	.021[a] (0.93)
Regularly to always		
Intermittency		
Never	20 (95)	
Occasionally		n.a.
Regularly to always	1 (5)	

Symptoms of dysfunction	No of patients (%)	Correlation with Ccr (p-value)
Sensation of incomplete emptying		
Never	18 (85)	24.81[b] (0.03)**
Occasionally to always	3 (15)	
Burning feeling after micturition		
Never	19 (90)	
Occasionally	2 (10)	n.a.
UTI since transplantation		
0	11 (52)	
1	7 (33)	-.602[a] (0.004)**
2,3	1 (5)	
4 and more	2 (10)	
Flow curve (N=18)		
Continuous	12 (67)	1.051[b] (0.31)
Intermittent	6 (33)	
PVR urine volume (mL) (N=18)		
Mean	22	
Range	0 – 55	-.456[a] (0.06)*
No. of children with res. urine $\geq$ 20 ml.	9 (50%)	
Number of voids 24 hrs (N=16)		
Mean	7	
Range	3 - 15	.064[a] (0.81)
No. of children with frequency $\leq$3 or $\geq$ 9	6 (38%)	
Bladder capacity[cd] (corr. for growth retardation) (N=16)		
Mean[e]	175%	
Range[e]	135% - 230%	.072[a] (0.79)
Children with increased BC (>120 mL)	12 (75%)	

[a] Pearson correlation * p< 0.1 ** p < 0.05; [b] T-test for differences among means; [c] Normal Bladder Capacity (NBC) for age: V = ((age/2) +6) * 28.35 $\pm$ 20% ; [d] Bladder Capacity BC : ($BC_{observed}$ / $NBC_{for\ age}$) * 100%
[e] Computed only for children with BC>120; n.a. Too few children with symptoms to compute correlations

Multivariate analysis

After transplantation, graft function is known to deteriorate with time. Also, the number of symptoms experienced since transplantation can be expected to be greater if the time since transplantation is longer. Consequently, the associations found in the bivariate analyses might be spurious effects caused by differences in the time since transplantation among the patients. To test for this possibility, it is necessary to control for graft age in the analysis. Another problem with the bivariate analysis was that patients with a low Ccr at study may have had a low Ccr directly after transplantation. If so, the relationship between LUTS and Ccr could not be a causal effect of the LUTS on renal transplant function. Therefore, it is also important to control for Ccr directly after transplantation.

To determine whether the significant effects found in the bivariate analyses remained intact while controlling for these potentially confounding factors, we performed three multivariate OLS regression analyses with Ccr at study as the dependent variable and besides the symptoms, also graft age and Ccr 2 months after transplantation as independent variables. The results of these analyses are presented in Table 3.

The data in Table 3 demonstrate that the effects found in the bivariate analyses were not spurious effects caused by differences in graft age or an initial low Ccr. All three symptoms that had a negative association with Ccr at study—a sensation of incomplete emptying, presence of UTI, and PVR urine volume—kept this effect on the multivariate analysis (P=0.07, *P*=0.003, and P=0.03 respectively).

Table 3. Multivariate OLS regression coefficients (B) with p-values for models with Ccr at time of study as dependent variable and one of three LUTS as independent variables and graft age and Ccr at transplantation as control factors

	Model I		**Model II**		**Model III**	
	B	p-value	B	p-value	B	p-value
Intercept	58.90	0.02**	50.82	0.01**	41.79	0.05*
Sensation of incomplete emptying	**-12.52**	**0.07***				
Presence of UTI			**-11.59**	**0.003****		
Residual urine					**-0.57**	**0.03****
Graft age	-0.28	0.21	-0.12	0.47	0.22	0.32
Ccr at transplantation	0.29	0.32	0.42	0.08*	0.46	0.10
Adj R^2	0.21		0.43		0.24	
N	21		21		18	

* p<0.1 ** p<0.05

Comment

We studied the effects of dysfunction of the lower urinary tract on transplant function in renal transplant children with an underlying nephrologic disease. We found substantial negative relationships between the Ccr at study and PVR urine volume, sensation of incomplete emptying, and UTI. To determine whether these associations were not just an effect of graft age or an initial low Ccr, OLS regression analyses were performed. Our results have made clear that both PVR urine volume (P=0.03) and UTI (P=0.003) are significantly and independently related to the Ccr at study. The effect of a sensation of incomplete emptying was marginally significant (P=0.07) in the multivariate analysis.

The negative effect of UTI on renal transplant function is in line with the studies by Abbot et al.[9] and Chuang et al.[10] about UTI after renal transplantation in the United States. It indicates that the conclusion of Lyerova et al.,[6] Mueller et al.,[7] and Takai et al.[8] that UTIs after renal transplantation are benign complications should be considered with care.

The negative effect of a sensation of incomplete emptying was only marginally significant and was based on a few cases. However, it points in the same direction as the PVR urine effect: incomplete emptying of the bladder may affect the function of the renal transplant negatively. The presence of PVR urine may be due to vesicoureteral reflux or dysfunctional voiding. In postmortem donors, the ureter is reimplanted in a transvesical way with no antireflux technique. From experience, we know that in 50% of the patients grade 1 to 2 reflux exists. In living-related donor procedures, a Lich-Gregoir antireflux

reimplantation is performed in the dome of the bladder. In the case of reflux, the renal transplant may be directly harmed by the urine, which flows back. In the case of dysfunctional voiding, no direct risk to the renal transplant is present. However, in both cases, the presence of PVR urine increases the risk of developing UTI, as has been documented in several studies[22–24] (and is also suggested by the marginally significant positive association between PVR urine volume and UTI), which according to our findings, might also be harmful to the renal transplant.

In renal transplant children prone to developing voiding disorders and UTIs, it is recommended to start micturition training after renal transplantation. This is a noninvasive therapy that aims at preventing PVR urine volumes and UTIs by teaching the children adequate voiding habits. To minimize PVR urine volumes, it is important that the child performs double voiding to effectuate an empty bladder after micturition at least twice a day. Given the explorative nature of this study, the relatively small sample size, and that part of the symptoms was only measured at the time of study, the results should be treated with care. Strictly speaking, no conclusions in terms of causal relationships can be drawn. Although we controlled for the initial Ccr, and the associations between PVR urine volume, UTI, and transplant function seemed rather robust, the possibility remains that these associations were caused by the influence of unmeasured other factors. Also, for some of the LUTS, no reliable association with Ccr could be established, because too few children had the symptoms. Thus, although for these LUTS no relationship with transplant function was established, it cannot be concluded that such a relationship does not exist. It is therefore important that our results are validated in a (preferably) prospective study using a larger group of children.

Conclusions

A PVR urine volume and UTIs after renal transplantation may result in renal transplant deterioration in children with an underlying nephrologic disease.

References

1. Parkhouse HF, Barratt TM, Dillon MJ, et al. Long-term outcome of boys with posterior urethral valves. Br J Urol 1988; 62: 59–62.
2. Salomon L, Fontaine E, Guest G, et al. Role of the bladder in delayed failure of kidney transplants in boys with posterior urethral valves. J Urol 2000; 163: 1282–1285.
3. Groenewegen AA, Sukhai RN, Nauta J, et al. Results of renal transplantation in boys treated for posterior urethral valves. J Urol 1993; 149: 1517–1520.
4. Ghanem MA, Wolffenbuttel KP, de Vylder A, et al. Long-term bladder dysfunction and renal function in boys with posterior urethral valves based on urodynamic findings. J Urol 2004; 171: 2409–2412.
5. Luke PPW, Herz DB, Bellinger MF, et al. Long term results of pediatric renal transplantation into a dysfunctional lower urinary tract. Transplantation 2003; 76: 1578–1582.
6. Lyerova L, Lacha J, Skibova J, et al. Urinary tract infection in patients with urological complications after renal transplantation with respect to long-term function and allograft survival. Ann Transplant 2001; 6: 19–20.
7. Mueller T, Resinger C, Ruffingshofer D, et al. Urinary tract infections beyond the early post-transplant period in pediatric renal graft recipients. Wien Klin Wochenschr 2003; 115: 385–388.
8. Takai K, Aoki A, Suga A, et al. Urinary tract infections following renal transplantation. Transplant Proc 1998; 30: 3140–3141.
9. Abbot KC, Swanson J, Richter ER, et al. Late urinary tract infection after renal transplantation in the United States. Am J Kidney Dis 2004; 44: 353–362.
10. Chuang P, Parikh CR, Langone A. Urinary tract infections after renal transplantation: a retrospective review at two US transplant centers. Clin Transplant 2005; 19: 230–235.
11. Van der Weide MJA, Van Achterberg T, Cornelissen EAM, et al. Lower urinary tract symptoms after renal transplantation in children. J Urol 2006; 175: 297–302.
12. Schwartz GJ, Haycock GB, Edelmann CM, et al. A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. Pediatrics 1976; 58: 259–263.
13. Jackson S, Donovan J, Brookes S, et al. The Bristol Female Urinary Tract Symptoms questionnaire: development and psychometric testing. Br J Urol 1996; 77: 805–812.
14. Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology in lower urinary tract function: report from the Standardisation Sub-Committee of the International Continence Society. Neurourol Urodyn 2002; 21: 167–178.
15. Misseri R, Combs AJ, Horowitz M, et al. Myogenic failure in posterior urethral valve disease: real or imagined? J Urol 2002; 168: 1844–1848.
16. Hellstrom AL, Hanson E, Hansson S, et al. Micturition habits and incontinence in 7-year-old Swedish school entrants. Eur J Pediatr 1990; 149: 434–437.
17. Norgaard JP, Van Gool JD, Hjalmas K, et al. Standardization and definitions in lower urinary tract dysfunction in children. Br J Urol 1998; 81(suppl 3): 1–16.
18. Wen JG, Tong EC. Cystometry in infants and children with no apparent voiding symptoms. Br J Urol 1998; 81: 468–473.
19. Aschendorff C, Offner G, Winkler L, et al. Adult height achieved in children after kidney transplantation. Am J Dis Child 1990; 144: 1138–1141.
20. Kaefer M, Zurakowski D, Bauer SB, et al. Estimating normal bladder capacity in children. J Urol 1997; 158: 2261–2264.
21. Dubourg L, Cochat P, Hadj-Aissa A, et al. Better longterm functional adaptation to the child's size with pediatric compared to adult kidney donors. Kidney Int 2002; 62: 1454–1460.
22. Hoebeke P, Van Laecke E, Van Camp C, et al. One thousand video-urodynamic studies in children with nonneurogenic bladder sphincter dysfunction. Br J Urol 2001; 87: 575–580.
23. Twaij M. Urinary tract infection in children: a review of its pathogenesis and risk factors. J R Soc Health 2000; 120: 220–226.
24. Shaikh N, Abedin S, Docimo SG. Can ultrasonography or uroflowmetry predict which children with voiding dysfunction will have recurrent urinary tract infections? J Urol 2005; 174: 1620–1622.

Chapter 7

Conclusions and discussion

Because little was known about the prevalence and nature of lower urinary tract dysfunction after renal transplantation, a research program was set up to study lower urinary tract symptoms (LUTS) in pediatric and adult renal transplant recipients. A literature study revealed that there are three important issues concerning the function of the lower urinary tract before, and after renal transplantation. First, there are no comprehensive data available about bladder function after renal transplantation in the general population of renal recipients. Second, there is a lack of indicators that can predict bladder dysfunction after renal transplantation. Third, little is known about the effects of bladder dysfunction on renal graft function in non-urological renal recipients. In our program, these issues were addressed by conducting five studies, the results of which were presented in the preceding chapters of this thesis. In these studies, we aimed to get an answer to the following five research questions:

1. What is the prevalence and nature of LUTS after renal transplantation in adults?
2. What are the causes of frequency and nocturia after renal transplantation in adults?
3. What is the prevalence and nature of LUTS after renal transplantation in children?
4. What are the causes of LUTS after renal transplantation in children?
5. What are the consequences of LUTS for the function of the renal graft?

To answer these questions, four rounds of data collecting took place, in which three different groups of renal recipients were studied, two groups of adults and one group of children. In the following sections, the five studies conducted on the basis of these data are briefly summarized. Furthermore, some general conclusions are drawn and the shortcomings of the research are discussed. Finally, the implications of the findings for clinical practice are addressed and some directions for further research are suggested.

Lower urinary tract dysfunction in adults

The first study in adults, was an explorative study on the prevalence and nature of lower urinary tract symptoms after renal transplantation. The results showed that patients with transplants needed to void significantly more often than controls both during the day and at night. In half of the patients (49%) we found a daytime voiding frequency of 7 times or more often. At night 62% of the patients with transplants needed to void 2 times or more often. Major finding of this study was that the reservoir function of the bladder might be impaired after renal transplantation.

The objective of the second study in adults, was to determine whether LUTS after renal transplantation changed over time. Major finding of this study was that frequency and nocturia in renal recipients are rather persistent phenomena. Furthermore, we concluded that the decrease in urgency might indicate that bladder sensation decreases over time.

The objective of the third study in adults, was to gain insight into the possible causes of frequency and nocturia. Major finding of this study was that daytime frequency after renal transplantation is associated with a small bladder capacity, which may be accompanied by bladder pain and dysfunctional voiding. Daytime frequency is also caused by high fluid intake. The presence of UTI's may indirectly lead to frequency by causing urgency and bladder pain. Nocturia is related to a high nocturnal urine volume, and to a small bladder capacity, which may be accompanied by dysfunctional voiding. About a quarter of patients has small bladders and another quarter has large bladders, the latter being associated with nocturnal polyuria.

Lower urinary tract dysfunction in children

The objective of our first paediatric study was to determine the prevalence and nature of LUTS after renal transplantation in children. Major finding of this study was that, children with either urological or nephrological causes of renal failure run the risk to develop myogenic failure due to increased bladder capacity. About half of the children had post void residual, UTI's, and a decrease of bladder sensation. Moreover we found that circumstances existing before transplatation, such as polyuria or anuria due to disturbed renal function might cause LUTS after transplantation.

The objective of the second paediatric study was to find out whether and to what extent LUTS, UTI's, and bladder capacity were risk factors for renal graft dysfunction in children with an underlying nephrological disease. The conclusion of this study was that PVR and UTI's may negatively affect renal graft function.

General conclusions

Taken together, the results of the five studies make clear that there is a high incidence of LUTS in renal transplant patients. In adult patients, the LUTS take the form of a high incidence of frequency and nocturia. In pediatric patients, the incidence of all LUTS is high and the majority of patients suffers from several LUTS. The symptoms are not restricted to patients with an urological background, where LUTS can be expected; they are also present in patients who underwent renal transplantation because of an underlying nephrological disease.

With respect to the lack of data about bladder function after renal transplantation, our studies are a major step forward. In the adult studies, there were three rounds of data collection, in which data for two different groups of renal recipients were gathered. With respect to the occurrence of frequency and nocturia the results for the groups were similar. Moreover, recently these finding were confirmed by Zermann et al. who studied 150 renal transplant patients and found frequency in 87% and nocturia in 93% of the patients.[1]

In our pediatric population, one round of data collection took place. Because data were not only gathered by the written questionnaire, but also by frequency/volume charts, free uroflowmetry, transabdominal ultrasonography, and medical records, the conclusions about bladder capacity, bladder evacuation, and urinary tract infections were based on the best non-invasive available methods. Importantly, we gathered information on children with an underlying nephrological disease as well as on children with an urological disease. Data on the function of the lower urinary tract after renal transplantation in a non high-risk population are now available. Whether these results are representative for all nephrological pediatric renal transplant patients should be confirmed in a larger group of children.

Regarding the second of the three issues addressed in our program, the lack of predicting factors for bladder function after renal transplantation, we studied for adult patients the effects of the type of renal replacement therapy, duration of dialysis treatment, the urine volume before transplantation, and the number of former transplants. However, no relationships were found between these indicators and the occurrence of LUTS after transplantation. It is possible that this negative result is due to the relatively small sample size of the study. Therefore, it cannot be definitively concluded from our findings that such relationships do not exist.

To find predicting factors for children, the effects of the underlying disease, nephrectomy, the type of renal replacement therapy, the time on dialysis, the type of donor, growth retardation, education level, and number of former transplants were studied. Of these factors, hemodialysis, the time on dialysis, and bilateral nephrectomy were related to LUTS. These findings indicate that bladder dysfunction after transplantation in children might be related to circumstances existing before transplantation, such as anuria or polyuria due to disturbed renal function.

With respect to the effect of bladder dysfunction on renal graft function in pediatric renal recipients, our findings indicated that post void residual urine and urinary tract infection after renal transplantation might lead to renal transplant deterioration. The significance of these findings were emphasized in an editorial comment on our paper, by the editor of Urology, who referred to the U.S. Renal Data System: USRDS 2005,[2] and commented that the incidence of urinary tract infections especially in children is a major problem, and that the long-term graft survival rates in children have not improved over the last decade.[3] The editor underlined the importance of urological follow-up after renal transplantation in children. Concerning the effects of bladder dysfunction on renal transplant function in non-urologic populations, studies have been done on the effect of UTI after renal transplantation on transplant deterioration in more extensive populations. However, the clinical relevance of UTI occurring after renal transplantation for transplant functioning is still under debate. Lyerova et al.[4], Mueller et al.[5], and Takai et al.[6],

concluded that UTI after renal transplantation was a benign complication. Conversely, Abbot et al.[7], and Chuang et al.[8] found that UTIs after renal transplantation in a general population were significantly associated with an increased risk of death. The finding in our study, that UTI negatively effect renal transplant function is in line with the studies by Abbot et al. and Chuang et al. It indicates that the conclusion of Lyerova et al., Mueller et al., and Takai et al. that UTIs after renal transplantation are benign complications should be considered with care.

Limitations of the research

The limitations of a study are as important as its merits in coming to conclusions about the value of its findings. There are a number of reasons why the results of our studies should be treated with care. A first restriction of our studies is the small sample size, especially of the pediatric studies. The pediatric study group consisted of 30 children, 21 with an underlying nephrological disease and 9 with an underlying urological disease. With such small groups, the possibilities to perform subgroup analyses are very restricted. Only symptoms that are present in at least a few children can be identified. Generally speaking, the findings of such small sample studies should be treated with care. Nevertheless, the occurrence of LUTS, increased bladder capacity, and urinary tract infections, in our pediatric study group were so high, that it seems likely that dysfunction of the lower urinary tract after renal transplantation is present in many children. However, to determine the extent and nature of these symptoms, a larger group of children should be studied.

In the adult studies our conclusions are based on two different groups of renal recipients. The occurrence of frequency and nocturia in both groups were similar. Moreover, these finding were recently confirmed by Zermann et al. who studied 150 renal transplant patients and found frequency in 87% and nocturia in 93% of patients.[1] Therefore, it may be concluded that these findings are rather robust.

Second, a closely related topic is the possibility that our results are distorted by selection bias. In this respect, the inclusion criteria used when recruiting the patients might have influenced our results. In all our studies, we excluded patients with a bladder catheter, a urinary diversion, insufficient command of the Dutch language, bad graft function, and poor general health status. In the first adult study cohort, 75 out of 97 patients met the inclusion criteria. In the second adult study cohort, 74 out of 127 patients met the inclusion criteria. Finally, in the pediatric study 58 out of 59 patients met the inclusion criteria.

Another source of selection bias is the refusal to participate of some of the patients who fulfilled the inclusion criteria. In the first adult study, 63 out of the 75 patients (84%) who met the inclusion criteria agreed to participate. In the follow-up study, 58 of the original 63

patients were accessible and 53 of them (91%) participated. In the second adult study cohort, 52 out of 74 patients (70%) agreed to participate. In the pediatric study, 34 out of 58 children (59%) participated, but four had to be excluded because the data were not usable. Of the remaining 30 children, only 23 were also willing to complete a frequency/volume chart and 24 were willing to undergo a free flow and post void residual measurement. It seems likely, that in all studies the participants may have differed from the patients who did not participate in various characteristics. Some of these differences might be related to the patient's health status and to the function of their transplanted kidney.

A final source of selection bias is the fact that all patients were transplanted in the same academic hospital and hence may differ in some respect from the general population of transplant patients. The technique of transplantation and follow-up is about the same in the Dutch transplantation centers. However, the population of the region of these centers are slightly different.

About the direction in which the various types of selection bias might have influenced our results the following can be said. Because the least healthy patients were excluded from our studies, and patients who refused to participate probably were less healthy than the participants, it seems likely that the prevalence of LUTS in the total population of transplant patients is still higher than was found in our studies. An indication pointing in this direction is that the prevalence of nocturia found by Zermann et al, was 29% higher than in our study.

Third, a disadvantage of the first two studies in adults was that data were only gathered with a written questionnaire. This questionnaire, the Bristol Female Lower Urinary Tract Symptom questionnaire, was developed to assess the nature, severity and impact on quality of life of lower urinary tract symptoms. It provides subjective information on the function of the lower urinary tract. More objective methods to evaluate bladder function are urodynamic investigation, frequency volume charts, free flow and abdominal ultrasonography. However, because these techniques are more labor intensive to perform and more invasive for the patients, in the first two explorative studies only the questionnaire was used. This means that these studies could only provide indications of bladder dysfunctions that should be confirmed in studies using more objective measures. Therefore, in our third study in adults and in our pediatric study we used beside the questionnaire also frequency/volume charts, free flow and abdominal ultrasonography.

Another disadvantage of using a written questionnaire is that patients may have answered the questions with a socially acceptable but inaccurate response. This might have happened for the following reasons. The majority of patients underwent dialysis before transplantation and they may have had dietary prescriptions, a limited fluid intake, and

anuria. After transplantation these restrictions were discontinued, which greatly improved their quality of life. It is very well possible that compared to the great problems they faced before transplantation, the remaining problems, including the LUTS, were experienced as rather futile. With respect to the quality of life questions, we found that patients who underwent renal transplantation tended to accept a high voiding frequency and nocturia, without complaining much about it. Apparently, we were dealing with a group of patients who were grateful of having received a kidney and felt no need to complain about these small inconveniences that seemed a small price to pay. It is even possible, that these patients perceived the change in voiding pattern after transplantation as positive, because they considered it to be an indication that the kidney was functioning properly.

Fourth, the fact that our data are mostly cross-sectional in nature implies that no strong conclusions regarding causal relationships can be drawn. In our pediatric studies, we found that hemodialysis, the time on dialysis, and bilateral nephrectomy were related to LUTS and that both PVR and UTI were related to renal graft function. In our adult patients, we found daytime frequency after renal transplantation to be related to small bladder capacity, bladder pain, dysfunctional voiding and high fluid intake. Nocturia was related to high nocturnal urine volume, small bladder capacity, and dysfunctional voiding. However, based on these data it is difficult to draw strong conclusions about the causes of frequency and nocturia.

In sum, given the relatively small sample sizes, the possibility of selection bias, the restrictions of the instruments used in part of the studies, and the cross-sectional data collection, the results of our studies should be considered with care. Replication in a larger and broader study population, using objective instruments, and if possible using a prospective design, is necessary before more definitive conclusions can be drawn.

Implications for clinical practice

Our studies clearly indicate that both children and adults might benefit from urological follow-up after renal transplantation. In adults such a urological follow-up might take the form of asking the patient to fill out a frequency/volume chart from time to time, because this would provide information about bladder capacity and nocturnal and daytime urine volumes. According to the International Continence Society Standardization rapport[11] the following measurements can be abstracted from frequency/volume charts, fluid intake, daytime frequency, nocturia, 24-hours frequency, 24-hours urine production, polyuria, nocturnal urine volume, nocturnal polyuria, and, maximum voided volume. Moreover, one should be alert on the presence of a UTI.

In case of excessive urinary output, a micturition regime, which means regular visits to the bathroom, should prevent bladder enlargement. When bladder capacity is already increased, intervention should prevent further enlargement so that the patient does not end up with myogenic detrusor failure. Because too large bladders tend to empty incomplete, we recommend urodynamic investigation to measure bladder contraction and maximum flow rate in these patients, especially if progression is seen with increasing residual urine. In case of post void residual due to hypocontractility of the detrusor, the patient could benefit from learning an adequate micturition technique or performing clean intermittent catheterization, to empty the bladder completely. In case of small bladder capacity, it is important to know whether the patient experiences bladder pain and whether voiding relieves the pain. If so, this might justify ultrasonography to measure thickness of the bladder wall and urodynamic investigation to measure bladder pressure. Interventions should be directed towards preventing high pressure in the lower urinary tract, which could be antimuscarinic medication eventually combined with clean intermittent catheterization, like we treat children with Spina Bifida. When there are recurrent UTI's, we recommend free flow, ultrasonography to find out whether the UTI's are due to post void residual or to structural abnormalities in the urinary tract. These patients could benefit from double voiding, an adequate micturition technique, or clean intermittent catheterization, in selected cases.

In children, we recommend urological follow-up after renal transplantation as described above. However, it seems important that pediatric patients are included in such a follow-up program directly after transplantation. Children with progressive renal insufficiency may go through a period with polyuria due to disturbed concentrating ability of the kidneys. Subsequently, urinary output may gradually decrease during dialysis treatment. The child may finally end up with anuria. Many pediatric renal recipients never had normal voiding habits. After transplantation, when the indwelling catheter is removed, the child should start voiding again. However, since the urethra is often irritated, passing urine can be painful, which is a bad start for restoring normal voiding habits. To prevent dysfunctional voiding, micturition training should start immediately after transplantation, when the indwelling catheter is removed supported with pain medication, if needed. Micturition training is a noninvasive therapy that teaches the child adequate voiding habits. To minimize PVR, it is important that the child performs double voiding to effectuate an empty bladder after micturition.

Directions for further research

With respect to directions for future research, we emphasize that as graft survival increases, research concerning factors that may involve a risk for long-term graft survival

becomes more and more important. To find out what the consequences of LUTS for graft survival are, bladder (dys)function in renal transplant recipients should be followed over a long period of time. Such a longitudinal study can for example be done by following the patients who participated in our studies.

Although we recommend urological follow-up both in children and adults, we realize that a lot of research is needed before we can offer these patients evidence based care and treatment. For the moment, only treatments based on experience in other populations with a dysfunctional lower urinary tract can be offered to transplant patients.[9,10] However, what about bladder training for patients with small bladder capacity? Is it safe for these patients to hold their urine to achieve a larger bladder capacity? What if double voiding is not effective, and the patient is not able to empty the bladder completely? How much residual urine is acceptable and when should we start with clean intermittent catheterization? Further research in renal transplant recipients is needed to address these issues.

One surprising finding of our studies was the high incidence of bladder enlargement. Large bladders were found in 78% of the children and in 27% of the adult patients. Our findings indicate that bladder enlargement may be related to nocturnal polyuria and reduced bladder sensation. However, further research is required to establish what the causes of bladder enlargement are, and this is a prerequisite for the development of preventive measures. Furthermore, a longitudinal study on how bladder capacity evolves over time should clarify whether and in what time span these patients end up with detrusor myogenic failure. In this respect, there is one group of patients we are very worried about, i.e. young adults who underwent renal transplantation at childhood. Many of these young adults probably suffer from enlarged bladder capacity and are on risk of developing detrusor myogenic failure.

References

1. Zermann D, Janitzky A, Hohne M, Schubert J. Frequency and nocturia after successful renal transpantation: a normal situation? BJU Int 2005; 97: 555-558.
2. Renal Data System. USRDS 2005 Annual Data Report:Atlas of End-Stage Renal Disease in the United States. Bethesda, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2005
3. Arlene C, Gerson AC. Editorial comment. Urology 2006; 67: 1065.
4. Lyerova L, Lacha J, Skibova J, et al. Urinary tract infection in patients with urological complications after renal transplantation with respect to long-term function and allograft survival. Ann Transplant 2001; 6: 19–20.
5. Mueller T, Resinger C, Ruffingshofer D, et al. Urinary tract infections beyond the early post-transplant period in pediatric renal graft recipients. Wien Klin Wochenschr 2003; 115: 385–388.
6. Takai K, Aoki A, Suga A, et al. Urinary tract infections following renal transplantation. Transplant Proc 1998; 30: 3140–3141.
7. Abbot KC, Swanson J, Richter ER, et al. Late urinary tract infection after renal transplantation in the United States. Am J Kidney Dis 2004; 44: 353–362.
8. Chuang P, Parikh CR, Langone A. Urinary tract infections after renal transplantation: a retrospective review at two US transplant centres. Clin Transplant 2005; 19: 230-235.
9. Wallace SA, Roe B, Williams K, Palmer M. Bladder training for urinary incontinence in adults. Cochrane Data Base Syst Rev. (1): CDOO1308, 2004.
10. Klijn AJ, Uiterwaal CS, Vijverberg MA, Winkler PL, Dik P, de Jong TP. Home uroflowmetry biofeedback in behavioral training for dysfunctional voiding in school-age children: a randomized controlled study. J Urol 2006; 175(6): 2263-8.
11. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, Van Kerrebroeck P, Victor A, Wein A. The standardisation of terminology in lower urinary tract function: Report from the standardisation sub-committee of the International Continence Society, Neurourol Urodyn 2002; 21: 167-178.

Summary

The aim of our research was to study the function of the lower urinary tract after renal transplantation. Central research questions were:

1. What is the prevalence and nature of lower urinary tract symptoms (LUTS) after renal transplantation in adults?
2. What are the causes of frequency and nocturia after renal transplantation in adults?
3. What is the prevalence and nature of LUTS after renal transplantation in children?
4. What are the causes of LUTS after renal transplantation in children?
5. What are the consequences of LUTS for the function of the renal graft?

To answer these questions, we have conducted five empirical studies, three focusing on adult renal transplant patients and two focusing on pediatric renal transplant patients.

Lower urinary tract dysfunction in adults

In our first study, (chapter 2) we explored the prevalence and nature of LUTS after renal transplantation at an average of 8 months (range 2–13) after transplantation. The research group consisted of 63 adult patients who underwent renal transplantation in 1998 at the University Medical Center St Radboud Nijmegen. The control group consisted of 74 patients with non-urological complaints who visited an outpatient clinic of the same university hospital. Data on symptoms of lower urinary tract dysfunction, were gathered with a written questionnaire and background information on the transplant patients was obtained from the medical records.

The results showed that patients with transplants needed to void significantly more often than controls both during the day and at night. In half of the patients (49%) we found a daytime voiding frequency of 7 times or more often. At night 62% of the patients with transplants needed to void 2 times or more often. The type of renal replacement therapy, the number of months the patient underwent dialysis, the urine volume produced before transplantation, and the number of former transplants were not related to the occurrence of frequency and nocturia after transplantation. Regarding bladder evacuation, no significant differences between the study group and the control group were found.

Based on these results we concluded that the reservoir function of the bladder might be impaired after renal transplantation. The findings raised the question whether bladder function was stabilized at the time of the study (on average 8 months after renal transplantation) or whether it still would change over time. To answer this question, a second study (chapter 3) was designed in which the same group of patients that participated in the first study (T1) was approached again in the third year after

transplantation (T2). Out of the 63 patients who completed the first questionnaire, 58 were accessible at T2, of which 53 (91%) completed the same questionnaire again.

Our analysis of the additional data showed that the high incidence of frequency and nocturia found in the earlier study was still present at three years after transplantation. At T2, 22 (42%) of the patients suffered from frequency and 26 (49%) had nocturia. The patients who had frequency and nocturia at T2 were mainly the same patients (63% and 68% respectively) who already had these symptoms at T1. We also found that the occurrence of urgency in the study group was at both T1 (42%) and T2 (26%) significantly lower than in the control group (59%). With respect to bladder evacuation, the sensation of post void residual (PVR) was at T1 significantly less frequent among the transplant patients than in the control group, but at T2 this difference had disappeared. Based on these results we concluded that frequency and nocturia in renal recipients are rather persistent phenomena. Because we found that the renal transplant group experienced significantly less urgency than the control group we concluded that there might be a decreased bladder sensation.

The finding of persistent frequency and nocturia after renal transplantation rose the question of what the causes of these symptoms would be. To answer this question, a third study (chapter 4) was conducted in 2005, in which new data were gathered from 52 renal transplant patients (none of which participated in the earlier studies) at five months after transplantation. This time, besides the written questionnaire also more objective instruments like frequency volume charts and urinary cultures were used. With these new data, the role of five potential causes of frequency and nocturia after transplantation were studied: bladder capacity, bladder pain, urgency, dysfunctional voiding and (high) fluid intake.

This new study reconfirmed the presence of high levels of frequency and nocturia after transplantation (in 54% and 60% of the patients respectively). There were 19 patients (38%) who showed both symptoms, but no significant association between frequency and nocturia was found. Sixty-five percent of the patients reported that they sometimes experienced a sensation of urgency. Polyuria was found in 23% of the patients and nocturnal polyuria in 64% of the patients. Urinary tract infections (UTI's) were diagnosed in 25% of the patients. Using Structural Equation Modeling (SEM) we found that frequency is influenced directly by daytime urine volume, bladder capacity, bladder pain, and urgency, and indirectly by UTI's. Nocturia was influenced by nocturnal urine volume, bladder capacity, bladder pain, and dysfunctional voiding. Moreover, we found that nocturnal urine volume was related to bladder capacity.

These findings led to the conclusion that daytime frequency after renal transplantation is associated with a small bladder capacity, which may be accompanied by bladder pain and dysfunctional voiding. A small bladder capacity was found in 13 (25%) of the patients. Daytime frequency was also related to high fluid intake. The presence of UTI's indirectly led to frequency via its relation with urgency and bladder pain. Nocturia was found to be related to a high nocturnal urine volume, and to small bladder capacity, of which the latter may be accompanied by dysfunctional voiding. Nocturnal polyuria may ultimately cause bladder enlargement. A large bladder capacity was found in 14 (27%) patients.

Lower urinary tract dysfunction in children

After our first study revealed that adult renal transplant patients frequently suffered from LUTS, a new study was designed to determine the presence and nature of LUTS after renal transplantation in children. Our study group consisted of 30 children, 16 boys and 14 girls; mean age was 14 years (range 6 to 19). From these 30 children, 9 (30%) had received a renal transplant because of an underlying urological disease and 21 (70%) because of an underlying nephrological disease. Data were gathered using a written questionnaire, frequency volume chart, free uroflowmetry, transabdominal ultrasonography and medical records. Using these data, two studies were done.

The first study (chapter 5) revealed a high incidence of LUTS in these children. This was true both for the children with an underlying urological disease (where LUTS could be expected) and for the children with an underlying nephrological disease. Only one of the children did not suffer from LUTS. The average number of LUTS in both groups of patients was three. Rather striking was the large number of children with increased bladder capacity. Of the children with an underlying urological disease, 86% had an average bladder capacity of 207% (hence more than double the normal bladder capacity for age). Of the children with an underlying nephrological disease, 75% had an average bladder capacity of 175% (75% more than normal bladder capacity for age). We also found that the longer the graft was in situ, the less urgency and bladder pain were experienced. Children who underwent hemodialysis before transplantation had a higher incidence of intermittent flow than those who were treated with peritoneal dialysis. Time on dialysis was positively related to the incidence of UTI. Children who underwent bilateral nephrectomy had a higher rate of intermittent flow after transplantation, but less hesitancy.

Based on the results of this study we concluded that both the urological and the nephrological children run the risk of developing myogenic failure due to increased bladder capacity. About half of the children had post void residual, UTI's, and a decrease of bladder sensation. Moreover, our data indicate that circumstances before transplantation,

such as polyuria or anuria due to disturbed renal function might cause LUTS after transplantation.

Given the finding of a high incidence of LUTS in children with a nephrological cause of renal failure, a second paediatric study (chapter 6) was designed aimed to determine whether and to what extent LUTS, UTI's, and bladder capacity are risk factors for the loss of renal graft function. For this purpose, the data gathered for the first pediatric study were enriched with data about the occurrence of UTI's after transplantation and with data about renal graft function. To get a homogeneous study group we excluded the 9 children with an underlying urological disease. Thus, the research group consisted of the 21 renal transplant children with an underlying nephrological disease (12 girls and 9 boys, mean age 13.5 years, range 6 to 18). To estimate renal transplant function, the calculated creatinine clearance rate (Ccr) according to Schwartz was used. The Ccr was measured at two points, 2 months after transplantation (T0) and at the moment of study (T1). The average graft age was 34 months (range 5 to 85).

We found a significant negative relationship between the Ccr at T1 and UTI. Furthermore, there was a significant positive relationship between Ccr at T1 and sensation of incomplete emptying , and a marginally significant negative relationship between Ccr at T1 and PVR. To determine whether these associations were not just an effect of graft age or an initial low Ccr at T0, multivariate regression analyses were performed. Our results indicated that both PVR urine volume (P=0.03) and UTI (P=0.003) were significantly and independently related to the Ccr at T1. These findings led to the conclusion that PVR and UTI's may negatively affect renal graft function.

Recommendations for urological follow-up

Our studies made clear that both children and adults might benefit from urological follow-up after renal transplantation. In adults such a urological follow-up might take the form of asking the patient to fill in a frequency/volume charts from time to time, because this would provide information about bladder capacity and nocturnal and daytime urine volumes. In case of recurrent UTI's, we recommend free flow and, post-void ultrasonography of the bladder. If these instruments show that the patient has a dysfunctional lower urinary tract, we recommend urodynamic investigation. In children, we recommend urological follow-up after renal transplantation as described above. However, it seems important that pediatric patients get such a follow-up directly after transplantation. Because many pediatric renal recipients never had normal voiding habits, they need micturition training after transplantation. Micturition training is a noninvasive therapy that teaches the child adequate voiding habits.

Directions for future research

With respect to directions for future research, we emphasize that as graft survival increases, research into factors that pose a risk upon long-term graft survival becomes more and more important. To find out what the consequences of LUTS for graft survival are, bladder (dys)function in renal recipients should be followed over a long period of time. For the moment, only treatments based on experience in other populations with a dysfunctional lower urinary tract can be offered to transplant patients. Further research in renal transplant recipients is needed to adjust all these interventions for this particular population.

Samenvatting

Doel van dit onderzoek was het bestuderen van de functie van de lagere urinewegen na niertransplantatie. Centraal stonden de volgende vijf vragen:

1. Wat is de prevalentie en aard van symptomen van de lagere urinewegen na niertransplantatie bij volwassenen?
2. Wat zijn de oorzaken van Frequency en Nocturia na niertransplantatie bij volwassenen?
3. Wat is de prevalentie en aard van symptomen van de lagere urinewegen na niertransplantatie bij kinderen?
4. Wat zijn de oorzaken van symptomen van de lagere urinewegen na niertransplantatie bij kinderen?
5. Wat zijn de consequenties van symptomen van de lagere urinewegen voor het functioneren van de getransplanteerde nier?

Om deze vragen te kunnen beantwoorden zijn vijf empirische studies verricht, waarvan drie bij getransplanteerde volwassenen en twee bij getransplanteerde kinderen.

Disfunctie van de lagere urinewegen bij volwassenen

In de eerste studie, (hoofdstuk 2) is de prevalentie en aard van symptomen van de lagere urinewegen na niertransplantatie in kaart gebracht. De onderzoekgroep bestond uit 63 volwassenen die in 1998 een niertransplantatie ondergingen in het UMCN St Radboud. De gemiddelde tijd tussen transplantatie en het moment van ondervraging was 8 maanden (range 2–13). De controlegroep bestond uit 74 niet urologische patiënten die een polikliniek van hetzelfde ziekenhuis bezochten. Gegevens over symptomen van disfunctie van de lagere urinewegen werden verzameld met een schriftelijke vragenlijst en achtergrondinformatie over de getransplanteerde patiënten werd uit hun medische status gehaald.

De resultaten van dit eerste onderzoek lieten zien dat getransplanteerde patiënten zowel overdag als gedurende de nachts significant vaker moeten plassen dan patiënten uit de controlegroep. De helft van de patiënten (49%) ging overdag zeven keer of vaker plassen. Gedurende de nacht moest 62% van de patiënten twee keer of vaker plassen. Het type niervervangende therapie, het aantal maanden dat de patiënt dialyse onderging, de urineproductie voor de transplantatie en het aantal voorgaande transplantaties waren niet gerelateerd aan het optreden van frequeny en nocturia. Met betrekking tot de evacuatiefunctie van de blaas werden er geen significante verschillen gevonden tussen de onderzoeksgroep en de controlegroep.

De resultaten van dit onderzoek doen vermoeden dat de reservoirfunctie van de blaas na niertransplantatie gestoord is. Op het moment dat het onderzoek verricht werd, waren de

patiënten gemiddeld 8 maanden geleden getransplanteerd. De vraag rees of de blaasfunctie op dat moment gestabiliseerd was of dat deze in de loop van de tijd nog zou veranderen.

Om deze vraag te kunnen beantwoorden werd een tweede studie (hoofdstuk 3) verricht. Hierbij werd tweeënhalf jaar na de eerste studie (T1) dezelfde groep patiënten opnieuw ondervraagd (T2). Van de 63 patiënten die de eerste vragenlijst invulden, waren er 58 die we opnieuw konden ondervragen, waarvan er 53 (91%) opnieuw een vragenlijst invulden. De nieuwe gegevens lieten zien dat de hoge incidentie van frequency en nocturia die wij in de eerste studie vonden drie jaar na transplantatie nog steeds aanwezig was. Op tijdstip T2, hadden 22 (42%) patiënten last van frequency en 26 (49%) van nocturia. De patiënten die op T2 frequency en noctuia hadden, waren voornamelijk dezelfde patiënten als op T1 (respectievelijk 63% en 68%). De resultaten van deze studie lieten zien dat het optreden van urgency in de onderzoeksgroep zowel op T1 (42%) als op T2 (26%) significant lager was dan in de controlegroep (59%). Met betrekking tot de evacuatiefunctie van de blaas, bleken de getransplanteerde patiënten op tijdstip T1 minder vaak een residugevoel na mictie te hebben dan de controlegroep. Op tijdstip T2 was dit verschil verdwenen. Gebaseerd op deze bevindingen werd geconcludeerd dat frequency en nocturia bij patienten die een nier hebben ontvangen tamelijk hardnekkige symptomen zijn. Omdat de transplantatiegroep significant minder urgency ondervond dan de controlegroep concludeerden we dat er mogelijk sprake was van een verminderde sensibiliteit in de blaas. Omdat werd aangetoond dat frequency en nocturia na niertransplantatie geen voorbijgaande verschijnselen zijn, werd in 2005 een derde studie (hoofdstuk 4) verricht, om de oorzaken van deze symptomen op te sporen. In deze derde studie werden vijf maanden na transplantatie gegevens verzameld van 52 getransplanteerde patiënten (geen van hen nam deel aan de eerdere studies). Dit keer werden naast de schriftelijke vragenlijst ook objectievere meetinstrumenten gebruikt zoals een mictiedagboek en urinekweken. Met deze nieuwe gegevens werd de rol van vijf potentiële oorzaken van frequency en nocturia na niertransplantatie bestudeerd: blaascapaciteit, blaaspijn, urgency, bemoeilijkte mictie en (grote) vochtintake.

Deze nieuwe studie bevestigde het in hoge mate optreden van frequency en nocturia na niertransplantatie (respectievelijk in 54% en 60% van de patiënten). Er waren 19 (38%) patiënten die beide symptomen vertoonde, maar we vonden geen significante relatie tussen frequency en nocturia. Vijfenzestig procent van de patiënten rapporteerde dat ze soms een gevoel van urgency hadden. Polyurie werd in 23% van de patiënten geconstateerd en nachtelijke polyuria in 64% van de patiënten. Urineweginfecties werden in 25% van de patiënten gediagnosticeerd. Bij het analyseren van de gegevens werd gebruik gemaakt van Structural Equations Modeling. Uit de analyses bleek dat frequency rechtstreeks wordt

beïnvloed door de urineproduktie overdag, blaascapaciteit, blaaspijn en urgency en indirect door urineweginfecties. Nocturia blijkt beïnvloed te worden door de nachtelijke urineproductie, blaascapaciteit, blaaspijn en bemoeilijkte mictie. Bovendien vonden we dat de nachtelijke urineproductie gerelateerd was aan blaascapaciteit.

Deze bevindingen leidden tot de conclusie dat het overdag vaak plassen na niertransplantatie samenhangt met een kleine blaas, en dat dit gepaard kan gaan met blaaspijn en bemoeilijkte mictie. Bij 13 (25%) patiënten werd een kleine blaascapaciteit gevonden. Het overdag vaak plassen hangt ook samen met een grote vochtintake. Urineweginfecties kunnen tot urgency en blaaspijn leiden op die manier indirect frequency veroorzaken. Het optreden van nocturia hangt samen met een grote nachtelijke urineproductie en een te kleine blaascapaciteit, waarvan laatstgenoemde gepaard kan gaan met bemoeilijkte mictie. Bij 14 (27%) patiënten werd een grote blaascapaciteit gevonden.

Disfunctie van de lagere urinewegen bij kinderen

Nadat onze eerste studies aangetoond hadden dat volwassenen na niertransplantatie last hadden van symptomen van de lagere urinewegen, werd een nieuwe studie ontwikkeld om na te gaan wat de aard en prevalentie van symptomen van de lagere urinewegen bij kinderen is. De studiegroep bestond uit 30 kinderen, 16 jongens en 14 meisjes; met een gemiddelde leeftijd van 14 jaar (range 6 tot 19). Van deze 30 kinderen hadden er 9 (30%) een niertransplantatie nodig vanwege een urologische ziekte en 21 (70%) vanwege een nefrologische ziekte. De gegevens voor dit onderzoek werden verzameld met een schriftelijke vragenlijst, een mictiedagboek, een uroflowmetrie, echo residubepaling en de medische status. Met behulp van deze gegevens werden twee studies verricht.

De eerste studie (hoofdstuk 5) toonde een hoge incidentie van symptomen van de lagere urinewegen aan bij deze kinderen. Dit bleek niet alleen het geval te zijn bij kinderen met een onderliggende urologische ziekte (waarbij je dit verwacht), maar ook bij kinderen met een onderliggende nefrologische ziekte. Slechts één kind had geen enkel symptoom van de lagere urinewegen. Beide groepen kinderen hadden gemiddeld 3 symptomen van de lagere urinewegen. Opvallend was het grote aantal kinderen met een te grote blaascapaciteit. Van de kinderen met een onderliggende urologische ziekte had 86% een te grote blaascapaciteit. Deze kinderen hadden gemiddeld een blaascapaciteit van 207% (dus meer dan het dubbelen van wat men op basis van hun leeftijd zou verwachten). Van de kinderen met een onderliggende nefrologische ziekte had 75% een te grote blaascapaciteit. Deze nefrologische kinderen hadden gemiddeld een blaascapaciteit van 175% (dus 75% meer van wat men op basis van hun leeftijd zou verwachten. Verder lieten de resultaten zien dat er minder urgency en blaaspijn werd ervaren, naarmate het transplantaat langer in situ was.

Kinderen die voor de transplantatie hemodialyse ondergingen hadden vaker last van een onderbroken plasstraal dan kinderen die voor de transplantatie peritoneaal dialyse ondergingen. Verder bleek er een relatie te bestaan tussen het aantal maanden dat de kinderen dialyse ondergingen voor de transplantatie en het optreden van urineweginfecties na de transplantatie. Kinderen die een bilaterale nefrectomie hadden ondergaan, bleken vaker een onderbroken plasstraal te hebben, maar juist minder vaak moeite met het op gang brengen van het plassen. De resultaten wijzen erop dat zowel kinderen met een onderliggende urologische ziekte als kinderen met een onderliggende nefrologische ziekte ten gevolge van een te grote blaascapaciteit gevaar lopen om spierzwakte van de blaasspier te ontwikkelen. Ongeveer de helft van de kinderen kan de blaas niet goed leegplassen, heeft urineweginfecties en verminderde blaassensibiliteit. Bovendien zijn er aanwijzingen dat de omstandigheden voor de transplantati, zoals polyurie of anurie veroorzaakt door een gestoorde nierfunctie, na transplantatie klachten van de lagere urinewegen kunnen veroorzaken.

Omdat we bij de kinderen veel symptomen van de lagere urinewegen vonden werd een tweede kinderstudie verricht (hoofdstuk 6). Het doel van deze studie was het vaststellen of en in welke mate symptomen van de lagere urinewegen, urineweginfecties en een te grote of te kleine blaascapaciteit een bedreiging vormen voor het functioneren van de getransplanteerde nier. Hiertoe werd het databestand van de eerste kinderstudie aangevuld met gegevens over het optreden van urineweginfecties na niertransplantatie en met gegevens over het functioneren van het transplantaat. Om een homogene studiegroep te creëren werden de kinderen met urologisch grondlijden geëxcludeerd. De onderzoeksgroep bestond dus uit 21 getransplanteerde kinderen met een onderliggend nefrologische lijden (12 meisjes en 9 jongens, tussen de 6 en 18 jaar, gemiddelde leeftijd 13.5 jaar). Om het functioneren van het niertransplantaat te bepalen werd de formule van Schwartz voor het berekenen van de berekende creatinine clearance (Ccr) gebruikt. De Ccr werd op twee tijdstippen gemeten, twee maanden na de transplantatie (T0), en op het moment van ondervraging, (T1). De tijd dat het kind het transplantaat had varieerde van 5 tot 85 maanden met een gemiddelde tijdsduur van 34 maanden.

We vonden een significant negatief verband tussen de Ccr op T1 en urineweginfecties. Verder bleek er een significant negatief verband te bestaan tussen Ccr op T1 en het gevoel niet goed uit te kunnen plassen en een marginaal significante negatieve relatie tussen Ccr op T1 en residu na mictie. Om te na te gaan of deze bevindingen veroorzaakt werden door verschillen in leeftijd van het transplantaat of door een initiële lage Ccr op T0 hebben we multivariate analyses uitgevoerd. De resultaten lieten zien dat zowel residu na mictie ($p=0.03$) als urineweginfecties ($p=0.003$) onafhankelijk van elkaar gerelateerd waren aan

Ccr op T1. Hieruit hebben wij geconcludeerd dat residu na mictie en urineweginfecties de functie van het transplantaat negatief kunnen beïnvloeden.

Aanbevelingen voor urologische follow-up

Uit onze studies blijkt dat zowel kinderen als volwassenen profijt kunnen hebben van urologische follow-up na niertransplantatie. Bij volwassenen zou deze follow-up kunnen bestaan uit het af en toe laten invullen van een mictiedagboek, omdat dit informatie verschaft over de blaascapaciteit en de nachtelijke urineproductie. Indien er sprake is van urineweginfecties adviseren wij een flowstudie met echoresidu bepaling. Als deze metingen aantonen dat er spraken zou kunnen zijn van disfunctie van de lagere urinewegen adviseren wij een urodynamisch onderzoek. Bij kinderen adviseren wij dezelfde urologische follow-up als bij volwassen. Echter bij kinderen lijkt het ons belangrijk dat de urologische controle direct na de transplantatie begint. Omdat veel getransplanteerde kinderen nooit normaal zindelijk zijn geweest moet hen dit na de transplantatie worden aangeleerd. Middels een niet belastende training kan het kind leren op tijd naar de wc te gaan en goed uit te plassen.

Aanbevelingen voor verder onderzoek

Met het toenemen van de levensduur van het transplantaat, wordt onderzoek dat zich richt op factoren die op de langere termijn een bedreiging voor het transplantaat vormen steeds belangrijker. Om te kunnen beoordelen wat de consequenties zijn van symptomen van de lagere urinewegen voor de overlevingskans van het transplantaat, is het belangrijk dat deze symptomen bij getransplanteerde patiënten over een langere periode gevolgd worden. Op dit moment kunnen wij transplantatiepatiënten slechts een behandeling aanbieden die alleen uitgeprobeerd is bij andere categorieën van patiënten met disfunctie van de lagere urinewegen. Meer onderzoek is nodig om de bestaande interventies aan te passen aan de speciale behoefte en problematiek van deze patiëntencategorie.

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Vanaf november 1989 ben ik werkzaam in het UMC St Radboud. In die jaren heb ik veel steun van anderen gekregen. Dat motiveerde me om steeds weer een stap voorwaarts te zetten. Ik wil daarom niet alleen degenen bedanken die rechtstreeks een bijdragen hebben geleverd aan het tot stand komen van mijn proefschrift, maar ook iedereen die in de jaren daarvoor bij mijn werk betrokken was.

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Curriculum Vitae

Marian van der Weide werd op 30 maart 1953 geboren in Boxtel. Na het behalen van haar diploma aan de School voor Laboratoriumpersoneel te Den Bosch was zij werkzaam als laboratoriumassistente bij het Koninklijke Shell Laboratorium te Amsterdam op de afdeling rubber en kleefstoffen. In 1976 startte zij met de opleiding tot A-verpleegkundige in het Slotervaartziekenhuis te Amsterdam die in 1980 werd afgerond in het Diaconessenziekenhuis te Breda. Van 1980 tot 1989 was zij werkzaam als zelfstandige verpleegkundige in de thuiszorg. In die periode reisde zij veel en maakte zeiltochten naar Zuid-Amerika, Afrika en door het Middellandse zeegebied. Vanaf november 1989 is ze werkzaam in het UMC St. Radboud, eerst als incontinentie/urodynamica verpleegkundige en daarna als verpleegkundig specialist voor patiënten met incontinentie en/of urostoma. In die periode ontwikkelde zij diverse protocollen en schreef zij twee boeken over haar vakgebied. In 1999 voltooide zij de opleiding Master of Science in Nursing. Sindsdien is zij In het UMC St Radboud werkzaam als verpleegkundig onderzoeker en verrichtte zij onder meer onderzoek naar de introductie van innovaties in de zorg en naar functiestoornissen van de lagere urinewegen na niertransplantatie. Dit laatste onderzoek resulteerde uiteindelijk in de totstandkoming van dit proefschrift. Naast haar reguliere onderzoekswerkzaamheden bij het UMC St Radboud Nijmegen voert marian momenteel een onderzoek uit voor de Nierstichting getiteld “Vaststellen van een richtlijn voor follow-up bij antenataal gedetecteerde afwijkingen van nieren en urinewegen”.

Publicaties

Wetenschappelijke artikelen

van der Weide MJA, van Achterberg T, Smits JPJM, Heesakkers J, Hilbrands LB. Why do many renal transplant patients suffer from Frequency and Nocturia? *Submitted, feb 2007*.

van der Weide MJA, Cornelissen E, van Achterberg T, Smits J, Feitz W. Dysfunction of the Lower Urinary Tract in Renal Transplant Children with Nephrological Disease: *Urology 2006; 67: 1060-65.*

van der Weide MJA, Cornelissen M, van Achterberg T, de Gier R, Feitz W. Lower Urinary Tract Symptoms after renal transplantation in children: *The Journal of Urology 2006; 175: 297–302.*

van der Weide MJA, Smits J. Adoption of innovation by specialized nurses: Personal, work and organizational characteristics *Health Policy 2004; 68: 81-92*.

van der Weide MJA, Hilbrands LB, Bemelmans BLH, Kiemeney ALM. Lower Urinary Tract Symptoms after renal transplantation: are there changes over time? *Urology 2004; 63: 442-446.*

van der Weide M, Smits J. The influence of ward characteristics on the adoption of Innovation in Nursing: *Nursing Economics 2001; 19(5): 220–227.*

van der Weide MJA, Hilbrands L, Bemelmans B, Meuleman E, Frederiks C. Lower Urinary Tract Symptoms after renal transplantation: *The Journal of Urology 2001; 166: 1237-1241.*

Cobussen-Boekhorst JGL, van der Weide MJA, Feitz W, de Gier R. Using an instruction model to teach clean intermittent catheterization to children. *British Journal of Urology International 2000; 85: 551- 553.*

van der Weide M. Innovation in Nursing: scriptie, School of Nursing Studies, University of Wales College of Medicine, Cardiff, UK, in collaboration with Hogeschool van Utrecht, 1999.

van der Weide M, Smits J. Acceptatie van innovatie. *Verpleegkunde 1999; (2): 106-115.*

Boeken

van der Weide MJA. Lower Urinary Tract Dysfunction after renal transplantation in children and adults. Dissertatie, Radboud Universiteit Nijmegen, 2007.

van Houten P, van der Linden M, van der Weide M. De gang naar het toilet bij zorgbehoevende ouderen. Utrecht: Uitgeverij Lemma BV, 2001.

van der Weide M. ‘Inkontinenz, Pflegediagnosen und Pflege-interventionen’. Bern: Hans Huber, 2001.

Kerrebroeck PhEV, van der Weide M. Incontinentie voor urine. In: Handboek Handicap en Chronische Ziekten. Maarssen: Elsevier De Tijdstroom, 1997.

van der Weide M. ‘Verpleegkundige diagnostiek en interventies voor patiënten met urine-incontinentie’. Utrecht: De Tijdstroom, 1996.

Richtlijnen en protocollen

Kwaliteitsinstituut voor de gezondheidszorg CBO. *Richtlijn voor continentiestoornissen.* Utrecht: Verpleegkundig Wetenschappelijke Raad (VWR), 1999.

Messelink EJ, Hoope CA, van Lieshout GJCM, Peddemors H, Slieker ten Hove MCPh, van der Weide MJA. *De overactieve blaas*. Amsterdam: Benecke Consultants, 2000.

van der Weide M, de Jong L, Verheij P, Feitz W, de Gier R. *De behandeling van kinderen met functiestoornissen van de lagere urinewegen volgens het Nijmeegs model; een verpleegkundige behandeling.* Nijmegen: UMC St Radboud, 1998.

Overige publicaties

van der Weide M, Cobussen-Boekhorst H, Smits-van der Camp A, Besselink J. Het reguleren van telefoongesprekken met een medische of verpleegkundige vraagstelling op de polikliniek urologie: *TVZ 2004; juni*.

van der Weide M, Roodbol G, De Hullu M. Bekwaam is bevoegd. *Tijdschrift voor Verpleegkundigen 2000; 8: 245-246*.

van der Weide M. Blaastraining als verpleegkundige interventie voor patiënten met urgency, frequency en urge-incontinentie *: Incourant 1999; (16): 17-21.*

van der Weide M. '*Outpatient training for children with functional incontinence*'. In het cursusboek 'Second course on paediatric urodynamics', uitgegeven door het Nederlands Kinderurologisch Gezelschap, september 1997.

van der Weide M. 'Incontinentie, kies het juiste materiaal'. *Nursing*1997; (3): 68-71.

van der Weide M. 'Zo wordt blaastraining een succes'. *Nursing* 1997; *(*6): 66- 70.

van der Weide M. '*Urine-incontinentie in het AZN'.* In de bundel uitgegeven ter gelegenheid van het verpleegkundig symposium van de Nederlandse Vereniging voor Urologie, op 19 april 1996, te Dronten.

van der Weide M. '*Verpleegkundig onderzoek naar de prevalentie van incontinentie in het AZN.* In de bundel uitgegeven ter gelegenheid van het symposium 'Incontinentie bij de Vrouw', op 21 februari 1996, te Ede.

van der Weide M. 'Wat maakt een beroep een beroep'. *Incourant* 1995; 4(7): 9-10.

van der Weide M. 'Blaastraining'. *Incourant* 1995; 4(8): 24-26.

van der Weide M. 'Urine-incontinentie in het AZN'. Onderzoeksverslag. Nijmegen: AZN, 1995.

van der Weide M. 'Verpleegkundige diagnostiek en interventies voor patiënten met urine-incontinentie'. Protocol voor verpleegafdelingen van het AZN. 1995

van der Weide M. De kwaliteit van zorg voor patiënten met urine-incontinentie. *Verpleegkundig tijdschrift AZN 1994;* 1(3): 12-13.

van der Weide M. 'Incontinentieproblematiek bij Multiple Sclerose'. In de bundel uitgegeven ter gelegenheid van het symposium 'Incontinentie bij neurologische ziektebeelden', op 27 mei 1993, te Amsterdam.

van der Weide M. 'Een verpleegkundige benadering van patiënten met urine-incontinentie'. In de bundel uitgegeven ter gelegenheid van het symposium 'Incontinentie bij de vrouw', op 3 december 1993, te Utrecht.

van der Weide M. 'De patiëntencategorie en de gezondheidszorg'. *Incourant 1994;* 3(5): 5-9.