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LOWER URINARY TRACT DYSFUNCTION IN CHILDREN WITH CHRONIC KIDNEY DISEASE

BEFORE AND AFTER RENAL TRANSPLANTATION

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To all the children with a chronic kidney disease and their families

ABSTRACT

Chronic kidney disease (CKD) in children is a complex condition with the risk of progression to end-stage renal disease (ESRD) requiring dialysis or renal transplantation. Children with CKD and pediatric renal transplant recipients face a variety of complications, such as side effects of the treatment and concerns about deterioration of graft function. Urinary tract infections (UTIs) are common complications that may harm renal function. In the general population lower urinary tract (LUT) dysfunction is a major risk factor for UTI, but less is known about LUT dysfunction in children with CKD or a renal transplant. The overall aim of this thesis was to evaluate LUT function in children with CKD before and after renal transplantation, and to study the role of LUT dysfunction in relation to UTIs. An additional aim was to gain knowledge about associations between LUT dysfunction and health related quality of life (HRQoL) in children with CKD before and after transplantation.

All studies were cross-sectional and included 40 children with CKD stages 3–5 (Studies III and IV), 68 children with a renal transplant (Studies I and II), and 59 children (Study V) with CKD stage 3–5 (n=23), or with a renal transplant (n=36). The documents and investigations used to evaluate LUT function were bladder diaries/questionnaires, uroflowmetry, bladder ultrasound (for measuring post-void residual urine), and, in Study IV, cystometry. The glomerular filtration rate (GFR) was assessed by the renal clearance of inulin or iohexol, or estimated by the plasma level of cystatin C. The history of UTI was obtained by reviewing the medical records. Two questionnaires, the Kidscreen-27 and Disabkids-37, were used for self-ratings of HRQoL and the modified Symptom Inventory for assessing associated subjective symptoms (Study V).

One or more signs of LUT dysfunction were found in 72.5% of children with CKD and in 72% of those with a renal transplant. Signs of LUT dysfunction were observed in all (100%) of the children with CKD along with underlying urological disorders and in 59% with non-urological disorders ($p = 0.0074$). Regarding LUT function in children with a renal transplant, no significant difference was found in groups with and without urinary tract malformations (74% vs. 71%, NS). In children with CKD, 47.5% had a bladder capacity larger than expected and the large bladder was often combined with reduced bladder sensation. A discontinuous urinary flow was found in 20% and 15% had residual urine. Corresponding figures in children with a renal transplant were 26%, 50% (17.6%, with a tower pattern excluded), and 32%. UTIs were more common in children with CKD and signs of LUT dysfunction than in those without (55% vs. 0%, $p = 0.0012$). In children with a renal transplant, recurrent UTIs were equally common in children with and without LUT dysfunction (35% vs. 42%, NS). Recurrent UTIs were, however, associated with a faster deterioration of GFR than in those without UTIs ($p = 0.02$). Children with CKD or a renal transplant with or without signs of LUT dysfunction reported a similar HRQoL, except those with incontinence, who reported lower HRQoL. Girls and older children rated well-being lower, as did those with a renal transplant. The entire study population perceived poorer well-being than healthy children, but similar to those with chronic conditions other than CKD.

In conclusion, LUT dysfunction is common in children with CKD stages 3–5 and pediatric renal transplant recipients, not only in children with urological disorders but also in those with non-urological disorders. Earlier UTIs and LUT dysfunction seem to correlate in children before, but not after a renal transplantation. The findings in this thesis contribute to our knowledge about LUT dysfunction in children with CKD stage 3–5 and pediatric renal transplant recipients, but also to our knowledge about the association between HRQoL and LUT dysfunction as well as possible impact of CKD status, sex and age. Further research is needed before general recommendations for possible interventions can be given.

LIST OF PUBLICATIONS

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LIST OF ABBREVIATIONS

BD	Bladder dysfunction
CKD	Chronic kidney disease
CIC	Clean intermittent catheterization
CNS	Central nervous system
CRF	Chronic renal failure
CBC	Cystometric bladder capacity
DCGM-37	Disabkids Chronic Generic Module-37
DD	Deceased donor
EBC	Expected bladder capacity
ED	Emptying dysfunction
EMG	Electromyography
ESRD	End-stage renal disease
GFR	Glomerular filtration rate
HD	Hemodialysis
HRQoL	Health-Related Quality of Life
ICCS	International Children's Continence Society
ICIQ-FLUTS	International Consultation on Incontinence Questionnaire Female Lower Urinary Tract Symptoms
LD	Living donor
LUT	Lower urinary tract
LUTS	Lower urinary tract symptoms
MMV	Maximum voided volume
PD	Peritoneal dialysis
QoL	Quality of Life
SPAR	Swedish population registry [Statens person och addressregister]
Tx	Transplantation
UTI	Urinary tract infection
UTM	Urinary tract malformations
VUR	Vesicoureteral reflux

1 INTRODUCTION

The idea for this project originated from our experience with and concerns for the children with recurrent urinary tract infections (UTIs) after renal transplantation. Our impression was that graft function declines faster in children who suffered from recurrent UTIs than in those without UTIs.

Although UTI is a common complication with a prevalence of approximately 25–50% in children after renal transplantation [1-3], the underlying pathogenesis is not yet fully understood. In otherwise healthy children, classical risk factors for UTIs are urinary tract malformations, such as vesicoureteral reflux (VUR) and obstructive uropathy, female gender and young age [4]. Consequently, these risk factors have also been evaluated in children with recurrent UTIs after renal transplantation, but with conflicting results [5]. However, children with a renal transplant differ from otherwise healthy children in an important aspect: they are treated with immunosuppressants. This treatment impairs the immunologic host defense mechanisms and increases the risk for various infections. The immunosuppression may therefore seem be an obvious risk factor candidate for recurrent UTIs. However, since other groups of patients with similar immunosuppressive treatment do not suffer from UTIs to the same extent [6], immunosuppression cannot fully explain the increased susceptibility to UTIs in renal transplant recipients.

When we planned this project, general knowledge was increasing about the importance of functional lower urinary tract (LUT) dysfunction as a risk factor for UTI in otherwise healthy children, but little was known about the impact of LUT dysfunction in children after renal transplantation. Furthermore, except for in children with urinary tract malformations, little was known about LUT function in children with chronic kidney disease (CKD), both before and after renal transplantation. We therefore decided to try to broaden this knowledge, and that was the starting point for this thesis.

2 BACKGROUND

2.1 CHRONIC KIDNEY DISEASE IN CHILDREN

Children with CKD face a life-long condition with a number of co-existing complications including cardiovascular disease, neurocognitive delay, anemia, growth failure, nutritional impairment, and metabolic disturbances, as well as the burden of the disease [7]. Early detection of childhood CKD and its complications is of the utmost importance in the management and progress of the condition [8]. However, no or only few signs of CKD are noticeable in the earlier stages by the patient, family and health care professionals [7], thus delaying the diagnosis and treatment and influencing the outcome. The long-term survival of children with end-stage renal disease (ESRD) has improved over the last decades, but is still about 30 times lower than among healthy children. The cause of death is mainly cardiovascular disease and infection [9].

2.1.1 Criteria and definitions of CKD

CKD has been defined by the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) [10] as presence of kidney damage, with or without decreased glomerular filtration rate (GFR), for 3 months or longer or GFR less than 59 ml/min/1.73m², with or without kidney damage, for 3 months or longer [7, 11]. Kidney damage is defined as structural or functional kidney abnormalities, for instance abnormal urinary sediment, albuminuria, electrolyte disorders or other tubular function abnormalities, histological abnormalities, structural abnormalities on imaging studies or a history of kidney transplantation.

CKD is classified into five stages according to the level of renal function, i.e. GFR [12, 13]. This classification indicates the severity of CKD with higher stages representing more severe renal impairment. Stages 1–3 represent normal to mild and moderate forms of reduced renal function, sometimes with no or few symptoms Associated complications become more evident in stages 4 and 5 with decline of renal function [12]. ESRD is a severe health condition requiring lifesaving renal replacement therapy, dialysis or renal transplantation [14].

2.1.2 Prevalence and causes of CKD

CKD is a rare health condition among children. Based on the Swedish prevalence study of Esbjörner et al. the prevalence of CKD, defined as GFR < 30 ml/min/1.73 m² body surface area, was 59 per million children under 16 years during 1986–1994. The corresponding ESRD annual incidence was 6.4 and the prevalence 38 [15]. Corresponding figures from the rest of the world can be exemplified by data from Belgium, where the prevalence of CKD 3–5 was 56 for children aged 0–19 years in 2001–2005 [9, 16], from Italy where the prevalence of CKD with GFR less than 75 ml/min/1.73 m^2 was 75 per million children aged 0-19 years in 2003 [17], and from the USA, where the annual incidence of ESRD today is approximately 15 per million children [7].

In approximately two thirds of cases, the underlying cause of childhood CKD is congenital disorders. These include malformations of the kidneys and urinary tract and hereditary kidney diseases. Renal hypo-/dysplasia, obstructive uropathies and posterior urethral valves are common congenital forms of malformations, and nephropathies such as juvenile nephronophthisis, autosomal recessive polycystic kidney disease, congenital nephrotic syndrome, etc., are hereditary disorders. Acquired kidney diseases, such as glomerulonephritis, vascular nephropathies, and other kidney disorders, are present in approximately one third of cases and are more frequent in older children [7, 15].

2.1.3 Clinical characteristics of CKD

CKD in children does not usually exhibit manifest signs and symptoms in its earlier stages, which may explain why the disease often remains undetected until later stages [16]. As a consequence of the delayed CKD diagnosis, complications may have already occurred before the diagnosis is made. The progress of CKD in children is influenced by the underlying disease, the severity of the initial kidney damage, and the presence of associated risk factors [7, 9].
In both adult and pediatric CKD patients the most important risk factors for renal disease progression are hypertension and proteinuria. Other common CKD related complications in children, such as dyslipidemia, acidosis, hypervolemia, and anemia, are associated with an increased risk of cardiovascular disease [8]. Complications, such as malnutrition, poor growth, and delay in neurocognitive development, and CKD-associated symptoms such as nausea, fatigue, sleep disturbances, skeletal pain and urinary incontinence, are all factors with negative consequences for the child's health-related quality of life (HRQoL) [8, 18]

2.2 TREATMENT OF CKD IN CHILDREN

Early identification of pediatric CKD is important for optimizing the child's health outcomes and capacity for normal growth and development. The goals for the treatment are to correct reversible causes of the disease, to prevent and to delay progression of CKD and to minimize the impact of CKD-related complications [7, 19, 20]. Furthermore, since childhood CKD is a lifelong condition, children and their caregivers need to be carefully informed about and aware of the progressive nature of the disease and the possible future need for dialysis or transplantation [19].

Management of CKD throughout its different stages often involves careful monitoring, pharmacological interventions, and dietary restrictions. The child may need repeated surgical procedures, such as vascular accesses, peritoneal catheters, gastrostomies, etc. Initiating an effective management of hypertension and proteinuria is beneficial already in early CKD stages [21]. Other important therapeutic interventions are correction of anemia, metabolic acidosis, and renal osteodystrophy, which are some of the factors leading to malnutrition and poor growth. In addition to early nutritional interventions, these children may need growth hormone therapy to optimize growth and, in the long term, improve psychosocial development and the quality of life (QoL) [8, 12].

2.2.1 Dialysis modalities

To manage ESRD, renal replacement therapy with peritoneal dialysis (PD), hemodialysis (HD) or kidney transplantation remains the treatments of choice. For children with ESRD, transplantation is considered to provide the best long-term survival and quality of life [22, 23]. However, preemptive transplantation, i.e., transplantation without previous dialysis, is not always possible and depends on the availability of a living or deceased graft donor. Dialysis is often necessary for a period of time for most children with ESRD [22]. The choice of dialysis modality is based on such factors as patient age, lifestyle factors, family prerequisites and availability of facilities and expertise at the pediatric unit [24, 25]. PD is the preferred modality in pediatric ESRD patients, especially in younger children, because the treatment can be performed at home by the parents and allows as much ”normality” as possible [22, 23]. For instance, the child can often attend school as usual. An additional advantage of PD is preservation of residual renal function compared to HD [24].
Hemodialysis is performed three to five times a week at the hospital and may be considered, if PD is not possible to perform, if the parental support is poor, or if HD is preferred by the child (in these cases often a teenager). Reasons for not being able to perform PD are for instance a history of complicated abdominal surgery, recurrent episodes of peritonitis, or inadequate dialysis with PD [24].

2.2.2 Kidney transplantation

Kidney transplantation (Tx) has been the preferable treatment goal for children with ESRD during recent decades. Patient and graft survival outcomes have improved substantially due to experience gained over time, better surgical techniques, and refined immunosuppressive regimens, especially the introduction of calcineurin inhibitors. Nowadays, renal transplantation is regarded as a safe and effective treatment for patients who previously were not considered suitable for transplantation, for example, very young children and children with systemic or metabolic diseases [26, 27]. Furthermore, children with urological diseases and LUT dysfunction are often accepted, provided that LUT dysfunction is properly managed before transplantation [28-30].

Data from the North American Pediatric Renal Trials and Cooperative Studies (NAPRTCS) [31] report increasing short- and long-term graft survival, as well as decreasing acute rejection rates. The American five-year graft survival rate was 86.5% for living donor (LD) recipients in the period 1987–2010, which is higher than the graft survival rate of 83.2% for deceased donor (DD) recipients [32]. In Europe, the corresponding figures for the period of 2003–2007 are 96.8% for LD and 95.3% for DD recipients [33]. Possible causes for this discrepancy in survival rates may be a higher proportion of living donor transplantations in Europe, socio-economic factors, access to health care and insurance matters.

Compared to dialysis, renal transplantation is associated with improved survival, better growth, and better cognitive development [25, 34]. Efforts have been made to increase access to transplantation for children and adolescents by changing deceased donor allograft policies as well as by developing methods to diminish donor-specific anti-HLA antigen antibodies [25, 26]. Despite the encouraging patient and graft survival rates in

children, there are still unsatisfied demands concerning post-transplant care [26]. To find strategies to optimize growth and cognitive development in these children is of great importance. Factors such as an increased risk for cardiovascular diseases, infections, and malignancy can compromise short- and long-term outcomes, thus focused efforts are required to prevent these complications [27, 32]. Adolescent kidney transplant recipients do not have as good survival rates as recipients under 10 years of age, especially in the long term [26]. This is mainly due to factors related to physical side effects of the immunosuppressive medication and subsequent non-adherence. In addition to age, transition to emotional independence in this period of life entails a risk of non-adherence [26]. Also other risk factors for non-adherence have been identified: socio-economic issues and low self-awareness due to poor cognitive abilities, as well as parental stress and disturbances in parent-child interactions [34]. Continued efforts to minimize complications and to optimize growth, neurodevelopment, and the HRQoL in children after transplantation are required [26, 34, 35].

All children considered for renal transplantation undergo a thorough pre-transplant evaluation in order to avoid post-transplant complications and optimize the outcome [27]. The content of such an evaluation may differ from one center to another, but it usually includes comprehensive laboratory, physiological, and imaging studies, exploring, among other things, CNS, lung, cardiovascular, and liver function. A urological evaluation including voiding cystourethrogram and urodynamic studies is of particular importance in children with congenital abnormalities of the kidneys and the urinary tract [27, 36, 37] and is often restricted to this group of patients. A psychosocial evaluation including risk factors for non-adherence is not to be overlooked in the pre-transplant evaluation process in order to be able to identify the need for interventions [27].

2.3 THE LOWER URINARY TRACT

The urinary tract consists of the upper urinary tract, i.e., the kidneys and ureters, and the LUT, i.e., the bladder, the urethra, and the sphincter system (Figure 1). In healthy individuals the kidneys produce urine continuously passing through the two ureters to the bladder for low-pressure storage until eliminated through the urethra. Several mechanisms prevent retrograde flow of urine to the upper urinary tract.

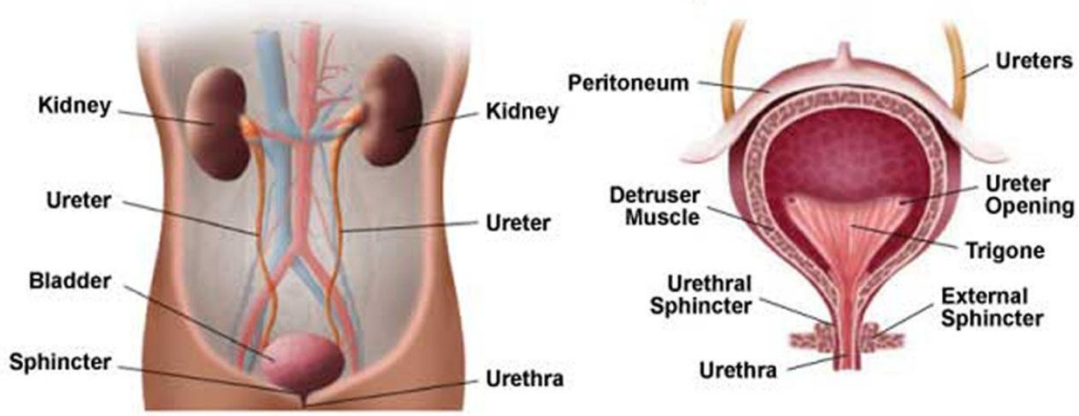

Figure 1. The upper and lower urinary tract.

2.3.1 Storage and emptying function

The urinary bladder has two main functions, the first is to serve as a reliable reservoir and the second is to empty the urine completely without any difficulties such as pressing or straining. Important requirements of the bladder are high compliance during bladder filling and the ability to generate adequate pressure to empty the bladder. In order to meet these demands, the urinary bladder is a highly expandable muscular sac in which the fibers of the main smooth muscle component, the detrusor, are arranged in spiral, longitudinal, and circular bundles [38]. The storage and emptying functions are controlled by a complexity of neurological interactions involving the central nervous system (CNS) and three sets of peripheral nerves: parasympathetic, sympathetic, and somatic nerves [38]. A proper "on-off"-like coordination between these components is essential for either maintaining continence or inducing micturition [39].

2.3.2 Micturition physiology in childhood

Maturation of the CNS as well as adequate social prerequisites is required for the development of voluntary bladder control. Higher CNS centers are already involved in micturition in newborns and the infant usually wakes up, at least for a short while, as the micturition occurs. Incomplete voiding during the first years of life is common owing to immature detrusor-sphincter coordination but disappears when voluntary bladder control is achieved [40], often the age of 5–6 years [41]. Bladder capacity and voided volumes increase gradually during toilet training allowing the child to hold the urine voluntarily. Voiding frequency is related to age and decreases from approximately once per hour in the infancy period [42] to 7–8 times per day in toddler years [43]. Most school-aged children (7 to 15 years old) void between 3 and 8 times per day [44]. Recent studies have shown that voiding control can be trained earlier than practiced nowadays in Western cultures. Toilet training before the first year of life has proved to facilitate a complete bladder emptying, thus, possibly to benefit those children with LUT abnormalities [45].

2.3.3 LUT function – terminology

The International Children's Continence Society (ICCS) provides guidelines on terminology and pediatric LUT evaluation in children [46, 47]. The guidelines describe different manifestations of LUT function and dysfunction aiming at facilitating understanding and communication between those who take care of children and adolescents with LUT dysfunction. The guidelines have recently been updated [48].

2.3.3.1. Definitions considering storage and voiding symptoms according to the ICCS guidelines [47, 48]

A *voiding frequency* of 3 to 7 voids daily is suggested to be normal for 7-year-olds, but it is influenced by diuresis and fluid intake.
Urinary incontinence means repeatedly occurring involuntary leakage of urine in children of at least 5 years of age. Incontinence is further divided into the categories continuous and intermittent incontinence, and daytime incontinence or enuresis.

Urgency refers to a sudden and unexpected need to void, and is often regarded as a sign of bladder overactivity.
Nocturia applies to children of at least 5 years of age who wake up at night to void. This symptom does not necessarily indicate LUT malfunction.
Hesitancy signifies difficulty in initiating voiding although the child is ready to void.
Straining implies an effort to increase intra-abdominal pressure to initiate and maintain voiding.
Weak stream is an observed urinary stream or uroflow of weak intensity.
Intermittency indicates micturition with several stop and start spurts. However, this is physiological up to the age of 3 years if straining is not present.

2.3.3.2. Voided volume, expected bladder capacity, and polyuria according to the ICCS guidelines [47, 48]

Voided volume characterizes the volume of urine measured at micturition and recorded in the voiding diary. The *maximum voided volume (MVV)* refers to the largest volume measured throughout a 24-hour cycle.
Expected bladder capacity (EBC) is defined according to the formula: 30 + (30 x age in years) ml and is applicable to children between aged 4–12 years. The MVV (obtained from bladder diary) is defined as small if found to be less than 65%, or as large if greater than 150% of the EBC.
Polyuria is considered to occur when the urine output exceeds 2,000 ml/m² body surface area.

2.3.4 Common functional LUT disturbances in children

The most common functional LUT disturbances in children without neurological or structural disorders are enuresis and daytime incontinence. The prevalence of enuresis and daytime incontinence is 5–10% in 7-year-old children [49, 50]. Daytime incontinence is often caused by detrusor overactivity [43] and is more common in girls who usually experience concomitant urgency symptoms. This condition tends to give rice to such as postponing micturition as long as possible using various “holding maneuvers”, e.g., squatting with the heel against the perineum. Constipation with or without fecal incontinence is common in these children and may play an important role in LUT dysfunction [51]. The same group of children may have incomplete voids with residual urine and is subsequently at higher risk of developing UTI [52]. The cause of detrusor overactivity is debated but it may originate from a mild delay in the maturation of the CNS which interferes with the ability to gain voluntary control over the micturition reflex [43, 52].
Enuresis occurs more often in boys and may be combined with daytime incontinence or urgency symptoms. Pathogenetic factors of importance are difficulty to wake up in response to activation of the micturition reflex, nocturnal polyuria, and/or inability to manage detrusor contractions [43].
Daytime incontinence and enuresis are known to have a negative impact on self-esteem and HRQoL in the affected children [53]. However, since self-esteem has been shown to become normalized after a successful treatment, it is important to offer treatment as soon as the child is motivated [54, 55].

2.4 URINARY TRACT ANOMALIES IN CHILDREN

In contrast to adults, about 35% of children with CKD in its advanced stages have underlying urological anomalies [56]. In adult patients with ESRD, congenital anomalies of the kidney and urinary tract account for less than 5%, with diabetic and non-diabetic glomerulopathies dominating the disease spectrum [9, 57].

Common congenital urological disorders include posterior urethral valve (PUV), vesico-ureteric junction (VUJ) and pelvi-ureteric junction (PUJ) obstruction, VUR, neuropathic bladder, and prune belly syndrome. Acquired urological disorders include renal tract stones, urethral strictures, neuropathic bladder, and tumors [58].

LUT abnormalities can have a devastating effect on renal function [56]. If unsolved, the ongoing urinary output in combination with urinary tract obstruction causes an increased pressure which dilates the collecting system proximal to the obstruction. The elevated pressure in turn damages the tubules, which leads to a decreased urine-concentrating ability and, consequently, polyuria. Polyuria may in turn lead to chronic bladder over-distension, bladder wall thickening, loss of compliance, secondary detrusor over-activity and subsequent problems involving incontinence and enuresis [56]. The impaired drainage of the urine from the upper urinary tract also imposes a risk for VUR, hydronephrosis, UTI, and renal damage [28, 56]. The injury to the glomeruli is often secondary to the processes mentioned above, but regardless of the cause, it leads to a reduced glomerular filtration rate (GFR) and progressive CKD [58].

Urological disorders in children often lead to voiding disturbances, which occurs for example in boys with PUV. Other underlying urological causes that affect bladder function are neuropathic bladder secondary to spinal abnormalities, VUR, and prune belly syndrome [28].

Children with CKD due to non-urological disorders may also suffer from polyuria. Many hereditary disorders affect tubular function and the ability to concentrate the urine. Even if not combined with an outflow obstruction, polyuria is associated with a risk of developing a large capacity bladder with impaired sensation of distension or over-distension with an underactive bladder as the clinical endpoint [59]. Severe oliguria or anuria is common in children on long-term dialysis and is associated with an increased risk of developing a small, defunctionalized, poorly compliant, high-pressure bladder, and subsequent upper urinary tract damage [56, 60].

LUT function in children with CKD due to other causes than urological ones is not a well-studied subject area. However, a large capacity bladder, emptying problems and incontinence, possibly indicating LUT dysfunction, were reported by Van der Weide et al. to be common also in children with CKD of non-urological origin [59].

2.5 THE LUT FUNCTION AND UTI

Several mechanisms are important in the host defense against UTIs, for instance, the interaction between normal bacterial flora and potential pathogens, desquamation of epithelial cells with adhering bacteria, local production of antibacterial peptides and other immunological mechanisms [61]. The most important defense mechanism is, however, a regular and complete emptying of urine from the bladder and the urinary tract. This will prevent bacteria from colonizing the bladder and invading the upper urinary tract [62]. In children with structural or functional LUT abnormalities, this most important defense mechanism is disturbed [61, 63, 64].

In the pre-antibiotic era children who did not die from their UTIs often recovered with substantial renal damage as a sequel of the infection [61]. Important research revealed the association between UTIs, vesicoureteral reflux (VUR), and renal damage [65, 66], and therefore much effort was concentrated on finding out how to deal with VUR. Further research showed that renal damage could be prevented equally well by either antibacterial prophylaxis or by anti-reflux operations [67]. However, in a substantial number of children who experienced recurrent UTIs and renal damage, no VUR was detected [64]. These children often suffered from incontinence and other signs consistent with LUT dysfunction, a condition that later proved to be another major risk factor for recurrent UTIs [63, 64].

2.6 EVALUATION OF LUT FUNCTION IN CHILDREN

A comprehensive history and physical examination are the cornerstone tools in the diagnostic evaluation of children and adolescents with LUT dysfunction. Further diagnostic tools are categorized into invasive and non-invasive urodynamics.

2.6.1 Non-invasive urodynamic investigations

A bladder diary consists of a 48-hour frequency and volume chart and is used to obtain information about such parameters as voided volumes, voided frequency, urinary outputs, fluid intake, and associated symptoms [47, 68]. Different scoring systems and questionnaires have been developed for measuring LUT dysfunction and the emotional impact of urinary incontinence [69-72]. However, few of them have been cross-culturally validated and tested for reliability.

Uroflowmetry measures the flow rate, the voided volume, and the voiding time during urination. The voiding pattern is presented as a uroflow curve. Five different curve shapes occur: bell-shaped, tower-shaped, staccato-shaped, interrupted-shaped, and plateau-shaped (see “Material and Methods”). These curve shapes may serve as guides to the underlying pathology [51]. Repeated measurements are required to confirm suspected dysfunctional voiding [48, 73]. Uroflowmetry may be combined with electromyography (EMG) to measure the pelvic floor muscle activity during voiding [74].

As mentioned earlier, a child should empty the bladder completely. Assessment of post-void residual urine is therefore an important diagnostic tool and the assessment should

be performed within a maximum of five minutes after completing the uroflow measurement. Real-time equipment is preferred for diagnostic use. Post-void residual urine exceeding 20 ml at repeated measurements indicates incomplete bladder emptying [47].

The bladder diary, uroflowmetry, and residual urine measurements may be referred to as "urodynamic screening".

2.6.2 Invasive urodynamic investigations: Cystometry

Invasive urodynamic studies (cystometry and pressure flow studies) are not routinely performed to evaluate LUT function in children but have a given place in the evaluation of LUT function in children with neurogenic bladder, structural anomalies of LUT, and/or functional voiding problems resistant to treatment [51, 52]. Since the investigation is known to be associated with psychological distress due to the transurethral or suprapubic catheterization, it is important to reduce child and parental distress by an adequate preparation prior to the procedure, and additionally, thereby also ensure a safe and reliable examination [48, 75, 76]. A non-invasive evaluation allows us to identify children who will benefit from invasive urodynamics [77, 78]. Cystometry is used to record urodynamic conditions during the filling phase of the micturition cycle. Bladder sensation, detrusor activity, bladder compliance, and bladder capacity are parameters concerning the obtained bladder storage function and serve as important markers to identify children at risk for upper urinary tract damage [52, 77, 79].

2.7 MANAGEMENT OF LUT DYSFUNCTION

The primary goal of treatment of LUT dysfunction is to normalize bladder function and to prevent kidney injury. Surgical interventions may be required as treatment for children with structural or neurogenic LUT anomalies.

The first-line treatment for children with various LUT disturbances is bladder rehabilitation. This treatment model is based on cognitive behavioral principles and includes such components as providing knowledge about normal LUT and bowel function and which behavioral changes are needed to correct the voiding habits. The child is given instructions about timed voiding in order to train the voluntary central nervous control of the micturition [80]. Training of a relaxed voiding posture is basic and can be administered by means of instructions and simple exercises to gain awareness of the relaxed or contracted pelvic floor muscles [81, 82]. Regular follow-up visits to repeat the instruction and increase understanding and motivation give valuable and encouraging support [80].

Voiding school was developed by Glad Mattsson et al. as an alternative to the individual treatment model [83]. This form is applicable for children in small groups and has shown positive results with regard to reducing UTIs and incontinence. More specific urotherapeutic nonmedical interventions used include different forms of biofeedback training, electrical stimulation, and clean intermittent catheterization (CIC) [84].

Children with anatomical LUT abnormalities, such as obstructive uropathy or a severe VUR, may need surgical corrections, often primarily, to relief the obstruction or facilitate urine drainage from the upper urinary tract. Older children with neurogenic bladder sometimes require enlargement of the bladder or other reconstruction procedures to improve bladder compliance [56].

Management of LUT dysfunction, when the causes are other than functional disturbances, may require additional interventions to achieve acceptable storage and emptying function. Frequent voids and double micturition are useful methods to optimize bladder emptying in children with post-void residual urine [56]. Anticholinergic medication is used as a complement to improve storage by relaxing the detrusor muscle and increasing compliance. Polyuria in children as well as infrequent voiding habits should be addressed in order to prevent bladder distension. Overnight catheter drainage has been reported to be an effective therapy in children with severe polyuria in order to prevent chronic bladder distension and kidney function deterioration [52, 56, 85].

CIC has become a safe and effective treatment option for children with severe bladder emptying problems of various etiologies [52]. CIC is the treatment of choice in children with neurogenic bladder dysfunction for minimizing the consequences of detrusor sphincter dyssynergia [52, 56]. Early treatment with CIC not only reduces the risk for UTIs and kidney damage but also helps to enhance urinary continence in these children [86, 87].

2.8 HRQOL

Over the last few decades, medical, surgical, and immunological advances have dramatically improved treatment outcomes and long-term survival rates for children with CKD or a kidney transplant [14, 26]. However, optimal care of pediatric renal patients should aim not only at excellent survival rates, but also at attention to how the children feel and get along with everyday life [88]. In this context, HRQoL has become an important health indicator for treatment outcome as well as measure of the impact of the condition in people suffering from various diseases, including children with CKD at different stages [88-90].

Definition of HRQoL

QoL is often used synonymously with HRQoL but is a general concept lacking consensus on a clear definition. QoL includes a broader range of aspects, e.g., environmental and economic issues, and can adapt different meanings to different individuals depending on the context [91]. The term has traditionally referred to health status, physical functioning, symptoms, psychosocial adjustment, well-being, life satisfaction, and happiness [92]. In the context of medical outcomes, QoL has a clear connection to subjective and objective health and disease and treatment-related well-being [93]. Health, as defined by the World Health Organization (WHO) [94] as -“a state of complete physical, mental and social well-being, and not merely the absence of disease”-, is an important component of quality of life [95].

HRQoL is a part of the broader concept of QoL. A variety of definitions and models across different health and illness conditions have been used to explain the concept HRQoL [96]. HRQoL is related to one's health and described as a "multidimensional concept covering physical, mental, social and behavioral components of well-being and function as perceived by patients and/or other observers" [93, 95, 96]. This latter definition of HRQoL agrees with the one used in this thesis.

2.8.1 Measure of HRQoL in children

Measuring HRQoL in children and adolescents encounters unique demands, compared to measuring in adults [89]. A meaningful development of a QoL instrument requires consideration of age-related issues, as well as maturity and cognitive development [93]. Another question has been how to get reliable answers from children. Agreement between child and parent ratings concerning the child's HRQoL has also been questioned. The child ratings are, however, preferable whenever possible even though HRQoL ratings obtained from a parent or caregiver may serve as an additional source of information [93, 97].

The development of appropriate instruments for measuring HRQoL in both healthy and chronically ill children has been encouraging, a number of them fulfilling requirements of age and cognitive appropriateness [89]. Generally, HRQoL measures can be divided into two main categories: generic and disease-specific measures [89, 91]. Generic questionnaires address issues not directly related to disease and can provide information from healthy children as well as children with different diseases or conditions. This allows comparisons across different groups and for comparisons with the general population. The criticism of generic instruments is that they may fail to capture information of particular concern in certain groups [91]. Disease-specific instruments may be useable for detecting important clinical information. Their limitation is, however, that a comparison of HRQoL measurements with those in other illness groups is not possible [93]. Generic measures with disease-specific modules are also available; an example being the widely used PedsQoL [98]. The European KIDSCREEN/DISABKIDS project has developed similar instruments for measure of generic, chronic illness generic and condition-specific (disease-specific) aspects of HRQoL [90, 99-101].

In this thesis, two questionnaires, one generic and one chronic generic, were used to measure the HRQoL. The Kidscreen-27 and the Disabkids Chronic Generic Module-37 (DCGM-37) instruments were chosen because they were developed in Europe and provide a European reference material. The two instruments allow assessment of generic and chronic illness generic aspects of HRQoL in children and adolescents and are usable in health research and clinical settings in different cultures [90]. The European KIDSCREEN and DISABKIDS projects developed the instruments in a cross-cultural approach, were in close collaboration with each other and used the same methodology. The developmental process included literature research, expert panels and focus groups with children in order to identify items and dimensions, and then finally field testing and pilot studies. The same methodological approach allows combining of both measures [90].

2.8.2 HRQoL in children with CKD or a kidney transplant

HRQoL in children and adolescents with CKD with a focus on different stages of CKD and different treatment modalities has been studied only sparsely. A few studies have evaluated HRQoL before the children has reached ESRD [12]. Gerson et al. [102] have described HRQoL in children with mild to moderate CKD and reported impairments in physical, school, emotional, and social functioning, as well as poorer overall HRQoL compared to the general population. Furthermore, anemia, short stature, and shorter disease duration were found to be variables predicting HRQoL impairments [102-104]. Gerson et al. reported that HRQoL was already affected in the early stages of CKD, but did not deteriorate between stages 1 and 3 [102]. Other researchers have studied children with CKD in advanced stages (stage 4 and 5) and reported reduced physical and psychosocial functioning in comparison with healthy children [105-107].

The CKiD (Chronic Kidney Disease in Children) Study identified important factors associated with a negative influence on HRQoL. Short stature ($<5^{th}$ percentile for height), sleep disturbances, fatigue, and urinary incontinence were found to be common conditions affecting HRQoL [102, 108-110]. The authors pointed out the importance of detecting and providing treatment for these problems.

Children and adolescents with ESRD have reported a variety of problems such as an impaired sense of self-worth, uncertainty about the future, and limitations in physical and psychosocial capacities [111], and children receiving long-term dialysis have been shown to have even lower overall health and well-being than those treated for newly diagnosed cancer [112]. Optimizing the care of children and adolescents with ESRD regularly and standardized assessments of HRQoL are necessary to identify areas where support is required [25, 113].

Kidney transplantation is a successful therapy with excellent outcomes in pediatric patients [114]. A number of reports have indicated better HRQoL in pediatric renal recipients than in those receiving dialysis [112, 114-116]. There are, however, conflicting results with other authors reporting no differences in most of HRQoL domains in children on dialysis as opposed to those with a renal transplant [106, 117, 118]. Several studies have pointed out factors which may have a negative influence on HRQoL in pediatric renal recipients. Neurodevelopmental delays and cognitive impairments interfering with psychosocial adjustment are some of them [119]. Impairments in physical functioning and exercise capacity contribute to diminished well-being [120]. Medication-related negative effects such as weight gain, headache and fatigue are other common factors affecting several domains of HRQoL and thus are important to pay attention to in pediatric renal recipients [104, 116, 119, 121-123].

3 AIMS OF THE STUDIES

The overall aim of this thesis was to evaluate LUT function in children with CKD before and after renal transplantation and to study the role of LUT dysfunction in relation to UTIs. An additional aim was to study potential associations between LUT dysfunction and HRQoL in these children.

Specific aims were:

Study I: To evaluate the prevalence and type of LUT dysfunction in children after kidney transplantation, and to evaluate whether LUT is more common in certain disease groups compared to others.

Study II: To evaluate the association between LUT dysfunction and UTI in children after kidney transplantation and to study the impact of recurrent UTIs on graft function.

Study III: To evaluate the prevalence and type of LUT dysfunction in children with CKD, to evaluate whether LUT dysfunction is more common in certain disease groups and, furthermore, to evaluate the association between UTIs and LUT dysfunction in these children.

Study IV: To further define LUT function with cystometry in children with CKD and LUT dysfunction according to non-invasive urodynamics. Additionally, to explore what information invasive urodynamics (cystometry) can add to the non-invasive technique in order to find out which children will benefit from this investigation in pre-transplant evaluations.

Study V: To evaluate potential associations between LUT dysfunction and HRQoL in children with CKD (with or without a renal transplant) and, further, to evaluate associations in relation to children with other chronic conditions and to those in the general population.

4 MATERIALS AND METHODS

4.1 STUDY DESIGN AND PARTICIPANTS

The participants in all of the five studies presented here were children and adolescents treated at the Pediatric Nephrology Unit at Astrid Lindgren Children's Hospital in Stockholm, which is a referral center for children with kidney diseases in Sweden. The center treats children from the middle and northern parts of Sweden (covering approximately two thirds of the pediatric population). The design was cross-sectional, descriptive, and comparative. Studies II and III were partly retrospective. An overview of the studies is presented in Table 1.

Table 1. Overview of the design and patient characteristics in each study

Study	I	II	III	IV	V
Design	Cross-sectional Comparative	Cross-sectional Retrospective	Cross-sectional Comparative Retrospective	Cross-sectional Comparative Descriptive Retrospective	Cross-sectional Comparative Descriptive
Participants	68	Same group as in Study I	40	17 A subgroup of Study III	59
Male/Female	37/31		27/13	14/3	30/29
Age range	5–20		5–18	6–18	8–19
CKD, stage 3-5			40	17	23
Tx	68				36
Urological disorders	23 (34%)		13 (32.5%)	11 (65%)	19 (32%)
Males	16		11	9	12
Non-urological disorders	45 (66%)		27 (67.5%)	6 (35%)	40 (68%)
Males	21		16	5	18

4.1.1 Study I

Studies I and II are based on the same population. Inclusion criteria were children referred to the clinic, aged 5 years or older, without a urinary diversion. Between 2002 and 2003, 73 children underwent their yearly follow-up examination after renal transplantation, including a renal function investigation (glomerular filtration rate, GFR). Of these children, 68 completed the routine control of bladder function including a questionnaire, uroflowmetry, and bladder ultrasound. The children were 5–20 (median 14.3) years old at examination, and the median time from kidney transplantation was 5 (range, 1–15) years. Causes for not participating (5 children) were other commitments (2), lack of time (2), and inability to perform uroflow measurements due to mental retardation (1).

4.1.2 Study II

The same population as in study I. The patients' medical records were retrospectively reviewed regarding UTI history (number and timing) and earlier graft function (GFR). Additionally, parents were questioned about their child's UTI history. UTIs within the first month after transplantation were excluded because of the known association with surgery-related matters (indwelling catheters, injury to the mucocutaneous surfaces and graft, etc.).

4.1.3 Study III

Between 2006 and 2008, a total of 40 children with moderate to severe CKD (GFR range 5–50 ml/min/1.73 m²), age 5–18 (median 11.5 years), and with bladder control and sufficient developmental maturity to understand the instructions, underwent their yearly check-up including an evaluation of renal and lower urinary tract function. All 40 children consented to participate in the study. Children younger than 5 years old without bladder control, those with urinary tract diversions, and those without sufficient cognitive ability to cooperate in the investigations were not approached.

4.1.4 Study IV

In the cohort of the 40 children in Study III, 29 were identified as having suspected bladder dysfunction based on the reported symptoms and abnormal findings from the bladder diary, uroflowmetry, or bladder ultrasound. These children were recommended invasive urodynamics (cystometry) to further explore their bladder function. Four of the children received a kidney transplant before investigation, 6 refused to participate, and 2 were lost to follow-up (transferred to adult care). Seventeen children, aged 6–18 years, accepted and consented to a cystometric investigation.

4.1.5 Study V

A sample of 64 eligible children, i.e. those over 8 years old, with CKD stage 3 to 5, or with a kidney transplant and with developmental maturity, was approached during 2011–2012 in the same setting as previously. Three declined due to lack of time (1) and simple refusal (2) and two children were excluded due to incomplete investigations, finally leaving 59 participants aged 8–19. A healthy comparison group of children, randomly selected from the Swedish population registry, SPAR, comprising 257

subjects (response rate 54%), aged 11–23 was recruited and asked to answer the QoL questionnaire, Kidscreen-27 [124]. In order to age-match our study group, only participants under 19 years old, a total of 203, were included as one of the comparison groups in the present study. To compare data obtained from the DCGM-37 questionnaires, the results from field studies comprising 1152 children, aged 8–16 years and with different chronic conditions [99, 125], were used as a reference for our data.

The number of children included in the studies and their overlapping is outlined in Figure 2.

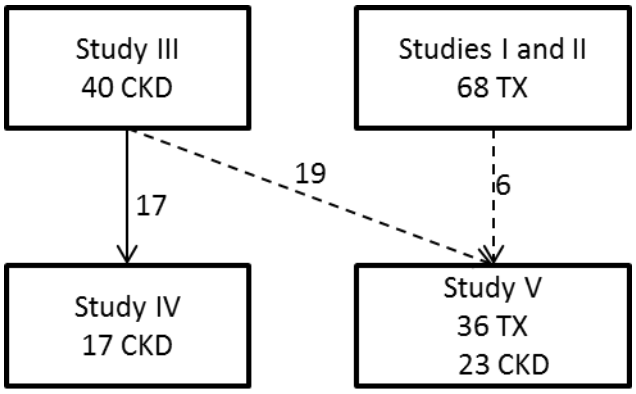

Figure 2. Overview of participants in Studies I-V and their overlapping.

4.2 UNDERLYING DISEASES IN STUDIES I-V

An overview of the causes of CKD or ESRD is outlined in Table 2. Diseases are grouped as congenital diseases with (UTM+) and without urinary tract malformations (UTM-) and acquired diseases.

Table 2. Overview of diagnoses in children with CKD or a renal transplant.

Diagnoses			Study I, II	Study III	Study IV	Study V
			N = 68	N = 40	N = 17	N = 59
Congenital disorders + UTM	Urological disorders	PUV	8 (12%)	5 (12.5%)	5 (29%)	5 (8.5%)
		Drash syndrome	2 (3%)			
		Prune belly	4 (6%)			
		Meatal stenosis	1 (1.5%)			
		VUR ± dysplasia		7 (17.5%)	5 (29%)	10 (17%)
		Neurogenic bladder		1 (2.5%)	1 (5.9%)	1 (1.7%)
		Other urinary tract anomalies				3 (5.1)
Congenital disorders -UTM	Non-urological disorders	Nephronophthisis	10 (15%)	4 (10%)	1 (5.9%)	5 (8.5%)
		Polycystic kidney disease	3 (4.5%)	4 (10%)		3 (5.1%)
		Congenital nephrotic syndrome	8 (12%)	1 (2.5%)		6 (10.2%)
		Jeunes syndrome	1 (1.5%)			
		Braun-Bayer syndrome	1 (1.5%)			
		Branchio-oto-renal syndrome	1 (1.5%)			
		Hypoplasia/dysplasia*	8 (12%)	5 (12.5%)	3 (17.6%)	7 (11.9%)
		Metabolic disease		2 (5%)	1 (5.9%)	1 (1.7%)
		Oligomeganephronia		1 (2.5%)	1 (5.9%)	1 (1.7%)
Acquired		Neonatal ischemia	5 (1.25%)	1 (2.5%)		4 (6.8%)
		Glomerulonephritis	10 (15%)	3 (7.5%)		5 (8.5%)
		Wegener's granulomatosis	1 (1.5%)			
		Atypical hemolytic uremic syndrome (aHUS)	1 (1.5%)	2 (5%)		2 (3.9%)
		Focal segmental glomerulosclerosis (FSGS)	3 (3%)			3 (5.1%)
		Nephrogenic diabetes insipidus	1 (1.5%)			
		Interstitial nephritis		2 (5%)		
		CKD of unknown cause		2 (5%)		3 (5.1%)

* In Study I classified as Congenital disorders + UTM

4.3 DEFINITIONS

4.3.1 CKD

CKD is classified into different severity levels (stages 1–5) according to the "Kidney Disease: Improving Global Outcomes" (KDIGO) clinical practice guidelines (2012) [11]. Moderate to severe stages of CKD and ESRD (stages 3 to 5) correspond to GFR 59 ml/min/1.73 m² or lower. Children with a renal transplant are sometimes referred to as having CKD-T (CKD transplant) as they have in fact a chronic kidney disease even though it is treated with a renal transplant. In most cases, renal function improves significantly after renal transplantation and a GFR of approximately 70–80 ml/min/1.73 m^2 is not uncommon at the first annual post-transplant control. Due to rejections, infections, toxic effects of the medication, and other complications, graft function often gradually declines over time, however, and the patient again reaches different levels of CKD according to the above-mentioned definitions. In this thesis, children with CKD stage 3–5, i.e., GFR 59 ml/min/1.73 m² or below were referred to as children with CKD; pediatric renal transplant recipients with different stages of CKD were referred to as children with a renal transplant or pediatric transplant recipients.

4.3.2 LUT dysfunction / bladder dysfunction

In this thesis, symptoms and conditions defining LUT function and dysfunction are according to the ICCS former guidelines [46, 47], i.e., the guidelines available when planning the studies. At the beginning of this project, entities within the concept of LUT dysfunction (or bladder dysfunction), such as overactive bladder, dysfunctional voiding, and underactive bladder had a clear definition in the literature. A definition of the broader concept "LUT dysfunction" was, however, lacking. We therefore defined LUT dysfunction ourselves. In Studies I and II, LUT dysfunction was defined as abnormal bladder capacity (bladder capacity exceeding 150% or less than 65% of that expected for age), abnormal urinary flow (tower, interrupted, fractionated, or plateau) and/or residual urine greater than 20 ml on repeated measuring. In Studies III–V, incontinence was added and the tower uroflow pattern withdrawn as signs of LUT dysfunction as advised by referees. Furthermore, urinary flow patterns representing disturbances in the emptying phase (staccato, interrupted, or plateau flow pattern) were summarized as discontinuous urinary flow patterns in these latter studies.

4.3.3 Polyuria and oliguria

Polyuria was defined as a urine output of 2000 ml/m² body surface area or more per 24 hours [47] and oliguria as less than 300 ml/m^2.

4.3.4 UTI

UTI was defined as significant bacteriuria, greater than 10^5 cfu/ml, for which antibacterial treatment was started on the clinical suspicion of UTI. Recurrent UTI was defined as 2 or more UTIs.

4.4 METHODS

An overview of the measures in Studies I–V is presented in Table 3.

4.4.1 Renal function

The glomerular filtration rate (GFR), reflecting renal function, was examined in all children according to the pre- and post-transplant programs. Different methods were used depending on such factors as tolerability for the child, ward staff resources, and changes in clinical practice. GFR can be assessed from the renal clearance of inulin or iohexol or estimated using the plasma level of cystatin C.

4.4.1.1 Plasma clearance of inulin

A substance, inulin (Inutest, 25% [sinistrin]; Fresenius Kabi, www.fresenius-kabi.no) is administered intravenously as a continuous infusion after a prime dose. A standard clearance technique, induced by oral intake of water in order to maintain adequate diuresis and enable the child to empty the bladder, consists of four urine collection periods with blood samples midway during each collection period. The mean value of the four clearance periods is calculated [126]. The method is viewed as the gold standard for kidney function assessments [127].

4.4.1.2 Plasma clearance of iohexol

The method of plasma clearance of iohexol (Omnipaque 300 mg/ml; GE Healthcare, md.gehealthcare.com) is based on a sloping curve of plasma concentration or a single-point measurement. A small dose of iohexol is administered intravenously and blood samples are collected from the contralateral arm after 180, 200, 220 and 240 minutes if GFR is > 50 ml/min/1.73 m²; otherwise, the time span to the first blood sample has to be increased [128]. This method has shown good agreement with renal clearance of inulin except in the lower range of GFRs [128].

4.4.1.3 Cystatin C estimated GFR

Cystatin C is an endogenous, small molecular weight protein that is produced by all nucleated cells in the body at a constant rate and eliminated solely by the kidneys. One of the advantages of cystatin C, compared to s-creatinine, is that it can detect even mild forms of GFR impairment [129]. A single blood sample of a very small amount (0.5 ml) is sufficient for the analysis.

4.4.2 Review of medical records

The children's medical records were subjected to a retrospective review in Studies II and III in order to obtain information about patient characteristics, ongoing medication, and earlier UTIs and GFR. The history of earlier UTI episodes was also ascertained by questioning the children and their caregivers.

4.4.3 Evaluation of LUT function

Evaluations and investigations of LUT function were performed according to the ICCS guidelines [46, 47] unless stated otherwise.

Table 3. Overview of measures used in Studies I to V.

	Study				
	I	**II**	**III**	**IV**	**V**
Measures					
GFR	x		x		x
Questionnaire/voiding habits, (ICIQ-FLUTS)	x		x	x	(x)
Bladder diary			x	x	x
Uroflowmetry	x	x	x	x	x
Bladder ultrasound	x	x	x	x	x
Cystometry				x	
Medical records (retrospective review)		x	x		
Kidscreen-27					x
Disabkids-37 (DCGM-37)					x
Subjective health and symptom inventory					x

4.4.3.1 Bladder diary

Different protocols for evaluating micturition habits have been used and called by different names in clinical contexts and research, e g., bladder diary, voiding diary, frequency-volume chart, questionnaire concerning micturition habits, etc. In Studies I and II, the aim of a questionnaire concerning micturition habits to be completed by the child or family at home was to record voiding-related symptoms and conditions. The questionnaire was then discussed at the clinical appointment with the urotherapist. In studies III, IV, and V, a 48-hour frequency-volume chart with daytime and nighttime recordings of volumes was added to the investigations of bladder function.

4.4.3.2 ICQ-FLUTS inventory

To ensure adequate data concerning LUT function, the Swedish version of the International Consultation on Incontinence Questionnaire Female Lower Urinary Tract Symptoms (ICIQ-FLUTS) inventory [130] was used in Study V as a complement to the comprehensive history mentioned above. The questionnaire also allowed grading of the severity of the symptoms on a ten-point Likert scale. The ICIQ-FLUTS inventory is a psychometrically validated instrument for assessing LUT in females of all ages and was chosen in this study due to the lack of validated questionnaires regarding LUT symptoms (LUTS) in children.

4.4.3.3 Uroflowmetry

All patients studied were examined using uroflowmetry for voiding patterns and, in Studies I–II, to measure maximum voided volumes. The uroflowmeter (Urodyn 1000, Medtronics Dantec, Skovlunde, Danmark) was installed underneath a toilet-like chair and placed in a natural toilet milieu where the child was allowed to sit relaxed and undisturbed. The child was properly informed about the procedure and asked to wait until the desire to void was strong. The child was encouraged to maintain a normal fluid

intake. The measurement was repeated at least once and the most normal flow curve was used for the evaluation.

A tower-shaped curve, produced by a powerful voiding contraction, appears as a steep rise and falls in flow with a high Qmax and may represent a condition of suspected bladder overactivity. A staccato-shaped curve is seen as a continuous but fluctuating flow with sharp peaks and troughs and displays intermittent sphincter overactivity throughout the voiding. A fractionated flow curve is characterized by interrupted voiding with discrete peaks displayed on the curve corresponding to the abdominal straining to achieve bladder emptying and suggesting an underactive detrusor. The flow pattern is displayed as separated peaks on the curve and segments with no flow between these peaks. A plateau-shaped curve is a recording of a flattened, prolonged outflow suggesting organic bladder outlet obstruction [46, 47].

4.4.3.4 Bladder ultrasound

Bladder ultrasound for detecting post void residual urine was performed within five minutes after uroflowmetry using real-time equipment, Aloka SSD-500 (Tokyo, Japan) or Aloka Prosound across the examinations. The assessment was repeated at least once. The smallest amount of residual was recorded. Volumes of 20 ml or more on repeated occasions were considered clinically significant. All uroflowmetry and bladder ultrasound measurements were performed by the same investigator.

4.4.3.5 Cystometry

The invasive urodynamics (cystometry) in Study IV was performed using standard techniques [78], and all investigations were conducted by the same personnel. All enrolled children were carefully prepared following the local preparation program for children and parents before transurethral catheterization. As a complement to the oral and written information, the procedure was demonstrated in an interactive manner using illustrative pictures and play material (doll and catheter) for the child and the caregiver [76]. All children were offered the possibility to watch a film as distraction during the procedure.

During the investigation the child was in a sitting or half-sitting position. The urodynamic equipment, Duet® Logic/MultiP (Medtronic AB, Sweden), was used for all studies. A 2-lumen 6 Fr catheter for cystometry was inserted and the bladder was completely emptied before starting the investigation. A rectal catheter was used to obtain an abdominal pressure. Both of these water-perfused catheters (3 ml/h) were connected to pressure transducers which recorded intravesical and abdominal pressures from which detrusor pressure was calculated (p ves – p abd). EMG activity was recorded simultaneously by perianally placed surface electrodes. Body-warm saline (0.9%) was infused at a rate of 5–10% of the expected bladder capacity (EBC) or of the maximum voided volume if that was known (from the bladder diary) to be significantly more than the EBC, expressed in ml/min. EBC was obtained using the formula 30 + (30 x age in years) ml up to 500 ml [47]. The filling was terminated at a high baseline detrusor pressure (> 50 ml/cm H_2O), at urge, complaints or uneasiness, at micturition, at an infused volume of > 150% of EBC with a detrusor pressure at the same time

exceeding 20 ml/cmH_2O, or at continuous leakage. In order to get a reliable result, the filling was performed twice and the second cycle was used for analysis. The parameters of interest during the filling procedure were detrusor activity, compliance, bladder sensation, bladder capacity, maximal detrusor pressure, and leakage. These parameters were defined and suggested by the ICCS [47]. To our knowledge, there are no internationally accepted definitions of reduced bladder sensation, reduced bladder compliance, and large bladder capacity. In this thesis, reduced bladder sensation was defined as a weak or no sensation of bladder filling at greater than EBC for age, a reduced compliance as compliance lower than 5% of the EBC in ml (expressed as ml per cm H_2O), and a large bladder capacity as a filling exceeding 150% of the EBC without a desire to void.

4.4.4 Evaluation of HRQoL

The QoL instruments, Kidscreen-27 and DCGM-37 self-reports, were used in Study V. The study group completed both of them on the same occasion during the clinical visits.

4.4.4.1 Kidscreen-27

The KIDSCREEN project developed a set of three HRQoL questionnaires including proxy versions for parents/caregivers, intended for 8 to 18-year-old healthy children and adolescents and those with chronic conditions. The project was carried out cross-culturally with 13 participating European countries. The identified dimensions describing HRQoL in the Kidscreen-27 were Physical Well-being, Psychological Well-being, Autonomy & Parent Relations, Social Support & Peers, and School Environment [95]. All items in the Kidscreen-27 refer to the latest week and the respondent gives a score on a 5-point Likert scale ranging from 1 (poor/not at all/never) to 5 (excellent/extremely/always). The raw scores from different dimensions were entered into SPSS statistical tool according to the guidance given in the handbook [95]. The different steps in the process result in T-values with means of 50 and a standard deviation of 10, with higher values indicating a better HRQoL. The Kidscreen-27 has been shown to be a valid measure of HRQoL in children and adolescents when tested psychometrically and cross-culturally [131, 132].

4.4.4.2 DCGM-37

The DISABKIDS questionnaires were developed in collaboration with seven European countries for the assessment of HRQoL involving children and adolescents with different chronic diseases and their proxies. The DISABKIDS self-reported measures, targeted at 8–16-year-old children and adolescents, include a chronic generic part, the DCGM-37, and seven condition-specific modules (asthma, arthritis, epilepsy, cerebral palsy, diabetes, atopic dermatitis, and cystic fibrosis). The DISABKIDS measure is available in short and long versions, as well as proxy versions. The longer version, DCGM-37, was used in this thesis and consists of 37 items belonging to 6 dimensions of HRQoL: Independence, Emotion, Social inclusion, Social exclusion, Physical limitation, and Treatment. All items refer to the last four weeks in question and use a Likert scale ranging from 1 to 5 (never, seldom, quite often, very often, and always). Raw scores from the dimensions are calculated and transformed using standard scoring algorithms

for the instrument, resulting in scale scores in a possible range of 0 to 100 [125]. The transformed summary data were used in our analyses with a higher score indicating a better HRQoL. DCGM-37 has been shown to have satisfactory reliability and validity in psychometric tests [99].

4.4.5 Comparison groups (Study V)

A comparison group of 500 individuals, aged 11–23, was randomly selected from the Swedish population registry (SPAR). Of these subjects, 257 (54%) participated and completed the Kidscreen-27 by telephone interviews, as has been reported elsewhere [124]. From this group, 203 age-matched participants were included in the present study for comparison with the general population. For comparisons with children with other chronic diseases, DCGM-37 data from the field studies provided by the DISABKIDS group [99] were used.

4.4.6 Subjective health and symptom inventory

In study V a self-assessment checklist covering subjective health and symptoms was used in order to further describe the patient group and get a better understanding of problems which may affect the everyday life of children living with CKD or a renal transplant. The checklist, designed and previously used for children with allogeneic stem cell transplants [133], was modified for use in children with CKD. The children were asked about participation in physical exercise activities and about selected subjective symptoms (fatigue, nausea, itching, headache, pain, heart/pulmonary problems, sleeping disturbances). They were also asked if they considered themselves to be overweight or short. Symptoms appearing most frequently were reported.

4.5 STATISTICAL ANALYSES

4.5.1 Descriptive statistics

Numbers and percentages were used to describe the distribution of patients and characteristics. The mean and the standard deviation were used when the data were normally distributed. The median and the range (min – max) were presented for non-normally distributed data.

4.5.2 Statistical methods

The statistical analyses were performed using Statistica (StatSoft Inc.) in Studies I–III and IBM SPSS Statistics (version 20 for Windows, IBM Corp) in Study V. Statistical significance was set at $p < 0.05$ throughout the studies.

Non-parametric statistics were used in Studies I and II. Chi-square testing was performed to test for differences between two proportions in categorical variables, and Kruskall-Wallis to test more than two groups. The Mann-Whitney-U test was used to test continuous variables in Study II. Fisher's exact test was used for categorical variables and Student's t test for continuous variables in Study III. Linear regression analyses were performed for correlation studies. Differences within and between groups were analyzed using independent-samples t-tests in Study V.

5 ETHICAL APPROVALS

Studies I–IV were approved by the local Ethical Committee at the Karolinska University Hospital, Huddinge (Dnr 704/03), and Study V was approved by the Regional Ethical Board in Stockholm (Dnr 2011/320 – 31/3).

6 RESULTS

All the studies (I–V) have a focus on bladder function in children with CKD or a renal transplant. Since the kidney disease was usually progressing from mild to severe forms of CKD to ESRD requiring dialysis or transplantation, the results from the studies in this thesis are presented in that order. Thus, the results from Studies III and IV are presented first, followed by Studies I and II and, finally, Study V.

6.1 LUT DYSFUNCTION IN CHILDREN BEFORE AND AFTER RENAL TRANSPLANTATION AND ASSOCIATION WITH UTI

6.1.1 LUT dysfunction and CKD (Study III)

The aim of **Study III** was to evaluate the prevalence and type of LUT signs and symptoms in children with CKD stages 3–5 and to compare signs and symptoms in these children with and without underlying urological disorders, and, furthermore, to report data concerning UTI. Eight (20%) of the included 40 children suffered from incontinence, 19 children (47.5%) had a large bladder capacity, 8 children (20%) had a discontinuous urinary flow, 12 children (30%) had a tower flow pattern, and 6 children (15%) had post void residual urine of 20 ml or more (Figure 3). Twenty-nine of the children (72.5%) showed one or more signs of LUT dysfunction (incontinence, large/small bladder capacity, and discontinuous urinary flow and/or post void residual urine). A large bladder capacity was the most common finding, followed by incontinence and discontinuous urinary flow.

Signs of LUT dysfunction were present in all 13 children (100%) with urological diseases and in 16 of 27 children (59%) with non-urological diseases. Mean age, GFR, and urine output, as well as the proportion of children with incontinence and small bladder capacity, were similar in these two groups. Large bladder capacity, a discontinuous urinary flow, and post-void residual urine were slightly more common in children with urological diseases, but the differences did not reach statistical significance.

Forty percent of all children had experienced one or more febrile UTIs, but infections were significantly more common in children with urological diseases, compared to those with non-urological disorders (77% vs. 22%, $p = 0.0017$), and in children with signs of LUT dysfunction compared to those with normal LUT function (55% vs. 0%, $p = 0.0012$).

6.1.2 Evaluation of LUT dysfunction with cystometry (Study IV)

The aim of **Study IV** was to further define LUT function in children with CKD in stages 3–5 and to compare the evaluation of bladder function using invasive urodynamics (cystometry) with non-invasive methods. From the previous cohort of 40 children (Study III), 29 with signs of LUT dysfunction (incontinence, large bladder capacity, discontinuous urinary flow, post-void residual urine), as evaluated with non-invasive

methods (history, bladder diary, uroflowmetry, bladder ultrasound) were recommended cystometry. Seventeen children accepted and underwent the investigation. A large cystometric bladder capacity (CBC) was the most common finding (12/17 children, 70.6%). A reduced bladder sensation was often combined with this finding (9 of 12, i.e., 75% of the children with a large CBC; 9 of 17, i.e., 52.9% of all children). No other cystometric abnormalities were found in the 12 children with a large CBC. Other abnormalities were found in two children (11.8%): one of them had a reduced compliance and reduced bladder sensation, and the other had reduced compliance and detrusor overactivity. Normal results were found in 3 of the 17 children (17.6%). A large bladder capacity and reduced bladder sensation was common in children with both urological and non-urological disorders. Detrusor overactivity and reduced compliance were observed only in children with urological disorders.

Results from the non-invasive screening revealed a large maximum voided volume in 10 of 17 children (58.8%) as the only abnormality. The results were confirmed by cystometry in 8 of 10 cases. In the remaining two cases, cystometry results were found to be normal. These two children had a maximum voided volume amounting to 160–165% of EBC for age (i.e., just above the upper limit of normal), but no other abnormalities in the non-invasive evaluation. The non-invasive screening showed abnormalities other than a large maximum voided volume in seven children (41.5%). In these children, the cystometric evaluation revealed normal results in one child, a large bladder capacity in four children, and other abnormalities in two. In children with a large maximum voiding volume as a single finding at screening, cystometry confirmed this or revealed normal findings.

6.1.3 LUT dysfunction after renal transplantation (Study I)

The aim of **Study I** was to report the incidence and type of LUT dysfunction in pediatric renal transplant recipients, to study the incidence of LUT dysfunction in different diagnostic groups, and, furthermore, to study the possible influence of LUT dysfunction on renal function. Sixty-eight children participated. One or more signs of LUT dysfunction were found in 49 children (72%). Post-void residual urine (in 22/68, 32%), abnormal bladder capacity (in 17/65, 26%), and abnormal urinary flow (in 34/68, 50%) including a tower flow pattern (in 22/68, 32%), were the most observed signs of LUT dysfunction (Figure 3). These findings were equally prevalent in children with congenital disorders with and without urological malformations and acquired disorders. Urinary incontinence was found in 8 (12%) of the 68 children. The groups with and without LUT dysfunction did not differ statistically regarding GFR.

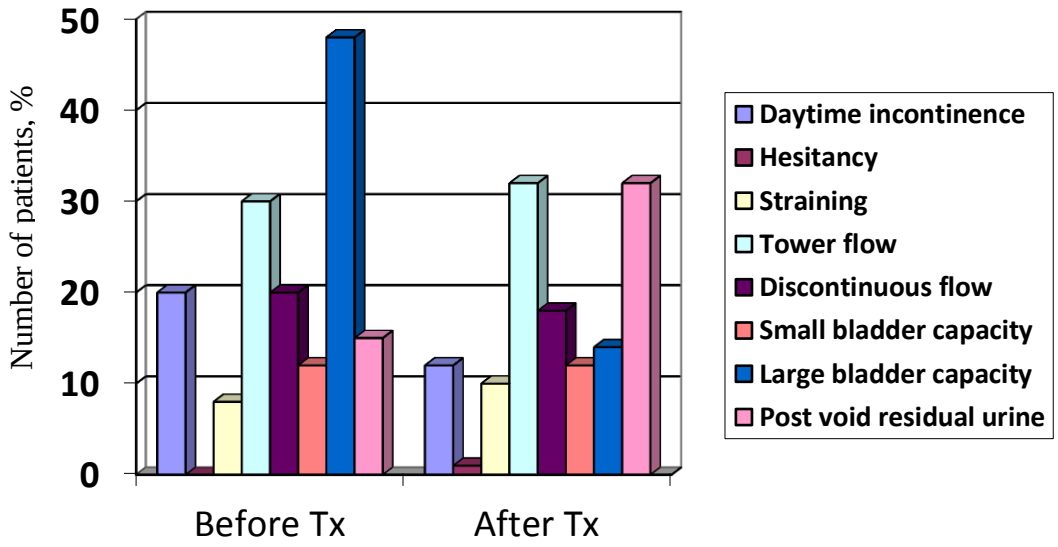

Figure 3. The percentage of different signs and symptoms of LUT dysfunction in children before and after renal transplantation.

6.1.4 UTI and LUT dysfunction after renal transplantation (Study II)

The aim in **Study II** was to evaluate the association between LUT dysfunction and UTIs in children with a kidney transplant and to study the impact of recurrent UTIs on graft function.

Almost half of the children in Study I (33/68, 48%) had experienced one or more UTIs after renal transplantation. UTIs were recurrent in 25 children (25/68, 37%). LUT dysfunction (abnormal urinary flow, abnormal bladder capacity for age, and/or post-void residual urine) was equally prevalent in children with and without recurrent UTI (68% vs. 74%, NS); nor did post-void residual urine influence the recurrence rate of UTIs. Urinary tract malformations was significantly more common in children with recurrent UTIs than in those without (44% vs. 9%, p = 0.009) and was the only identified risk factor for UTIs among the children investigated.

GFR was significantly lower (mean GFR 45 vs 57 ml/min/1.73m², p = 0.02) at four years after transplantation in children with recurrent UTIs compared to those without, indicating a faster deterioration of renal function in those children.

6.2 SELF-REPORTED HRQOL

6.2.1 LUT dysfunction and associations to HRQoL (Study V)

The aim of **Study V** was to investigate the association between LUT dysfunction and HRQoL in children with CKD or a renal transplant. The association with other potential risk factors, such as CKD status, sex, and age, on HRQoL was also studied. In addition, the results from the entire study population were compared with those from children with other chronic conditions and with healthy children.

At least one sign of LUT dysfunction (incontinence, large bladder capacity, discontinuous urinary flow, and/or post-void residual urine) was found in 32 (58%) of the children. These children experienced a HRQoL similar to that of those without LUT dysfunction, with the exception of children with incontinence, who reported physical limitations, lower in in the treatment dimension, and lower general score (Table 4). Girls and older children reported a lower HRQoL compared with boys and younger children. Children with a renal transplant rated a lower physical well-being and independence than did those with moderate to severe CKD. The entire study population reported an impaired HRQoL regarding physical and psychological well-being compared with the general population but a similar one to those with other chronic conditions.

Table 4. Comparisons of self-reported HRQoL between groups with and without LUT dysfunction, urinary incontinence, and urological disorders. Mean and p values

	LUT dysfunction			**Incontinence**			**Urological disorders**		
	No	Yes	*P* [a]	No	Yes	*P* [a]	No	Yes	*P* [a]
N=	23	32		44	15		39	20	
KIDSCREEN-27									
Physical Well-being	44.6	46.5	0.414	45.5	44.7	0.757	44.6	46.8	0.360
Psychological Well-being	49.4	50.3	0.750	50.1	47.9	0.484	50.3	47.9	0.407
Autonomy & Parent relation	53.9	51.0	0.227	53.1	48.5	0.079	53.0	49.7	0.169
Social Support & Peers	54.9	53.3	0.504	52.7	54.4	0.595	52.6	54.3	0.572
School	54.3	53.4	0.727	53.9	53.1	0.781	54.2	52.6	0.531
DISABKIDS-37									
Independence	78.8	80.7	0.673	81.1	75.8	0.279	80.3	78.5	0.690
Physical limitation	73.4	76.3	0.544	77.7	66.9	**0.035**	78.6	67.3	**0.017**
Emotion	74.8	74.3	0.934	77.3	65.0	0.057	76.3	69.9	0.302
Social exclusion	84.8	82.2	0.559	84.7	76.4	0.100	84.8	77.9	0.139
Social inclusion	76.2	75.3	0.858	75.0	74.2	0.873	75.6	73.2	0.619
Treatment	80.2	69.0	0.078	78.9	57.5	**0.002**	71.9	76.2	0.481
Total DCGM-37	78.0	76.3	0.685	79.1	69.2	**0.020**	77.9	73.9	0.322

LUT, lower urinary tract
LUT dysfunction = large MVV, post void residual urine, discontinuous urinary flow, and/or incontinence
[a] Group mean differences were assessed with the independent-samples t test.

6.3 SUBJECTIVE HEALTH SYMTOMS

Associated subjective symptoms were reported by 50 (85%) of the children and were rated as mild by 23 (39%) or moderate to severe by 27 (46%). Twenty of the children with CKD (87%) reported mild (48%) or moderate to severe (39%) symptoms. Thirty of the children with a renal transplant (83%) reported mild (33%) or moderate to severe (50%) symptoms. The most reported subjective complaints were headache, fatigue, sleep disorders, short stature, and stomach disorders.

7 DISCUSSION AND FUTURE PERSPECTIVES

The results from Studies I–V show that signs and symptoms consistent with LUT dysfunction are common in children with CKD both before and after transplantation. This finding is supported by the findings of Van der Weide et al. [59], but, otherwise, it has not been described earlier.

LUT dysfunction was common in children with CKD, both before and after renal transplantation, and the cause of bladder dysfunction therefore does not seem to be the transplantation *per se*. More likely, LUT dysfunction is caused by factors already present before the transplantation, e.g., LUT abnormalities, polyuria, or oliguria. Moreover, children with CKD may suffer from disorders similar to those of the general population, for instance, functional bladder disorders and constipation. Unfortunately, the latter disorder was not included among the evaluated variables in this thesis, but it will be addressed in future studies.

Definition of LUT dysfunction

A main issue throughout this work has been the definition of LUT dysfunction. A clear definition of LUT dysfunction was lacking when we planned this project and is still lacking today.

In Studies I and II we defined LUT dysfunction (at that time "bladder dysfunction") in terms of urinary flow, a maximum voided volume (at that time "bladder capacity"), and/or a bladder emptying function that was not normal according to the ICCS guidelines [46]. This definition can, however, be questioned. Within the concept of LUT dysfunction, there are several conditions, such as, for instance, enuresis, overactive bladder, underactive bladder (former lazy bladder), and dysfunctional voiding. It is not clear, however, if these conditions exclusively or all signs and symptoms thereof that are not normal according to the ICCS guidelines qualify as LUT dysfunction. Furthermore, signs that under "normal conditions" are abnormal may not be so under other conditions. For instance, a voiding frequency of 3–7 voids per day presupposes a normal urine production. If a child suffers from polyuria, the daily voiding frequency or voided volumes will necessarily have to increase. Most children with overactive bladder empty the bladder with a tower-shaped curve, but there is no evidence that a tower-shaped curve always indicate an overactive bladder or other pathology. Furthermore, even though regarded as abnormal, this curve shape does not generally indicate a need for further investigation, as opposed to curves indicating a functional, anatomical, or neurological obstruction [51]. This topic has been debated comprehensively by scientists for years, but there is still room for individual interpretations [134].

The definition used in Studies I and II was later questioned by referees of Study III. They suggested that the tower urinary flow should be excluded and urinary incontinence included in the definition and since we agreed, we modified the definition accordingly.

LUT function before and after renal transplantation

Patient characteristics and data on LUT function from Studies I–IV according to the latter definition (i.e., the definition in Papers III, IV, and V) are updated and presented in Table 5. By this concordant definition, LUT dysfunction was more frequent in children with CKD before than after renal transplantation (72.5% vs. 55.9%, NS). The proportion of children with incontinence, a small maximum voided volume/bladder capacity, a tower urinary flow, and a discontinuous urinary flow was, however, similar before and after transplantation. Only a large maximum voided volume/ bladder capacity was more usual before transplantation and residual urine was more usual after transplantation (Table 5). The latter difference did not reach statistical significance, however.

A main finding within this project is the high proportion of large capacity bladders in children with CKD stages 3–5. Nearly half of the children had a maximum voided volume exceeding EBC for age at the non-invasive screening and in nearly 75% of the children investigated with cystometry, the large bladder capacity was combined with reduced bladder sensation. The results from Study III show that the maximum voided volume/bladder capacity increases with increasing urine production. It therefore seems probable that these large-capacity bladders are caused in most cases by a large urine output; however, other underlying mechanisms cannot be ruled out.

A large cystometric bladder capacity or a large maximum voided volume is often associated with detrusor underactivity and incomplete bladder emptying or infrequent voiding [135] and, in such cases, a potential risk factor for UTIs, hydronephrosis, and renal damage. If, however, there is no hydronephrosis and normal intravesical pressure and bladder emptying is complete, the importance of a large bladder capacity or a large maximum voided volume is unclear. But when the urine output decreases, as will happen after renal transplantation, there are three possible scenarios. If the child retains habits from before renal transplantation and continues to drink excessively after transplantation, this behavior may maintain a large urine production and counteract normalization of the bladder capacity. If the child normalizes fluid intake and bladder sensation also normalizes, the patient will void at normal intervals and with normal voided volumes. If, however, bladder sensation does not normalize, the patient is at risk of developing infrequent voiding habits and, in the worst case scenario, UTIs [63]. In Study I, eight of 68 children (13.8%) had large capacity bladders after transplantation even though the mean urine production was lower in children after as compared to before renal transplantation (2210 ml vs.1366 ml per 24 hours, $p < 0.01$) and mean maximum voided volume decreased from 147% of EBC for age before transplantation to 104% after transplantation. The reason why some children have large capacity bladders even after transplantation is unclear, but it may be explained by the reasons discussed above. However, since we still have no longitudinal data extending from before to after transplantation, we do not know what happens at transplantation at the individual level and this obviously has to be explored in future studies.

Table 5. Patient characteristics and data on LUT function according to the definitions in Studies III–V.

	Before Tx	After Tx	P value‡
Number	40	68	
Age, years, mean ± SD	11.6 ± 4.1	14.4 ± 4.2	
Male sex (%)	27/40 (67.5%)	37/68 (54.4%)	0.2253
Uro (%)	13/40 (32.5%)	15/68 (22.1%)	0.2607
GFR, ml/min/1.73 m^2, mean ± SD	25.4 ± 12.7	56.1 ± 20.6	
Urine production, ml, mean ± SD	2210 ± 1237	1366 ± 618	**0.000021**#
Polyuria (%)	14/40 (35%)	NA	
MVV, % of EBC for age, mean	147%	104%	**0.0298**#
LUT function			
Incontinence (%)	8/40 (20%)	8/68 (11.7%)	0.2713
Small MVV (%)	5/40 (12.5%)	8/65 (12.3%)	0.7736
Large MVV (%)	19/40 (47.5%)	9/65 (13.8%)	**0.0002**#
Tower urinary flow (%)	12/40 (30%)	22/68 (32.4%)	0.8335
Discontinous urinay flow (%)	8/40 (20%)	12/68 (17.6%)	0.8008
Residual urine (%)	6/40 (15%)	22/68 (32.4%)	0.0680
LUT dysfunction (%)*	29/40 (72.5%)	38/68 (55.9%)	0.1027
History of UTI (%)	16/40 (40%)	33/68 (48.5%)†	0.4284

* Defined as presence of any of the following: urinary incontinence, abnormal bladder capacity, discontinuous urinary flow and/or residual urine more than 20 ml (alone or in combination).

† Counted from one month after renal transplantation

‡ Fisher's exact test, two-tailed, for categorical variables and T-test for continuous variables.

Significant values

As mentioned above, residual urine was more common after renal transplantation, compared with before. One possible explanation for this is that a bladder (over)distended by polyuria prior to transplantation does not regain normal emptying function after transplantation or that it takes time. This does not, however, seem likely since most children examined before transplantation could empty their bladders completely despite a large bladder capacity before transplantation and only one out of eight children with a large bladder capacity after transplantation had residual urine.

Other potential explanations may be neurological complications and/or adverse effects of medication.

LUT dysfunction in different disease groups

LUT dysfunction was common in children with both urological and non-urological diseases. Before transplantation LUT dysfunction was more prevalent in children with urological disease compared to those with non-urological diseases (100% vs. 59%), but no difference in various disease groups was found after transplantation.

In Studies I and II, pediatric transplant recipients were categorized into three different groups according to the underlying diseases: congenital disorders with urinary tract malformations, congenital disorders without urinary tract malformations, and acquired disorders. Since the number of patients was small and the frequency of LUT dysfunction did not differ between the three groups, we decided to reduce the number of groups and categorize the children to either urological or non-urological disorders in the remaining studies (III to V). Another reason for this was that LUT function was previously evaluated mainly in children with urological diseases and little was known about other underlying disorders. It therefore seemed natural to compare urological diseases with non-urological diseases. Since we had no children with acquired urological disorders, all children categorized as having congenital disorders with urinary tract anomalies in Studies I and II were categorized as having urological disorders in Studies III–V. All other children were categorized as having non-urological disorders.

LUT dysfunction and UTI

The incentive for this thesis was our concern for the children with recurrent UTIs, but the thesis finally came to focus more on LUT function in children with CKD than on UTI. Nevertheless, the results concerning UTIs are worth discussing. In the CKD group (children with CKD but without a renal transplant) recurrent UTIs were more usual in children with LUT dysfunction than in those with normal function. The frequency of earlier UTIs was highest in children with emptying difficulties (discontinuous urinary flow and/or residual urine) (78%) and those with urological disorders (77%) and lowest in children without any sign of LUT dysfunction (0%). The frequency of UTIs in children with bladder dysfunction was 55%.

In children with a renal transplant, no association between LUT dysfunction and UTIs was found. This finding was surprising since the association between LUT dysfunction and recurrent UTIs is well established in the general pediatric population [136]. A possible explanation for the lack of association is that the UTI frequency was overestimated. Information regarding UTI was obtained from the medical records and the diagnosis was based on the combination of a suspicion of UTI, a positive urine culture, and subsequent antibiotic treatment. It is, however, possible that the high degree of surveillance might have led to too generous diagnosing of UTI. This suspicion may be supported by the fact that we report a slightly higher incidence of UTI than in other studies [5]. Another, perhaps even more probable, explanation is that we overestimated the frequency of bladder dysfunction by including a tower flow pattern in the definition. Hopefully, future prospective studies will clarify this issue.

Even though it is possible that they were not caused by LUT dysfunction, recurrent UTIs in renal transplant recipients were associated with a more rapid decline in graft function. This conflicts with the results from some groups [3, 137], but is supported by others [138-140]. One possible explanation for the conflicting results is that we had a longer follow-up compared to others. However, the results underline the importance of continuing efforts to clarify the underlying mechanisms that promote UTIs after renal transplantation and what consequences UTIs may have in this patient population.

LUT dysfunction and HRQoL

Study V concerning HRQoL was added to this project in order to find possibly links between everyday problems and LUT dysfunction in children with CKD or a renal transplant. In clinical practice, a subgroup of these children is given advice about, for instance, timed voiding and double voiding in order to normalize bladder capacity and counteract post void residual urine with the intention to prevent UTIs. However, in actual clinical practice, the children with CKD or a renal transplant seldom adopt this advice, which makes one wonder whether these signs and symptoms of LUT dysfunction bother the children or not. A knowledge of how these children rate their HRQoL and whether HRQoL is influenced or not by signs of LUT dysfunction may provide information and guidance concerning what aspects and interventions might be of value in the care of children with CKD or of renal transplant recipients with LUT dysfunction.

Study V revealed that LUT dysfunction, in terms of a discontinuous urinary flow, a large bladder capacity, post-void residual urine, and/or incontinence, did not generally affect well-being in the everyday life of children with CKD or a renal transplant, compared to those without these signs. However, some important findings were that the subgroup of children with incontinence reported lower HRQoL in the areas Physical limitation and Treatment and a lower total score and that the children with CKD with urological disorders reported a lower score in the area Physical limitation. To the best of my knowledge, the impact of LUT dysfunction on HRQoL has been very sparsely studied in this population, but with regard to incontinence and children with CKD due to urological disorders, similar findings were reported by Dodson et al. [108, 141]. Other aspects of LUT dysfunction such as a discontinuous urinary flow, a large bladder capacity, and post-void residual urine, were more prevalent, but did not affect HRQoL. It is possible that, in contrast to incontinence, which is known to affect HRQoL even in healthy children [53, 54, 142], abnormal urinary flow, large bladder capacity and post-void residual urine may not have a priority in the everyday life of these children. An alternative explanation may be that these children simply do not take notice of these conditions. This new information might help healthcare professionals to find feasible strategies for advising these children with respect to large voiding volumes and post void residual urine and not to overlook the incontinence.

HRQOL in children with CKD or a renal transplant

To gain knowledge about potential associations between HRQoL and everyday life in children with CKD or a renal transplant, we also evaluated differences in well-being between boys and girls, younger and older children, and between children with moderate to severe CKD and those with a renal transplant. Well-being in the entire group was also

compared to that of children in the general population and children with chronic conditions other than CKD.

Impairments in HRQoL in girls and older children in this study might not be a surprising finding; a number of authors have previously reported similar findings regarding children with CKD [143] and other chronic conditions [142, 144], as well as regarding healthy children [145-147]. The discrepancy between younger and older children may be explained by developmental processes, including a physical and social transition from childhood to adulthood, and an adaptation to a changing body and a new gender identity [148]. Pubertal development is known to start earlier and is more sudden in girls, so as to require a more rapid physical and psychological adjustment [148].

CKD or transplantation-related complications, such as anemia, short stature, and weight gain, have been reported to influence HRQoL negatively [102, 122, 143] and may influence HRQoL more in girls and older children since we know that older children and girls are more prone to worry about their bodies and appearance [145, 147]. However, it should be mentioned that, although the two age groups in our study were similar in the number of children, girls dominated the older age group, which may have affected the results. Despite a potential bias in age categories, the results still underline the importance of identifying factors that contribute to impaired HRQoL in girls and older children.

Renal transplantation is a well-established treatment for children with ESRD and yields excellent treatment outcomes [26, 27]. The unexpected finding that renal transplant recipients, despite a higher GFR (mean, 55 vs. 29 ml/min/1.73 m²), reported lower well-being compared to children with moderate to severe CKD (stages 3–5) deserves to be mentioned, as one might expect, if not entire recovery, then at least improved health. However, this finding may have been influenced by the fact that none of the children with CKD stage 3 to 5 were on dialysis. Clinical improvement in children after renal transplantation is expected to have a favorable effect on HRQoL compared to those on dialysis, as has been confirmed by a number of studies [35, 112, 115, 116, 149]. There are few studies comparable to ours, but, in an article by McKenna et al., similar observations were reported [106]. In our study, children with a renal transplant rated lower in the dimensions Physical well-being and Independence than did those with moderate to severe CKD, which may reflect many challenges in everyday life that these children still have. Concerns about physical problems such as short stature, overweight, and exercise capacity, as well as the necessity of lifelong medication and a fear of graft loss are some of the possible factors with a negative influence on HRQoL [34, 119-123]. The experience of a life-threatening disease may contribute to overprotective attitudes from parents and healthcare staff, which, in turn, limits the development of an autonomous life of the child and may lead to a lower perceived HRQoL in this area [120, 150, 151]. However, the discrepancy in the HRQoL areas Physical well-being and Independence, which is disadvantageous for renal transplant recipients, calls for a more extensive evaluation. What we did not investigate, but should analyze in future studies, is the influence of other possible factors such as socioeconomic issues, rejection episodes, and associated complications.

Subjective symptoms such as headache, fatigue, sleep disorders, poor growth, and stomach complaints were equally common both before and after transplantation, but they were reported to be more troublesome by children with a renal transplant. The measure was aimed at describing the study population; however, a possible association with impaired HRQoL needs to be elucidated in further studies.

Ratings from children with CKD stages 3 to 5 and renal transplant recipients revealed a similar picture in all HRQoL areas in comparison with children suffering from asthma, arthritis, cerebral palsy, cystic fibrosis, dermatitis, epilepsy, or diabetes mellitus. However, the entire study population reported an impaired HRQoL regarding Physical and Psychological well-being in comparison with children from the general Swedish population. This finding was, however, not surprising, because other authors have reported similar findings [119, 120, 123]. The results suggest that a renal transplantation, even though constituting a lifesaving treatment, still results in a chronic condition that may have an adverse influence on everyday life in many ways. It is important, however, to transform this information into a clinical context and to find ways to meet every child's unique prerequisites and needs. To gain a more in-depth knowledge of needs in the everyday life of pediatric renal patients with and without LUT dysfunction, a study using qualitative methods might be a preferable approach.

7.1 METHODOLOGICAL CONSIDERATIONS

Strengths and shortcomings

One strength of this study is the unique approach. Associations with LUT dysfunction before and after renal transplantation have not been widely studied so far in children with CKD of other causes than urological ones. Thus, the present study, although comprising a limited number of participants, serves as a valuable contribution to increasing knowledge about LUT dysfunction in children before and after renal transplantation, regardless of whether the underlying disease is of urological or non-urological origin.

An additional strength of this study is that a large proportion of Swedish children with CKD was included. However, since the prevalence of CKD in children is low, the number of patients is, nevertheless, relatively small. This makes it difficult to draw firm conclusions. My intention is therefore to continue studying this patient population prospectively and longitudinally through different CKD stages and beyond renal transplantation. Hopefully, this will make it possible to determine the association and the nature of the association between the cause of the underlying disease, bladder function, UTIs, and deterioration of renal function more clearly.

An additional limitation in this thesis is the absence of comparison groups in studies I to III. Limited financial support forced us to rely on historical controls. Hopefully the results from this thesis can generate better financing for future studies.

8 CLINICAL IMPLICATIONS

The findings in this thesis imply that identification of LUT dysfunction in children with CKD is important. A clinical evaluation using non-invasive methods (detailed voiding history, frequency-volume chart, uroflowmetry, and bladder ultrasound for measuring post void residual urine) might already be justified in stage 3, regardless of the urological and non-urological disease background, but of course earlier when urological anomalies are known. This early screening and recognition of LUT dysfunction allows correction and prevention of the worsening of dysfunction in the long term, especially with respect to renal transplantation. Attention to the children with polyuria, with the risk of developing a large capacity bladder and reduced bladder sensation, is warranted in order to prevent the development of bladder emptying problems and subsequent UTIs. However, since the number of patients in this study is limited, the results must be confirmed in larger studies before definitive recommendations can be given.

Our knowledge about the physical, psychological, and social well-being of children who are undergoing medical treatments due to various chronic conditions has become an important key area in monitoring treatment outcomes. This information can distinguish severe clinical problems from other outcome perspectives than medical ones, which are important to be detected and addressed at medical follow-up visits. HRQoL data in this thesis provided information about the association between urinary incontinence and a negative influence on well-being. This is an additional finding to the already existing ones supporting the need for awareness of the problems associated with urinary incontinence in children with CKD.

This thesis recognized lower well-being in some of the areas in children with a renal transplant, as well as in girls and older children. Additionally, physical and psychological impairments were evident in the entire patient group compared to children in the general population. To prove causality in these issues will require more evaluation in further studies. However, the present results point out significant problems implying that it is important to acknowledge psychosocial issues at clinical follow-up visits and that the need for supportive interventions should be considered.

9 SUMMARY AND CONCLUSIONS

From the studies included in this thesis, we conclude that:

- Signs and symptoms consistent with LUT dysfunction are frequent in children with CKD stages 3 to 5 and in pediatric renal transplant recipients.

- A large bladder capacity is the most frequent sign of LUT dysfunction in children with CKD stages 3–5. A large bladder capacity is often combined with reduced bladder sensation.

- Residual urine is the most frequent sign of LUT dysfunction in pediatric renal transplant recipients.

- LUT dysfunction is more frequent in children with urological disorders, but it also occurs frequently in children with non-urological disorders children with CKD stages 3–5. In pediatric renal transplant recipients, LUT dysfunction was equally frequent in children with urological and non-urological disorders.

- A history of UTIs was more frequent in children with LUT dysfunction than in those with normal LUT function in CKD stages 3–5, but this association was not found in pediatric transplant recipients.

- Among children with CKD stages 3–5 and no signs of LUT dysfunction, no child had experienced earlier UTIs.

- Among children with CKD stages 3–5 and discontinuous urinary flow and/or residual urine, 78% had experienced earlier UTIs.

- Renal function in children with recurrent UTIs after renal transplantation deteriorated faster than in children with one or no UTIs.

- Children with CKD stages 3–5 and pediatric renal transplant recipients with and without LUT dysfunction reported similar HRQoL, with the exception of children with incontinence. Children with incontinence reported physical limitations and treatment-related concerns.

Since signs and symptoms consistent with LUT dysfunction are common in children with CKD, regardless of the underlying cause of the disease, I recommend all children with CKD to be screened for LUT dysfunction.

10 SVENSK SAMMANFATTNING

Kronisk njursjukdom (CKD) hos barn är ett livslångt tillstånd. Sjukdomen är ovanlig, uppskattningsvis har ca 120 barn i Sverige en allvarlig eller grav njurfunktionnedsättning. CKD är en progredierande sjukdom som delas in i olika svårighetsgrader (CKD stadier 1–5). I dess mildare former ger sjukdomen sällan några symtom och upptäcks inte alltid, men med tilltagande njurfunktionsnedsättning framträder allt fler komplikationer. I slutstadiet är dialys eller njurtransplantation de återstående och livsuppehållande behandlingsalternativen. Vanliga symptom och komplikationer som illamående, trötthet, anemi, högt blodtryck, proteinuri, kortvuxenhet, neurokognitiva förseningar eller biverkningar av medicinering är vanliga hos barn med CKD stadium 3–5 och även till viss del hos de som genomgått en njurtransplantation. Behandlingen syftar till att förebygga och behandla komplikationer, samt att förhindra försämring av njurfunktionen. Urinvägsinfektioner (UVI) är en vanlig komplikation som kan skada njurarna. Blåsdysfunktion (”LUT dysfunction”) är en känd riskfaktor för UVI hos friska barn, men det saknas kunskap om blåsdysfunktion hos barn med CKD eller som har genomgått en njurtransplantation. CKD eller njurtransplantation ställer krav på många aspekter i vardagslivet hos barn och därför är också barnets välbefinnande ett viktigt utfallsmått att beakta i vården av dessa barn. Det övergripande syftet med denna avhandling har varit att utvärdera de nedre urinvägarnas/urinblåsans funktion före och efter njurtransplantation, samt att studera vilken roll blåsdysfunktion har i relation till urinvägsinfektioner. Ett ytterligare syfte har varit att ta fram kunskap om eventuell association mellan blåsdysfunktion och HRQoL.

Alla fem delarbeten var tvärsnittstudier och inkluderade 40 barn med CKD stadium 3–5 (studier III och IV), 68 barn som genomgått njurtransplantation (studier I och II), och 59 barn med CKD stadium 3-5 (n=23) eller njurtransplantat (n=36) i studie V. Barnen genomgick en kartläggning av blåsfunktionen med strukturerad miktionsanamnes, miktionsdagbok, upprepade urinflödesmätningar för bestämning av blåstömningsmönster, ultraljud av urinblåsan för bestämning av residualurin samt i studie IV också cystometri. Njurfunktionen undersöktes med inulin- eller iohexolclearance, eller estimerades utifrån plasmavärdet av cystatin C. Uppgifter om tidigare UVI hämtades från patientjournaler. I studie V användes två frågeformulär, Kidscreen-27 och DCGM-37 för självrapportering av HRQoL och ett modifierat hälso- och symtomformulär för rapportering av associerade subjektiva symptom. Blåsdysfunktion definierades i studierna I och II som onormalt urinflöde, residualurin >20 ml, och/eller onormalt liten eller stor blåskapacitet och i studierna III till V som inkontinens, liten/stor maximal blåsvolym, oregelbundet urinflödesmönster och/eller residualurin.

Ett eller flera tecken på blåsdysfunktion noterades hos 72.5% av barnen med CKD och hos lika många barn (72%) som hade genomgått en njurtransplantation. Tecken på blåsdysfunktion fanns hos alla barn (100%) som hade CKD till följd av urologiska sjukdomar, och hos 59% av de barn som hade CKD av icke-urologiska orsaker ($p = 0.0074$). Förekomst av blåsdysfunktion hos barn som hade genomgått en njurtransplantation skiljde sig inte i grupperna urologiska/icke-urologiska sjukdomar (74% vs. 71%, NS). 47.5% av barnen med CKD hade en maximal blåsvolym som var

större än förväntat, vilket ofta var kombinerat med nedsatt uppfattning om blåsfyllnaden. Ett oregelbundet urinflödesmönster hittades hos 20% och residualurin hos 15 % av dessa barn. Motsvarande fynd hos njurtransplanterade barn var en stor blåsvolym hos 26%, ett avvikande urinflödesmönster hos 50% (hos 17.6% med tornformade urinflöden borträknade), och residualurin hos 32%. UVI var vanligare hos barn med CKD och tecken till blåsdysfunktion jämfört med barn utan blåsdysfunktion (55% vs. 0%, p = 0.0012). Hos barn som hade genomgått en njurtransplantation, förekom UVI i samma utsträckning hos dem med och utan blåsdysfunktion (35% vs. 42%, NS). Återkommande UVIer var dock associerat med snabbare försämring av njurfunktionen jämfört med dem utan UVIer (p = 0.02). Barn med CKD och de som hade genomgått en njurtransplantation rapporterade likadana resultat i HRQoL-mätningarna när man jämförde grupper med eller utan blåsdysfunktion, men en subgrupp av barn med inkontinens rapporterade lägre välbefinnande. Signifikanta skillnader hittades hos flickor och äldre barn samt hos njurtransplanterade barn som skattade HRQoL lägre i jämförelse med pojkar, yngre barn respektive barn innan njurtransplantation. Hela gruppen (CKD+Tx) skattade sitt välbefinnande inom fysiska och psykologiska områden lägre än friska barn, men inga skillnader hittades i jämförelser med barn med andra kroniska sjukdomar.

Sammanfattningsvis förekommer blåsdysfunktion ofta hos barn med CKD stadium 3–5 och hos de som har genomgått en njurtransplantation. Blåsdysfunktion var vanlig inte bara hos barn med underliggande urologiska sjukdomar, utan även hos barn med icke-urologiska sjukdomar. Tidigare UVIer var vanligare hos barn med CKD som hade blåsdysfunktion men efter njurtransplantation återfanns inte denna skillnad. Fynden i denna avhandling bidrar till vår kunskap vad gäller blåsfunktion hos barn med CKD stadium 3–5 och njurtransplanterade barn men bidrar även med kunskap om associationer mellan välbefinnandet i vardagslivet och blåsdysfunktion samt ytterligare aspekter såsom kön och ålder samt om barnet genomgått njurtransplantation eller ej. Det behövs dock ytterligare studier innan rekommendationer om eventuella interventioner kan ges.

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