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THE STOCKHOLM SPINAL CORD URO STUDY

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The Stockholm Spinal Cord Uro Study

THESIS FOR DOCTORAL DEGREE (PhD)

By

Elisabeth C Farrelly

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To my sons Jens and Stefan

”Att ägna sig åt forskning är att delta i ett internationellt samtal om hur saker och ting verkligen hänger ihop”

‘To engage in medical research is to take part in a global conversation on the true relationships in human biology’

Inge-Bert Täljedal, Professor of Histology and Cell Biology, Umeå University, 1980

POPULAR SCIENCE SUMMARY OF THE THESIS

Background Spinal cord injury (SCI) affects the conduction of nerve signals between the brain and all parts of the body below the head. SCI can be caused by trauma to the neck or back, inflammation of the spinal cord itself, or injury to blood vessels which supply the spinal cord. In Sweden, traumatic SCI affects approximately 150 persons per year and about 6000 persons live with this condition. In the Stockholm area a majority of the regional SCI population are registered at the out-patient centre the Spinalis clinic for medical service and annual check-ups.

SCI causes complex health issues related to various organs in the body and some of the most frequent problems concern the urinary tracts. The interruption of nerve signalling in the spinal cord affects the reflexes which govern normal bladder function, thus causing neurogenic bladder dysfunction. Bladder filling may give rise to reflexive strong contractions of the bladder muscle at low volumes which can cause incontinence and a harmful backward pressure transmission to the kidneys. Bladder emptying may become difficult or impossible without the use of catheters or surgical alterations of the bladder or urethra. Urinary tract infections (UTI) and stone formation in the bladder are common secondary problems. Traditionally, scientific studies have addressed complications among persons with the most severe types of SCI who were often examined in hospitals. However, in the regional patient population at the Spinalis clinic it was possible to interview and examine persons who had all different types of SCI and who lived active lives in the general society.

Aims The aims of this study were to evaluate the urological situation in the regional group of persons with a traumatic SCI of all different neurological levels and severity; to estimate risk factors for frequent complications of the urinary tracts; to investigate ways of improving follow-up programmes for neurogenic bladder dysfunction after SCI.

Methods 412 persons who attended an annual check-up visit agreed to participate in the study. They answered questions included in a national follow-up programme of medical complications after SCI, a regional programme focussed on the urinary organs, and a questionnaire regarding problems with the kidneys or bladder during the preceding year. Blood and urine samples, ultrasound examinations of the kidneys, and measurement of residual urine in the bladder after voiding were performed. Urodynamic studies were done investigating the coordination of nerve and muscle activity in the bladder, urethra, and pelvic muscles. Information was collected from the patients' medical files regarding previous urine tests and prescriptions of antibiotics, previous urodynamic studies and bladder emptying regimes, and previous urologic surgical procedures and their long-term results.

Results The proportion of men/ women was 320(78%)/ 92(22%). The mean age was 49.1 years, and the mean duration of SCI was 16.4 years. All levels of SCI in the back or neck and all various grades of completeness of injury were represented, as were all different methods of bladder emptying. Signs of kidney complications were found among one-fourth of the patients and nearly half reported urinary tract complications during the previous year. Urinary tract infection (UTI) was the most frequent problem, reported by 44%. 15.3% had >3 UTIs and 5% had a febrile UTI which required hospital treatment. The number of reported UTIs was not influenced by the presence or volume of residual urine, nor by the use of medications, vitamins, or health foods to prevent UTI. Urodynamic studies were completed by 211 patients. There

was a statistically significant relationship between reflex bladder muscle contractions that lasted more than one-third of the filling phase and signs of kidney complications. Among patients who did not have current reflex contractions, some had a history of this pattern in the early years after SCI and this was connected to current signs of renal complications. Urological surgery had been carried out in 137 patients with a total/ mean number of 262/ 1.9 procedures. Mean time of follow-up was 10-19 years for the various types of surgery. Essential surgery due to urinary stones, severe infections or to ensure bladder emptying constituted half of all procedures and were mostly carried out within two years after SCI. Reconstructive surgery with alterations of the bladder, urethra, or construction of a urostomy was performed to improve long-term voiding and continence. One-fourth of all patients had ≥3 urological procedures and among them 59% had developed signs of kidney complications. Risk factors for kidney complications, more frequent/ more severe UTIs, and urgent or repeated surgery overlapped to a great extent. They were identified as an SCI at the level of the neck or upper back, a more complete injury, and long periods of reflex bladder contractions during bladder filling. Additional risk factors for UTIs included having an SCI for more than 10 years, using a catheter for voiding, and having a bladder with reflex muscle activity. Patients with an incomplete SCI and largely preserved muscle and sensory function had a low frequency of UTIs. However, three-fifths had reflex bladder contractions and one-fifth had signs of kidney complications.

Conclusions Overall, the regional group of patients had a relatively stable and healthy situation regarding the urinary tracts. However, signs of kidney complications were frequent and nearly half of all patients had UTIs during the preceding year. Risk profiles for more frequent and more severe complications were identified. Follow-up programmes for bladder and kidney dysfunction after SCI can be improved taking these risk profiles into account. Prior to urological surgery all risk factors for kidney complications must be observed and further exposure prevented.

ABSTRACT

Aims To evaluate urinary tract function and complications in a regional population with chronic traumatic spinal cord injury (SCI), to estimate risk profiles for recurring complications and improve follow-up for neurogenic lower urinary tract dysfunction (NLUTD) after SCI.

Materials and methods 412 patients were included in the study as they consecutively attended an annual check-up visit at the regional out-patient centre the Spinalis clinic. A regional programme for follow-up of NLUTD after SCI was applied, including S-creatinine, S-cystatin-C, urine culture, residual urine, renal ultrasound, and urodynamics. A study specific questionnaire was used for patient-reported data of complications during the preceding year. A national programme for medical follow-up after SCI was applied registering data on autonomic dysfunctions such as spasticity, autonomic dysreflexia, neuropathic pain, and pressure ulcers. A study-specific database was created. Information was added from retrospective reviews of patient files on urine cultures and antibiotics prescriptions during the preceding year (paper II), primary urodynamic observation after SCI and bladder management through the following years (paper III), and urologic surgical interventions and outcomes (paper IV). A re-analysis was undertaken of all urodynamic graphs (paper III).

Results The male/female distribution was 320(78%)/ 92(22%). The mean age/ mean SCI duration was 49.1/16.4 years. All neurological levels and severity of SCI and all types of bladder management were represented. Signs of renal complications were present in one-fourth. Nearly half of all patients reported complications during the preceding year. Urinary tract infection (UTI) was the most frequent problem, reported by 44%. 15.3% had >3 infections and 5% had a febrile UTI requiring hospital treatment. There was no relationship between residual urine or use of preventive medications/ vitamins/ health foods and the number of reported UTIs. Urodynamic studies were completed by 211 patients. There was a statistically significant relationship between a duration of detrusor overactivity during more than one-third of the filling phase and signs of renal complications among patients with an SCI duration 11-20 years. Among patients with a current underactive/acontractile or normal detrusor, a primary observation of neurogenic overactive detrusor and a previous history of voiding by bladder reflex triggering emerged as an important factor for renal impairment. Urological surgical interventions had been carried out in 137 patients with a total/ mean of 262/ 1.9 procedures. Follow-up was a mean 10-19 years for the various types of surgery. Imperative surgery due to urinary stones, severe infections, and to ensure voiding via a suprapubic catheter constituted half of all procedures and were mostly carried out within two years after SCI. Reconstructive surgery was performed to improve long-term voiding and continence. One-fourth of all patients had ≥3 urological procedures and among them 59% had developed signs of renal complications. Risk profiles for renal complications, more frequent/more severe UTIs, and imperative or repeated surgery overlapped to a great extent. They were identified as a cervical-thoracic neurological level of SCI, AIS grades A-C, and a duration of detrusor overactivity of more than one-third during bladder filling. Further risk factors for UTIs included an SCI-duration >10 years, catheter-assisted voiding, and having a neurogenic overactive detrusor. Patients with an AIS D lesion had a lower frequency of UTIs. However, three-fifths had neurogenic detrusor overactivity, and one-fifth had signs of renal complications.

Conclusions Overall, the regional population had a relatively stable and healthy situation regarding the urinary tracts. However, signs of renal complications were frequent and nearly half of all patients had UTIs during the preceding year. Risk profiles for more frequent and more severe complications were identified. Follow-up programmes for NLUTD after SCI can be improved taking these risk profiles into account. Prior to urologic surgical interventions risk indicators for renal complications must be observed and further exposure prevented.

LIST OF SCIENTIFIC PAPERS

I. The Stockholm Spinal Cord Uro Study: 1. Basic characteristics and problem inventory. Elisabeth Farrelly, Lena Lindbo, Hans Wijkström and Åke Seiger. Scand J Urol 2019;53(6):403-410.

II. The Stockholm Spinal Cord Uro Study: 2. Urinary tract infections in a regional prevalence group: frequency, symptoms, and treatment strategies. Elisabeth Farrelly, Lena Lindbo, Hans Wijkström and Åke Seiger. Scand J Urol 2020;54(2):155-161.

III. The Stockholm Spinal Cord Uro Study: 3. Urodynamic characteristics in a regional prevalence group of persons with spinal cord injury and indications for improved follow-up. Elisabeth Farrelly, Lena Lindbo and Åke Seiger. Scand J Urol 2021;55(5):412-418.

IV. The Stockholm Spinal Cord Uro Study: 4. Changing patterns of urological surgery in a regional prevalence group through 50 years. Outcomes and implications for the future. Elisabeth Farrelly, Lena Lindbo and Åke Seiger. *Manuscript.*

CONTENTS

LIST OF ABBREVIATIONS

AIS	**A**merican Spinal Injury Association **I**mpairment **S**cale
ANLUTD	Adult neurogenic lower urinary tract dysfunction
ASIA	American Spinal Injury Association
CIC	Clean intermittent catheterization
DO	Detrusor overactivity
DSD	Detrusor-sphincter dyssynergia
GFR	Glomerular filtration rate
ICS	International Continence Society
ISCoS	International Spinal Cord Society
NDO	Neurogenic detrusor overactivity
NLUTD	Neurogenic lower urinary tract dysfunction
nOAB	Neurogenic overactive bladder
nUAB	Neurogenic underactive bladder
OR	Odds ratio
PFMT	Pelvic floor muscle training
PVR	Post void residual urine
SCI	Spinal cord injury
SSL	Suprasacral spinal cord lesion
SSCL	Sacral spinal cord lesion
SUI	Stress urinary incontinence
UTI	Urinary tract infection
VUR	Vesicoureteral reflux

1 INTRODUCTION

Many paths in my professional life have been the result of one-half choice and one-half coincidence. Urology was a choice because it is a surgical speciality, and a result of coincidence because it was available as a first position after medical school in Umeå. This field of medicine proved to be more extensive and more fascinating than the brief course in medical school had conveyed.

During the latter part of medical school, I was employed part-time in the Department of Clinical Physiology at Umeå University Hospital and found that reading the urodynamic graphs was the most interesting part of the job. Here, the choice was simply to earn extra money and the coincidence that Clinical Physiology accepted student workers.

Neurogenic bladder dysfunction was not my first choice in urology. Kidney and prostate surgery seemed much more obvious fields to dig into. However, a specialist course in neurogenic bladder dysfunction and my previous interest in urodynamics slowly geared me toward a reluctant choice of embracing neuro-urology. It became clear to me that this was an area with much learning and discovery to be enjoyed and a field which encompassed both simple and advanced diagnostics, and minimal as well as complex interventions. By coincidence, a phone call from Stockholm invited me to become involved with the Spinalis clinic as a neuro-urology consultant.

My involvement with the Spinalis clinic was combined with a position at Huddinge University Hospital where I was introduced to reconstructive urology by my mentor, the late Hans Wijkström. This was an irresistible choice! The attempt by surgery to convert a person's desire for more manageable bladder function and improved quality of life was such a challenging and compelling idea. To work under the supportive and patient supervision of Hans was a delight.

The Spinalis clinic provided an environment filled with new ideas, new colleagues, and prospects of teamwork. Immersion into this environment was like moving to a new country, learning a new language. Most of all, I am forever indebted to all the patients in the Spinalis clinic who have taught me about symptoms, signs, and experiences with neurogenic bladder dysfunction. The patient narrative is powerful – if you ask and if you are prepared to listen with an open mind, there is a chance to learn something new every day.

Now I have also had the opportunity to learn how to ask questions with a scientific mind, analyse the responses and balance them against prior knowledge – to take a small part in that global conversation on "how things are truly related in human biology".

2 BACKGROUND AND LITERATURE REVIEW

2.1 The urinary tract and the micturition reflex

The urinary tract is composed of the kidneys, the ureters, the bladder, and the urethra. In men the prostate, although strictly a genital organ, is often considered part of the urinary tract because of its anatomical position and interaction with the bladder neck and urethra. The male genital organs the prostate, seminal vesicles, epididymides, and the testes are all connected with the urethra through the vas deferens.

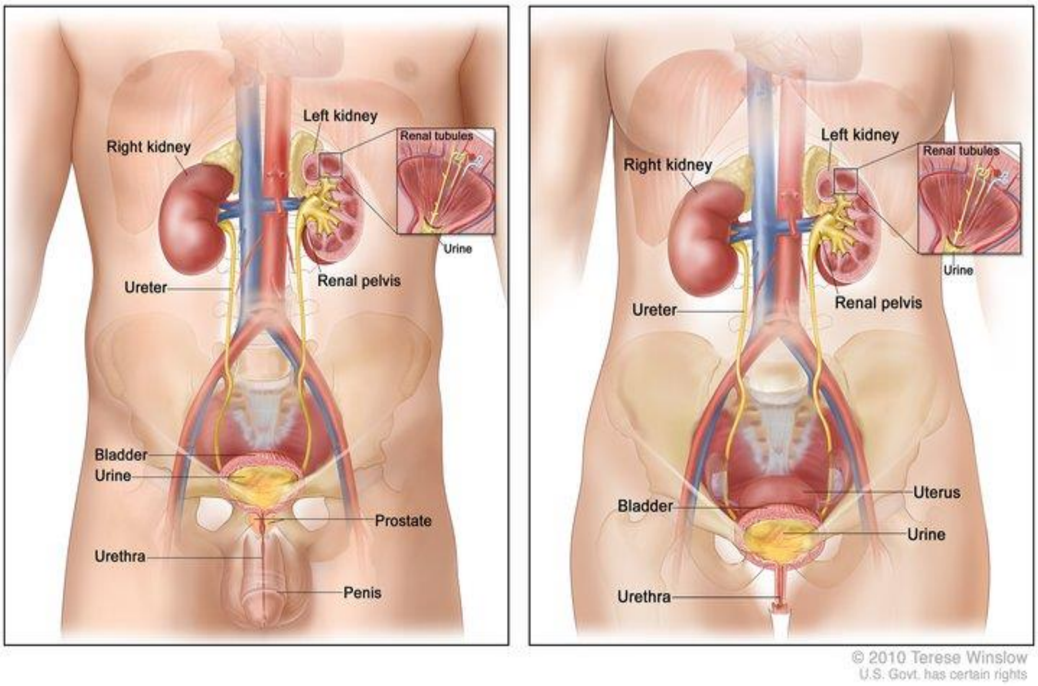
The upper urinary tracts include the kidneys and ureters. Vital physiological tasks such as regulation of blood pressure, body pH, fluid and electrolyte balance, and excretion of waste products and toxins are carried out by the kidneys around the clock. Regulation of renal filtering occurs by secretion of antidiuretic hormone from the pituitary gland in the brain and by the amount of blood flow that reaches the kidneys with every heartbeat. The filtering function of the renal tubules is very sensitive to increased pressure in the renal pelvis and may be damaged temporarily or long-term by outflow resistance to urine. The ureters transport urine to the bladder by peristaltic movements regulated by intrinsic musculature. The uretero-vesical junctions have the shape and function of a valve, which opens with every spurt of urine into the bladder, then closes and thus protects the upper tracts from reflux of urine, waste products, microbes, and other potential adverse substances from the outside world.

The lower urinary tract consists of the bladder, the urethra, and the pelvic floor muscles acting as a coordinated system to secure storage and emptying of urine at low pressures and at appropriate times. Bladder and urethral anatomy and physiology are well adapted to this task.

In the bladder, receptors for tension, volume and noxious stimuli are situated in the mucosal and submucosal layers of the bladder wall. The detrusor muscular layer of the bladder wall is organized in a network of muscle bundles around the upper body of the bladder and circular layers around the bladder neck. The bladder wall is normally stretchable, compliant, and well vascularised. Thus, the mechanics of the bladder allow for storage of adequate volumes of urine, and efficient emptying through contraction of the detrusor. During voiding the detrusor contraction lifts and opens the bladder neck and at the same time compresses the body of the bladder to expel urine.

The urethra extends from the bladder neck through the pelvic floor and then through the penis in men and the anterior vaginal wall in women. In men, the prostate is situated around the urethra immediately below the bladder neck and cranial to the pelvic floor. The bladder neck has a distinguishable ring of circular smooth muscle fibrils, the internal sphincter, the principal function of which is to facilitate sperm outflow through the urethra by contraction during the ejaculation reflex. The external sphincter is situated below to the prostate at the level of the surrounding pelvic floor muscles and consists mainly of striated muscle which is partly under sympathetic autonomic control during bladder filling and mainly under voluntary control.

Figure 1. The urinary tract in the male and female.



Reproduced from https://visualsonline.cancer.gov
US Department of Health and Human Services/ National Institutes of Health/National Cancer Institute/US.gov

In women the sphincter area is not as clearly defined and the continence mechanism is upheld through a combination of actions from smooth and striated muscle, vascular components in the urethral wall, and the texture of the mucous membrane to generate a urethral seal effect. Urethral smooth muscle is organised in a submucosal inner longitudinal layer and an outer circular layer. This means that the circular layer can assist in the continence mechanism, while the longitudinal layer serves to shorten and open the urethra during voiding.

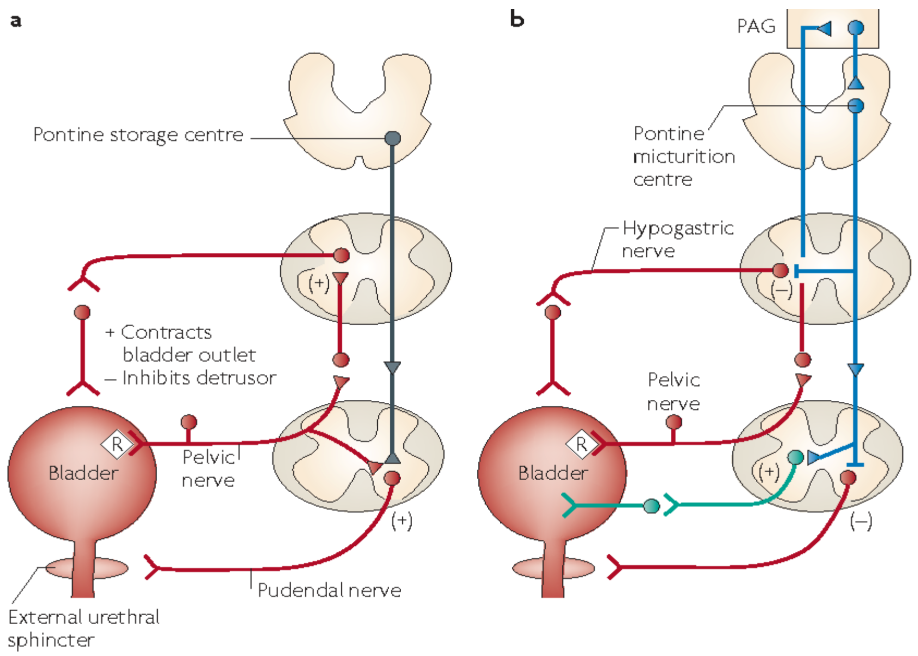
The pelvic floor is made up of skeletal muscles which are organised in several layers to form a firm base, a 'floor' for the pelvic organs. There are three main openings in the muscle base for the rectum, the urethra and in women the vagina. Main muscular components are the broad levator ani muscles in the dorsal portion and the urogenital triangle in the ventral portion (1).

The lower urinary tract is regulated by a series of nerve circuits which make up the micturition reflex and enable complex interaction between the organs and muscles involved (2). Nerve connections of the reflex extend from the bladder urothelium through the bladder wall, the pelvic nerves, spinal cord, brainstem, and midbrain to the prefrontal cortex. Multiple polysynaptic pathways, feedback systems, relay centres and coordinating nuclei are involved. Knowledge of this complex system has increased considerably during the past twenty years with the advent of imaging techniques like positron emission tomography and functional magnetic resonance imaging. Interaction and 'cross talk' between cells in the bladder urothelium occur in response to noxious stimuli from urine contents or tension on the bladder wall elastic components (3,4) and the bladder is truly an active organ.

During bladder filling there is continuous firing of nerve signals from tension and volume receptors and from nociceptors in the urothelial and sub-urothelial layers. In the suburothelium a layer of myo-fibroblasts, also called interstitial cells, are situated near nerve endings. It is probably the myo-fibroblasts, smooth muscle cells and urothelium that act together as a stretch receptor. The afferent signals are relayed via pelvic nerves to the lumbosacral part of the spinal cord. Low levels of afferent firing activate efferent sympathetic nerve signals at the spinal cord level. These serve to maintain the storage phase by keeping a relaxed bladder wall and closed urethral sphincter. Higher levels of firing in contrast activate circuits in the brain and spinal cord which produce parasympathetic signalling in efferent pathways to the bladder and inhibit the sympathetic outflow to the sphincter so that the voiding reflex may commence. The switch from storage to voiding probably involves several cerebral circuits in the prefrontal cortex and thalamus.

Low level firing occurs by spinal reflex pathways and represents a primitive 'guarding reflex' which promotes continence. *High level firing* produces signals that travel via afferent pathways through the spinal cord to the brainstem where they pass through neurons in the periaqueductal grey area and on to the micturition centre in pons. Signals are filtered through the thalamus and then enter the prefrontal cortex where sensations from the bladder reach consciousness. When timing is appropriate voiding can be consciously permitted.

Figure 2. The micturition reflex.



a. Bladder storage b. Bladder voiding
Reproduced from Fowler CJ, Griffiths D, de Groat WC. The neural control of micturition. Nat Rev Neurosci. 2008;9(6):453-66

Inhibitory reflexes are then turned down, and the pontine micturition centre is allowed to stimulate parasympathetic outflow to the bladder and internal sphincter smooth muscle. Nerve signals to the striated muscles of the urethral sphincter are voluntarily started and relayed via Onuf´s nucleus in the S2-S4 region of the spinal cord to the pudendal nerve.

The sacral reflex arch consists of afferent nerves from the pelvic organs to the sacral regions of the spinal cord, the spinal nuclei and interneurons, and the efferent nerves to the same pelvic organs. This arch transmits reflex activity as a response to afferent stimuli. In humans it is active from birth and responsible for reflex voiding in infants. As the nervous system matures, inhibitory and modulatory signals from higher centres are successively established and come into play to form the normal micturition reflex as described above.

Lesions in the micturition reflex can occur at any level of the bladder/ urethra, pelvic nerves, spinal cord or brain and have noticeable effects on bladder control and in some cases secondary effects on the upper urinary tracts (1).

2.2 Neurogenic lower urinary tract dysfunction, NLUTD

The International Continence Society (ICS) has produced and regularly updates sets of terminology for normal function and dysfunctions of the lower urinary tract (5). The terminology is internationally recognized, used by other scientific organizations and in evidence-based guidelines for clinical care (6, 7). Adult neurogenic lower urinary tract dysfunction (ANLUTD) is defined in a consensus-based report (8) as 'abnormal or difficult function of the bladder and/ or urethra (and prostate in men) in a mature person in the context of clinically confirmed relevant neurologic disorder'. The report covers terminology for ANLUTD storage, voiding and post micturition symptoms, signs, urodynamic observations, and definitions as well as clinical diagnoses and treatment definitions. NLUTD is the abbreviation for 'neurogenic lower urinary tract dysfunction'.

The ICS endorsed terminology is used in this thesis.

2.3 Spinal cord injury, SCI

Spinal cord injury (SCI) affects transmission of nerve signals between the brain and spinal cord segments below the level of injury resulting in loss of motor and sensory function and affecting body reflexes which are normally regulated and modulated from higher centres in the brain.

SCI may be caused by trauma to the vertebral column, infection or inflammation of the nervous system, haemorrhage or thrombosis affecting the spinal cord. Worldwide, the annual incidence of traumatic SCI is 250 000-500 000 (9,10). In Sweden the corresponding figure is approximately 150 individuals per year and about the same number sustain a lesion of non-traumatic origin (11). The prevalence of patients with chronic traumatic SCI is about 6000.

Causes of traumatic SCI are falls, traffic accidents, sports injuries, violence, intentional self-harm (suicide attempts), vascular accidents, or complications of back surgery.

A terminology and classification system for SCI has been devised by the International Standards Committees of the American Spinal Injury Association (ASIA) and the International Spinal Cord Society (ISCoS). It is based on clinical examination of motor and sensory function and is internationally recognized as the ASIA Impairment Scale (AIS) (12). The following key definitions are included:

Tetraplegia: loss of motor and/or sensory function in arms as well as the trunk, legs and functional impairment of pelvic organs caused by a lesion of the spinal cord at the cervical neurological level.

Paraplegia: loss of motor and/or sensory function in the thoracic, lumbar, or sacral (but not the cervical) segments of the spinal cord caused by a lesion in the subcervical spinal cord. Function of the arms is spared. Depending on the level of injury the trunk, legs and/or pelvic organs (lower urinary tract, bowel, sexual organs) are affected.

Sensory level: The most caudal segment of the spinal cord with normal sensory function bilaterally.

Motor level: The most caudal segment of the spinal cord with normal motor function bilaterally.

Neurological level: The most caudal segment of the spinal cord with both normal sensory and motor function bilaterally.

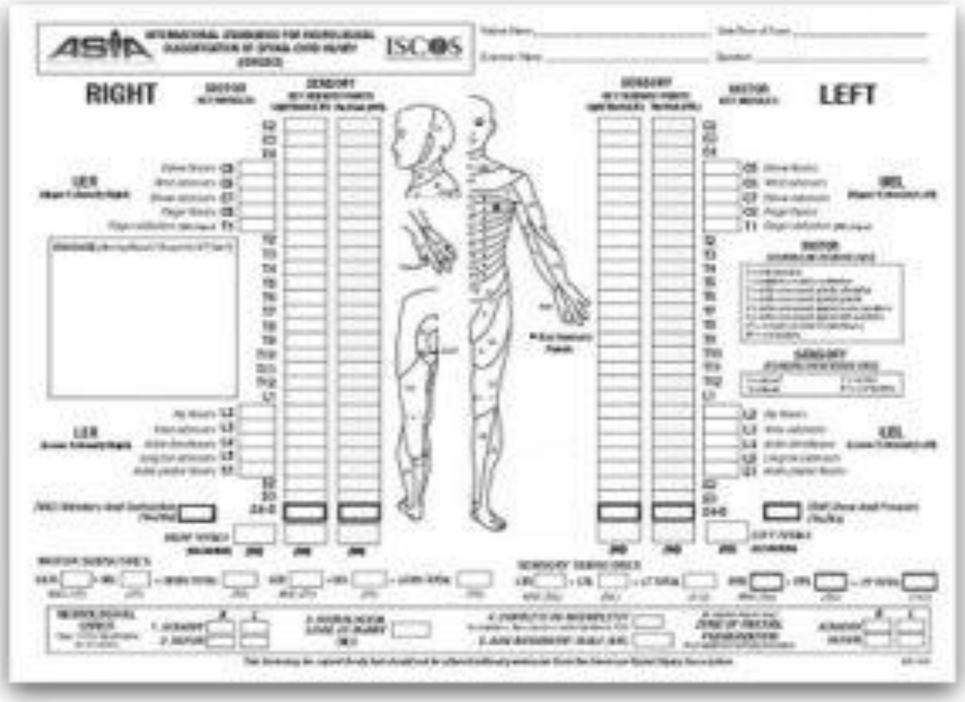
Complete injury: Absence of motor and sensory function in the lowest sacral segments.

Incomplete injury: Lesion with partial preservation of sensory and/or motor function present below the neurological level of injury and including the lowest sacral segments.

Further basic data sets for examination of organ systems after SCI have been established by ASIA and ISCoS in co-operation, including bladder, bowel, and cardiovascular function (7, 13, 14). Definitions of bladder function are congruent with those established by the ICS. A key definition relevant to the function of pelvic organs is:

Autonomic dysreflexia: Signs and/or symptoms in persons with SCI above the thoracic neurological level segment 5-6 in response to noxious or non-noxious stimuli below the level of injury. Autonomic dysreflexia is characterized by an increase in systolic blood pressure and may include headache, flushing and sweating above the level of the lesion, vasoconstriction below the level of the lesion, and dysrhythmia.

Figure 3. ASIA neurological examination sheet. Reproduced from the American Spinal Injury Association, https://asia-spinalinjury.org/



American Spinal Injury Association (ASIA) Impairment Scale (AIS) grades:
A Complete. No motor or sensory function is preserved in the sacral segments S4-S5.
B Incomplete. Sensory function preserved but not motor function is preserved below the neurological level and includes the sacral segments S4-S5.
C Incomplete. Motor function is preserved below the neurological level, and more than half of key muscles below the neurological level have a muscle grade less than 3.
D Incomplete. Motor function is preserved below the neurological level and at least half of key muscles below the neurological level have a muscle grade of 3 or more.

2.4 Neurogenic lower urinary tract dysfunction after spinal cord injury

Lower urinary tract function is nearly always affected after spinal cord injury, also among patients who recover and subsequently display normal motor and sensory function on AIS testing. Two main types of dysfunctions can be described based on the neurological level of lesion to the spinal cord (8).

A *suprasacral spinal cord lesion (SSL)* is a lesion in suprasacral (cervical, thoracic, or lumbar) segments of the spinal cord. Afferent nerve signals to the modulatory and coordinating nuclei in the brain are impeded or blocked and consequently the resulting efferent outflow to the pelvic nerves and organs is affected. The result is decrease or loss of control from higher centres on the micturition reflex. When the sacral reflex arch is intact detrusor overactivity with incontinence is common, with or without detrusor-urethral sphincter dyssynergia (DSD), often resulting in a significant post void residual urine (PVR) and high levels of intravesical filling pressure.

The clinical diagnosis is *suprasacral spinal cord lesion (SSL)* and the urodynamic observation is termed *neurogenic detrusor overactivity (NDO)*.

In a complete lesion sensation of bladder filling is absent. However, the person may learn to recognize the presence of bladder fullness by general spasticity or autonomic dysreflexia, which is triggered by the rising pressure in the bladder.

A *sacral spinal cord lesion (SSCL)* is a neurological lesion in the sacral segments of the spinal cord. The sacral reflex arch is not intact. There is loss of parasympathetic control of the detrusor and somatic denervation of the external urethral sphincter. The detrusor is underactive or acontractile with or without decreased bladder compliance usually with impaired sphincter activity. In a complete lesion sensation of bladder filling is absent. Stress urinary incontinence (SUI) may be present in case of damage to Onuf's nuclei resulting in sphincter deficiency and a decreased tone of the pelvic floor muscles.

The clinical diagnosis is *sacral spinal cord lesion (SSCL),* and the urodynamic observation is termed *neurogenic underactive bladder* or *neurogenic acontractile bladder*.

Additional key definitions in the ICS terminology for NLUTD are:

Detrusor-sphincter dyssynergia (DSD): a detrusor contraction concurrent with an involuntary contraction of the urethral and/or periurethral striated muscle. It is present when the pontine micturition centre pathways are impaired and coordination of the voiding phase does not take place, typically in an SSL. The result is bladder outflow obstruction and high amplitudes of intravesical pressure caused by detrusor contractions against the closed outlet.

Post void residual urine (PVR): the volume of urine left in the bladder at the end of micturition.

Spinal shock phase: loss of sensory, motor, and reflex activity below the neurological level of injury. Complete painless urinary retention is part of the spinal shock. This is usually a temporary phase following an acute neurologic insult which may last for hours or several months.

Neurogenic overactive bladder (nOAB): a clinical syndrome characterized by urgency, with or without urgency incontinence, usually with increased daytime frequency and nocturia in the setting of a clinically relevant neurologic disorder with at least partially preserved sensation.

Neurogenic detrusor overactivity (NDO): a urodynamic observation characterized by involuntary detrusor contractions during the filling phase, (which may be spontaneous or provoked) in the setting of a clinically relevant neurologic disease.

Neurogenic detrusor overactivity incontinence: urinary leakage due to involuntary NDO.

Neurogenic underactive bladder (nUAB): a clinical syndrome characterized by a slow urinary stream, hesitancy and straining to void, with or without a feeling of incomplete bladder emptying sometimes with storage symptoms in the setting of a clinically relevant neurologic disorder (15).

Neurogenic detrusor underactivity: a urodynamic observation made during the voiding phase and defined as a detrusor contraction of reduced strength and/ or duration, resulting in prolonged bladder emptying and/or a failure to achieve complete bladder emptying in the setting of a clinically relevant neurologic disorder.

Neurogenic acontractile detrusor: a urodynamic observation where a detrusor contraction cannot be demonstrated during the voiding phase, in the setting of a clinically relevant neurologic disorder.

Stress urinary incontinence (SUI): involuntary leakage of urine on effort or physical exertion (e.g., sporting activities) or on sneezing or coughing (16).

Mixed suprasacral and sacral cord lesions are not uncommon and may occur in up to 37% of all cases (17). A thorough classification of bladder and bowel function including physical examination of the pelvic area with anal reflex testing (18) and urodynamic investigation is paramount to characterize the NLUTD in the individual patient. Repeated testing is necessary as reflex activity returns and increases after the spinal shock phase and because improvements in nerve signal transmission may occur during months and years after the SCI.

From the mid-1990's until today the trend in middle- and high-income countries is a greater incidence of incomplete SCI lesions as well as conversions from complete to incomplete lesions during the first two years post injury (19), attributable to improved emergency care and specialized early rehabilitation. Other trends are increasing age at injury, an increasing proportion of female patients, and falls as the most prevalent etiology (9,20). Incomplete lesions make for a greater variability in the recovery of nerve function. Higher age implies that age-related changes in lower urinary tract function may even be present at the time of SCI. These factors underline the importance of repeated evaluation of lower urinary tract function.

Suprasacral spinal cord lesions (SSL) are associated with an increased *risk of renal impairment* due to the common presence of NDO and DSD (21). Reflex detrusor activity in the course of time usually progresses and exerts stronger and longer lasting contractions as they work against the closed bladder outlet (22). During contractions urinary outflow is blocked at the ureteral entry into the bladder, causing increased backward pressures against the renal pelvis and the vulnerable tubular structures. With impaired urinary outflow from the kidneys there is an increased risk of infections and stone formation in the upper urinary tracts. Sacral spinal cord lesions (SSCL), in contrast, are usually associated with a *low risk of renal impairment* because of the absence of NDO.

2.5 Symptoms and signs of NLUTD after spinal cord injury

SSL is typically associated with a neurogenic overactive bladder (nOAB). This condition includes a decreased functional bladder capacity, sudden onset urgency to void, increased frequency of micturition, and often detrusor overactivity incontinence. In the presence of detrusor-sphincter dyssynergia (DSD) postvoid residual urine (PVR) is frequent. If ordinary sensation is absent bladder filling is often experienced by autonomic symptoms such as trunk and leg spasticity, sweating and shivering in body parts above the neurological level of lesion. Even if some sensory function is intact, autonomic symptoms may be bothersome because NDO is a potent visceral drive for general spasticity. Catheterization or bladder reflex triggering (pinching or tapping on the lower abdomen or genitalia to elicit an artificial voiding reflex) is necessary to empty the bladder. Bacteriuria is prevalent. Bladder stones may form from residues of bacteria and waste products in the urine.

SSCL is commonly associated with decreased or absent sensation of bladder filling or urge to void. Bladder fullness may be experienced by a diffuse sensation from the lower abdomen. Residual urine is prevalent and bladder stones may form. Incontinence is prevalent due to weakened muscle tone in the sphincter area and skeletal muscles of the pelvic floor, and potentially large bladder volumes. Stress urinary incontinence may occur when abdominal pressure increases upon moving the wheelchair, during transfers to and from different positions, when bending over or picking up things from the floor. Stress urinary incontinence has been reported from quality-of-life studies to have more negative effects than the extent of the SCI as such (23).

2.6 Bladder management after SCI. Development of scientific evidence and clinical practice.

During the spinal shock phase after SCI, there is an apparent need for catheterisation of the bladder to empty urine. Usually, an indwelling urethral catheter is placed. Catheterisation to remedy urinary retention has been described since ancient times. About one hundred years ago, researchers suggested catheterisation at the earliest possible moment after SCI and then intermittently at regular intervals, usually 3 times in 24 hours (24). The aim was to keep the bladder free of an indwelling tube as much as possible to avoid infections. When antibiotics became available in the 1940's sterile intermittent catheterisation was suggested by Guttman and practiced at the first spinal unit in the United Kingdom (25). In the 1960's 77% of patients from this SCI unit were discharged from the hospital without a catheter in place. Patients would be encouraged to use bladder reflex triggering if sacral arch reflex activity had returned or bladder expression by applying manual external pressure over the lower part of the abdomen.
However, in many other settings the introduction of antibiotics led to longer periods of catheterisation and urinary tract infections were treated when symptoms appeared. When eventually catheter-free, many male patients used condom catheters with or without active periodic bladder reflex triggering. Condom catheters had become available in the late 1800's with the introduction of large-scale manufacturing of rubber (26). Voiding through the condom catheter could secure continence and independence but the long-term use of spontaneous or triggered reflex NDO for voiding inferred a risk for renal deterioration. In 1971 Lapides introduced routine clean intermittent self-catheterisation (CIC) which greatly enhanced the treatment of NLUTD (27). Complete bladder emptying was enabled without the need for an indwelling catheter, and greater independence became possible for many patients.
With technical development of urodynamic investigations an understanding began to develop of the effects of elevated intravesical pressures on renal function (28) and methods were sought

to counteract detrusor contractions. The first ’bladder-selective’ pharmaceutical substance for detrusor relaxation that became available in Sweden was emepronium bromide in the 1970’s (29).

From the 1980’s there has been strong development in multiple areas of treatment of NLUTD. Several anticholinergic drugs for the urinary tract have successively come into clinical use, partially replacing one another as more selective substances have been identified. The first beta-adrenergic medication for the treatment of overactive bladder became available around the year 2000. Anticholinergic drugs target the antimuscarinic receptors of the bladder while beta-adrenergics bind to adrenergic receptors, both receptor systems being active parts of bladder contractions. Technical evolution and basic research on the micturition reflex was the background for sacral anterior root stimulation, launched in 1982, (30) where a combination of dorsal rhizotomy of the S2-S4 nerve roots and implantation of electrodes on the ventral nerve roots is performed. Stimulation of the sacral anterior roots is conveyed from a subcutaneously placed stimulator which is controlled externally by the patient. This surgical-technical solution enables treatment of detrusor overactivity, incontinence, and voiding difficulty with a system that the patient can control independently. Significant side effects are caused by the dorsal rhizotomy, whereby sensation in the genitalia is lost as well as reflex erection in men, and reflex lubrication of the genitalia in women.

Continent urinary reservoirs were initially developed for patients who underwent removal of the bladder due to cancer surgery but became part of the treatment possibilities for selected patient groups with NLUTD. In a continent reservoir the ureters are disconnected from the bladder and connected to a pouch which is constructed from a portion of intestine. The intraabdominally placed pouch is equipped with a catheterizable outlet to the abdominal wall, fashioned from the same intestinal segment. For patients with good hand function and sufficient trunk stability, the potential gain is increased bladder capacity, amelioration of detrusor overactivity incontinence, and ease of catheterisation. Negative side effects are a high frequency of re-operations and long-term renal deterioration (31,32).

Artificial implants for the treatment of stress urinary incontinence (33) and erectile dysfunction (34) have been developed starting in the 1970’s. The artificial urinary sphincter (AUS) and an inflatable penile prosthesis were both developed by Scott and co-workers in Texas and the implants have since undergone re-design in many stages through the years. Both types of implants are managed entirely by the patient from the exterior by a small pump mechanism placed in the scrotum, and for a woman with an AUS, in the labium. These implants are suitable for selected patient groups, where they have been shown to produce good functional results. Side effects are re-operations because of technical malfunction or erosion of implant material into surrounding tissues, and infections which may warrant explantation of the prosthesis.

Bladder augmentation by enterocystoplasty was originally described in 1889 by von Mikulicz (35) and has remained a treatment option for patients who have refractory NDO despite anticholinergic drugs. In this procedure, the bladder wall is incised widely, and a portion of opened ileum is inserted to make the bladder larger and more compliant as the detrusor muscle network is divided. Surgical techniques for creation of a catheterizable conduit to the abdominal wall were introduced in the 1980’s and 1990’s (36,37) and a critical improvement for patients who are not able to carry out catheterization via the urethra. With enterocystoplasty, detrusor overactivity is counteracted, intravesical filling pressures decreased and the original ureterovesical junction is left in situ, protecting the upper urinary tracts. Functional results and patient-reported outcomes are generally favourable. Bladder augmentation is now considered standard treatment that should be offered if CIC combined with bladder relaxant medication or botulinum toxin treatment fails (38).

The introduction of injection therapy with botulinum toxin in 1998 (39) has revolutionised the management of neurogenic detrusor overactivity and decreased the need for surgery. Botulinum toxin blocks signal transmission in the synapses between vesical nerves and detrusor muscle cells, breaking off the sacral reflex arch and efficiently prohibiting NDO. The effect lasts a mean 7-9 months before the injection needs to be repeated in a quick outpatient cystoscopy procedure. In general, detrusor overactivity is significantly decreased to render low intravesical filling pressures and about 40% of patients achieve continence (40).

2.7 Current recommendations on bladder management after SCI

Current consensus is available from several international expert groups (6,41-43) based on evidence of efficacy and potential complications of each method. These are the common denominators at present (autumn 2021):

CIC is the preferred method of bladder emptying. Indwelling catheters should be reserved for patients where CIC is not possible either by self-catheterisation or by assisting persons. Indwelling suprapubic catheter is preferred over a urethral catheter.
Oral antimuscarinic therapy is the first choice for treatment of NDO. Beta-adrenergics are a possible second choice. Intravesical oxybutynin can be offered when oral antimuscarinic treatment is not tolerated.
Botulinum toxin should be offered to patients with NDO when oral therapy is not effective or cannot be tolerated.
Bladder augmentation can be used as a surgical option when NDO is not treated effectively by oral therapy or botulinum toxin.
A catheterizable conduit can be offered with the bladder augmentation.
A sub-urethral sling procedure can be offered to women with neurogenic stress incontinence.
An artificial urinary sphincter can be offered to men with neurogenic stress incontinence.

Optimal bladder management must consider the neurological level and extent of SCI, the patient's hand function, transferability into and inside toilet facilities, availability of assisting persons, living conditions, work setting, and social activities.

The ratio of complete to incomplete SCI has changed in middle- and high-income countries over the last few decades from about 46%/54% during the period 1990-2000 to 32%/68% in 2015-2019 (44). A higher prevalence of AIS C-D lesions implies a higher prevalence of persons who use normal voiding, albeit not entirely normal micturition in urodynamic terms. The guidelines of the American Urological Association (41) include adaptations of several methods to the SCI group, that are normally employed in the treatment of non-neurogenic overactive bladder or incontinence, for example, pelvic floor muscle exercises, peripheral nerve stimulation, and sacral neuromodulation for select patients with incomplete SCI.

Incomplete SCI opens possibilities for further development of technical aids to rehabilitate the micturition reflex and at the same time increase knowledge of the neuroplasticity after SCI, for instance trials on neuromodulation (45).

2.8 Urinary tract complications after SCI

Lower urinary tract infection

Bacteriuria is the term used for presence of bacteria in two consecutive urine cultures but without current infection-related symptoms.

Urinary tract infection (UTI) is the term used for presence of bacteria as demonstrated by a positive urine culture and concurrent infection-related symptoms.

UTI is the most frequently reported complication after SCI in many studies worldwide [46-48] and a cause of significant morbidity. It may cause the common symptoms of frequency, urgency and pain in the lower abdomen or genitalia but also febrile illness, aggravated autonomic symptoms and neuropathic pain (49). An episode of UTI may lead to restrictions in daily activities and an increased need for assistance by others. Risk factors for UTI include a cervical neurological level of injury and AIS grades A-B (50), bladder management by indwelling catheter or CIC (51) and lifestyle issues such as smoking and reduced physical activity (52).

Inability to use normal voiding entails a risk of residual urine. Until recently, it was commonly believed that urine is normally sterile. However, abundant research connected with the Human Microbiome project which was initiated by the United States National Institute for Health (53) in 2008, has demonstrated that the normal lower urinary tract has a stable colonization of low- or non-virulent bacteria, primarily Lactobacillus strains. More virulent pathogenic strains may invade transiently but are usually washed out with the flow of urine. In the presence of residual urine an environment is created where these strains can more easily attach to the bladder mucosa. It has been demonstrated that nearly 85% of E coli in urinary specimens from non-neurogenic populations (54) can create biofilm, and species like Klebsiella, enterococcus, proteus and Pseudomonas also have this ability. Up to 60% of chronic infections in humans are caused by bacteria from biofilm (55). Urinary specimens from patients with NLUTD without current infection related symptoms (bacteriuria) frequently display classic uropathogens such as Klebsiella, Pseudomonas and Enterococcus as part of their urinary microbiome, in contrast to the Lactobacilli which dominate in normal healthy bladders. Bacteriuria is common in NLUTD and thus reflects the changed environment in the urinary bladder because of the altered urodynamic situation.

In the current literature (6) there is consensus that antibiotic *treatment* should be instituted without delay in cases of evident infection-related symptoms, a positive urine culture and blood chemistry findings indicative of an acute infection. Antibiotics should be administered in relation to the patient’s symptoms, the clinical severity of the infection and in accordance with bacterial resistance testing and regional antibiotics programmes. Bacteriuria alone should not be treated.

Prevention of UTI includes an adequate and efficient bladder emptying method, a balanced intake of fluid, regular bowel function, physical activity, and cessation of smoking.

There is currently no evidence for a preventive effect of oral intake of cranberries, vitamin C, oral probiotics or methenamine hippurate. Low-dose oral antibiotics may prolong intervals between UTIs and can be used for restricted periods of time but usually cause an increase of bacterial resistance. Weekly cycling of two different types of antibiotics has demonstrated efficacy in a group of patients with spinal cord injury and a 'stable bladder situation' who were followed at an infectious disease out-patient clinic. Intravesical gentamicin instillations can reduce UTI frequency in selected patients practicing CIC without increasing the number of multi-resistant bacteria. Bladder instillation of non-virulent bacteria is a promising alternative (56). Research is on-going to develop compounds that may hinder the formation of biofilm and thus reduce bacterial counts (57). There is some evidence that bladder instillations with exogenous glycosaminoglycans which are used to restore and strengthen the innermost layer of the bladder mucosa may reduce the frequency and severity of UTIs, but this has not yet been shown in patients with NLUTD (58).

Epididymitis and prostatitis

The prevalence of epididymitis among men with SCI has been reported at 9-28% (59,60). Symptoms are often general malaise, genital pain, increased urinary frequency, spasticity, and other autonomic dysfunctions. Epididymitis may develop into a febrile illness requiring in-hospital treatment. Sometimes symptoms are restricted to a palpable mass in the scrotum. If treatment is delayed the infection can lead to scrotal abscess, fistulae, and chronic infections. There are risks of azoospermia or reduced sperm counts due to post-infectious duct obstruction in the epididymis (61).

Epididymitis is treated with antibiotics after a urine culture with bacterial resistance testing has been secured and in accordance with regional antibiotics programmes. In case of mild infectious symptoms ultrasound of the scrotum should be used to verify the epididymitis, as testicular tumour is a differential diagnosis. Follow-up with clinical examination and repeat ultrasound should be carried out after treatment.

The prevalence of prostatitis has been estimated at 5-30% (59,62). Among men without NLUTD who practice normal voiding the prevalence is about 1%.

The symptoms of prostatitis are genitourinary discomfort or pain and UTI. For a conclusive diagnosis a specimen of prostatic secretion should be secured for culture.

Adequate treatment is antibiotics according to microbiological findings and resistance pattern. Eradication of bacteria is often not feasible, and treatment should be directed toward reduction of symptoms (63). In case of negative bacterial cultures there is no indication for antibiotics and treatment can be administered in line with programmes for non-bacterial prostatitis (64). Other possible causes of symptoms that mimic those of an active infection should be ruled out, for instance pressure ulcers, constipation, and haemorrhoids.

Upper urinary tract infection/ pyelonephritis

The prevalence of upper UTI among patients with traumatic and non-traumatic SCI was about 23% over a three-year period in a study in Japan (64). Symptoms of upper UTI are febrile illness, increased spasticity and other autonomic dysfunctions, intense feelings of sickness, urogenital and/or flank pain. The diagnosis is based on a positive urine culture and blood chemistry indicative of an active infection with concurrent clinical symptoms. Ultrasound of the kidneys is important to rule out outflow obstruction. *Treatment* is usually administered in-hospital with intravenous antibiotics due to the severity of symptoms. *Follow-up* is important including radiology for detection of stones or other structural abnormalities in the urinary tracts. Any underlying causes of the infection should be treated such as improvement of bladder emptying method and voiding frequency, eradication of urinary stones, treatment of high intravesical pressures, and treatment of concurrent pressure sores.

Stone formation in the urinary tracts

Stone formation is the second most prevalent urinary tract complication after SCI (65). Studies have identified the long-term prevalence of stones in the upper urinary tracts at 7-20% and bladder stones at 14-49% (66,67). During the initial 3-6 months after traumatic SCI immobilization frequently leads to an outflow of skeletal calcium into urine which may induce formation of calcium stones. In contrast, during following years up to 98% of all stones in upper and lower urinary tract are apatite (calcium phosphate) or struvite (magnesium ammonium phosphate) in composition (68).

Symptoms of the presence of urinary stones are recurring or febrile UTIs, pain, increased autonomic dysfunctions, impaired bowel function as a side effect of autonomic dysfunction, haematuria, incontinence, or difficulty with bladder emptying. Acute onset of symptoms from an upper urinary tract stone may be severely limiting due to autonomic dysfunction while symptoms from a bladder stone may develop gradually.

Historically, formation of staghorn calculi with resulting renal damage was a prominent and feared cause of renal failure and death. With the gradual introduction of follow-up programmes after SCI, overviews now indicate that mortality due to urinary causes is less than 10% in middle- and high-income countries (69). However, interventions for urinary stones remain the most prevalent urological surgery. Stone formation is related to bladder management, with indwelling catheters and bladder reflex triggering with condom catheter voiding demonstrating the highest prevalence (67,68).

Stone treatment has developed from open surgery of the kidneys and ureters in earlier decades to extracorporeal shock wave lithotripsy, and less invasive methods like endoluminal ureteral procedures, and percutaneous nephrolithotomy. Open surgery of bladder stones changed to transurethral cystolithotripsy during the 1960´s and 1970’s. Modern stone disintegration includes efficient laser fragmentation which has improved stone clearance rates greatly (70). The evolution into less invasive surgical methods has generally reduced the risks of complications and the length of hospital stay. Radiological methods have improved steadily with digitalization, for example with visualisation of urinary stones in three dimensions (71).

Prevention of stone formation for patients with NLUTD includes choice of optimal bladder management for the individual patient, where regular and efficient emptying should be aimed for. Prevention of UTI is essential. Bladder washouts with saline or the acidic solution polyhexanide may prevent encrustation on indwelling catheters (72). Classification of stone components or a metabolic investigation by blood and urine testing may be warranted in select cases. Smoking cessation is advisable as tobacco use has been indicated as a risk factor for kidney stone formation as well as recurring UTIs (73).
For renal stones metabolic evaluation should be considered, bacteriuria decreased, and fluid intake increased (74).

Vesicoureteral reflux

A prevalence of vesicoureteral reflux (VUR) of 33% over the course of 40 years after traumatic SCI has been described (66). An incidence of 17-25% has been noted during the 1980´s (1). VUR is associated with a cervical neurological level of injury and elevated intravesical pressure during filling and voiding of the bladder.
Symptoms are recurring UTIs.
The diagnosis can be established by radiology, video-urodynamics, or a radionuclide cystography with uretero-renal scan.

Treatment should be initiated as soon as VUR is diagnosed with normalization of intravesical pressure by pharmaceutical agents or augmentation cystoplasty. Endoscopic treatment with injection of bulking agents around the ureteral orifice is standard treatment of VUR in children and adults without NLUTD and has been studied in patients with SCI with success rates of about 60% (75).
Prevention is carried out by establishing and maintaining low intravesical pressures.

Bladder diverticula

The prevalence of bladder diverticula has not been clearly described in the literature but in clinical experience small bladder diverticula are not uncommon in patients with SSL and NDO of some years' duration. They are associated with elevated intravesical pressure during filling and voiding of the bladder, typically in the presence of detrusor-sphincter dyssynergia and among patients who void by bladder reflex triggering. Symptoms may be discrete. Most commonly the diverticulum is discovered during a cystoscopy which is undertaken because of recurring UTIs. Other symptoms may be a decreased functional capacity of the bladder, new-onset or worsening of incontinence. Stones may form in the diverticulum (1).

The most important aspect of treatment is to establish low-pressure filling and voiding of the bladder. Large diverticula may need surgical excision.

Urethral diverticula and injuries

Urethral diverticula, most commonly occurring in the penoscrotal urethra, are noted in approximately 5% of SCI men undergoing urethrography and urethral strictures have been reported in 25% of SCI men who performed CIC (74). In general, radiological studies suggest a risk of urethral trauma in SCI patients of about 20%, depending on how patients were selected for the investigations and the time from injury.

Incontinence

Incontinence after SCI is prevalent. The type of incontinence depends on the neurological level and extent of the spinal cord lesion and the resulting type of NLUTD. A thorough evaluation should be performed within 3 months after injury including validated questionnaires, bladder diary, physical examination with neuro-urological testing and urodynamics to specify the dysfunction and make adequate treatment possible.

Incontinence is frequently rated by patients as a major obstacle in everyday life, along with recurring UTI (38,76).

For patients with an SSL treatment includes life-style changes, pharmaceutical treatment with bladder relaxant oral medications (anticholinergic or beta-adrenergic) as first-line measures and botulinum toxin injections as second-line therapy. Surgical options are bladder augmentation or in select cases urinary diversion.

For patients with an SSCL and stress urinary incontinence surgery with implant of a urethral sling or an artificial urinary sphincter are possible options (43).

Among patients with incomplete SCI pelvic floor muscle training (PFMT) with or without concurrent intravaginal electrical stimulation has been studied. PFMT alone resulted in significant improvement over 12 weeks, but there was no added effect of electrical stimulation (77). Minimally invasive periurethral injections with bulking agents and duloxetine (an oral serotonin-noradrenaline re-uptake inhibitor) have been tried in clinical practice. However, there are no relevant studies on adult patients with SCI.

Anticholinergic and beta-adrenergic treatment has well-documented effects and side-effects. There is accumulating evidence that anticholinergic effects over long periods of time or from multiple medications (anticholinergic load) may cause cognitive impairment and even dementia (78), which calls for diligent follow-up of these medications.

Prevention of incontinence first and foremost entails a precise classification of the NLUTD in the individual patient, then establishment and follow-up of an adequate voiding method. Evaluation of fluid intake, prevention of UTIs, and treatment of NDO are important measures as well as evaluation and treatment of co-morbidities and life-style issues such as diabetes, overweight, and smoking.

Lesions of genitalia and the lower urinary tract

Indwelling catheters may cause pressure ulcers or lesions of the genitalia (42). A pressure ulcer may develop on the abdomen at the point of insertion of an suprapubic catheter. An indwelling urethral catheter may cause an ulcer in the genitalia for non-ambulant women, a spatulation of the meatus, or an erosion of the male urethra through the penile shaft. Incontinence may cause and maintain pressure ulcers around genitalia and the ischiorectal area ('the sitting region').

Prevention involves avoiding indwelling catheters whenever possible. The relevant skin areas should be checked frequently for bruising or ulcer development. Catheters and collecting bags can be placed in alternating locations and padding around an suprapubic catheter can be used to avoid constant pressure in one localized spot. Incontinence should be minimized. In my clinical experience a scrutiny of pressure ulcers should be part of the work-up for incontinence.

Urothelial and squamous cell carcinoma

The overall incidence of bladder cancer in patients with SCI has been reported at 6% as compared with a worldwide cumulative risk of 0.6% to 75 years of age in the general population (79). The estimated proportions of cancer types among SCI patients were squamous cell cancer 37% and urothelial cell cancer 46%. Long-term use of an indwelling catheter has been considered an underlying factor as the constant irritation and low-grade inflammation may imply a risk for squamous cell cancer. More recent studies have indicated that the increased cancer risk exists also for patients without indwelling catheters and particularly after SCI duration of >10 years.

A limitation in the current literature is that smoking, which is a well-known risk factor for bladder cancer, has generally not been well registered in this patient population. There have been conflicting reports on the sensitivity and efficacy of scheduled screening. Some international bodies now advocate that cystoscopy, urine cytology and urine markers for urothelial cancer should be part of the urological follow-up (6,80).

Renal impairment

Historically renal impairment was a feared complication after spinal cord injury and a major cause of mortality. Prior to the introduction of monitoring programs for upper and lower urinary tract function renal failure-associated mortality was 50% (74). By the early 1990´s this rate had decreased to 24%, and recent rates are less than 10% (69). Urogenital disease and renal impairment still cause considerable morbidity and the cumulative risk of moderate and severe renal deterioration after 45 years of injury has been reported at 58% and 29%, respectively (81). Active monitoring remains important and in the aging population with SCI special attention must be given to co-morbidities which may have an influence on kidney function (82).

Known risk factors for renal deterioration are cervical-thoracic neurological level of lesion, AIS grades A-B, male gender, presence of NDO with high intravesical pressures during filling and/ or voiding (22,83), long duration of detrusor overactivity during filling (84), vesicoureteral reflux, bladder emptying by use of reflex triggering or an indwelling urethral catheter (66).

2.9 The role of the neuro-urologist in SCI rehabilitation and follow-up

The responsibility of a neuro-urologist involved with SCI is two-fold:
To assist patients with

- preservation of renal function, providing opportunities for a long life
- treatment and prevention of lower urinary tract dysfunctions, providing opportunities for a good life

To achieve these goals accurate diagnostic methods, meticulousness, dedication, and feasible as well as patient-friendly follow-up programmes are fundamental ingredients.
In a holistic approach to the global management of secondary complications after SCI it becomes apparent that management of NLUTD is interrelated with the management of bowel function, lifestyle issues, other autonomic dysfunctions, mobility aspects and many other parts of the new life post SCI.

2.10 Follow-up programmes for NLUTD after SCI

Lower urinary tract dysfunction because of SCI was recognized as part of the acute paralysis in ancient times, but in general SCI was considered 'an ailment not to be treated' (85). Follow-up programmes for NLUTD after SCI were initiated with establishment of the first specialised SCI unit in the United Kingdom in 1944 and the pioneering work of Sir Ludwig Guttmann. At the same time early 'spinal units' were started up in the United States. Initial focus was on securing bladder drainage and following the effect on renal function. Guttmann introduced intermittent sterile catheterisation of the bladder to avoid recurring bouts of sepsis (25). Improvements in morbidity and mortality were dramatic. Through the following years the focus on renal function prevailed. With the development of antibiotics and improved outcomes of upper urinary tract infections, attention turned to renal health in the longer term. Urodynamic studies as an investigative method of urinary tract function were introduced during the 1970's -1980's. During the coming decades standards for urodynamic examinations, equipment, and reporting were internationally agreed. An improved understanding of the nervous control of the lower urinary tract and the pathophysiologic changes following SCI gradually evolved. CIC as a method for bladder emptying was introduced in the 1970´s (26) and gradually spread to many countries where single-use catheters could be afforded.

Traditionally, mainly patients in tertiary hospital settings with the most severe SCI were followed up and interventions were geared toward care measures suitable for these settings. However, Guttman had introduced the idea that rehabilitation should aim not only for a longer and less complication-ridden life, but also through sports activities prepare for a return to work and other social situations. Gradually, it was recognized in high-income countries that the increased life expectancy would raise possibilities of a broader inclusion into society (86). Quality of life issues became more important, joined by a focus on treatment of incontinence and recurring UTIs. Patients with less severe SCI were now included in some follow-up programmes.

In the early 2020´s, some eighty years after Ludwig Guttman's pioneering work, follow-up programmes have now been published and are regularly updated by international urological associations (6,41). The International Spinal Cord Society (ISCoS) (87) has developed reporting standards and practical data sets to aid clinicians and researchers in follow-up and registration of complications. There is international agreement on the terminology of NLUTD established by the ICS, which facilitates communication between clinicians and researchers worldwide.

In recent years a series of reviews have been published from several international collaboration groups and research societies regarding the management and follow-up of NLUTD after SCI (73,79). There is general agreement that the following elements should be included:

- Medical history
  Clinical examination
  Renal laboratory tests: creatinine, cystatin-C + estimated Cystatin-C-related-GFR
- Imaging surveillance of the upper urinary tract by renal ultrasound

- Urodynamic study. If available, video urodynamics will provide simultaneous anatomical and functional information.

- Cystoscopy and urine cytology
- Cystoscopy should be performed when indicated by new symptoms. Macroscopic haematuria should be evaluated in the same manner as in the general population.
- There is no evidence to support that screening cystoscopy can detect bladder cancer at a pre-clinical or early stage. Urine cytology unfortunately has low sensitivity and specificity in this patient group due to frequent inflammatory changes of the bladder mucosa in NLUTD.
- There are diverging viewpoints regarding the timing of follow-up**.** Annual clinical examinations with laboratory tests and renal ultrasound seems to be the consensus.

A *urodynamic study* is a measurement of physiological parameters of the lower urinary tract and provides information on the coordination of nerve and muscle activity in the patient. Catheters supplied with pressure transducers are placed in the bladder and in the rectum or vagina for recordings of intravesical and abdominal pressure, respectively. Pressure dynamics during bladder filling and voiding are registered. The patient reports on sensation during the procedure. Urodynamics are necessary for classification of NLUTD in the individual patient and provide important information on risk factors for renal function. However, it is an invasive method of investigation and possible complications include UTI, haematuria, and discomfort.

A *cystoscopy* is a visual examination of the inside of the urethra and bladder with the use of fibre optics mounted in a catheter-like instrument. This examination provides information on the morphology of the lower urinary tract, the state of the bladder/urethral wall and the mucous membranes lining the inside, for example on inflammations, infections, the appearance of the ureteral orifices, the presence of diverticula, bladder stones or tumours.

Urine cytology is an examination of the cells present in the voided urine.

2.11 The Spinalis clinic

The Spinalis clinic was established in 1991 as the first regional comprehensive outpatient centre in Sweden for life-long follow-up after SCI. The establishment coincided with The Stockholm Spinal Cord Injury Study, an inventory of medical, economic, and psychosocial outcomes in the regional prevalence population (88). Activities were organized according to the real-world medical needs of the SCI population. Services included annual follow-up visits focussing on medical complications, and rehabilitation programs within the medical, vocational, and psychosocial areas. A consultant neuro-urologist was recruited at an early stage for in-house patient consultations, diagnostic and surgical interventions. An important objective was to serve as a bridge between the out-patient service and the Karolinska University Hospital.

A follow-up programme for neurogenic bladder dysfunction secondary to SCI was established in 2003, and revised in 2013 (89), prior to the establishment of many now available international follow-up programmes. It was designed for systematic assessment of all patients with the two-fold responsibility of preserving renal function and treating urological dysfunctions.

A majority of the regional prevalence population with a chronic SCI is registered for follow-up at the Spinalis clinic which continues to offer a unique learning and research environment. Patient-centred research is carried out with the aim of timely conversion of outcomes into evidence-based medical practice. Scientific reports and theses in multiple medical areas have contributed to a more holistic understanding of life with a chronic SCI. Follow-up and prevention programmes for medical complications are continually updated. Close collaboration is maintained with clinical departments at the Karolinska University Hospital. The Spinalis outpatient clinic is now part of Aleris Rehab Station (90), a hospital dedicated to neurological and post-traumatic rehabilitation.

2.12 The regional prevalence population and new research questions

Studies on urinary tract complications in chronic SCI were traditionally focused on populations with higher neurological levels and severity of injury who required hospital treatment in tertiary centres. More recently, reports on community samples of patients have been added to the literature (49,91,92). Following the establishment of the Spinalis clinic we identified a knowledge gap concerning the impact of NLUTD on the morbidity, complications, and daily life in patients with *all* neurological levels and severity of traumatic SCI, and the need to improve follow-up programmes to address the issues of “a long life” as well as “a good life” for *all patients*.

Several *research questions* were identified:

How frequent are known risk factors for complications of the urinary tract in the regional prevalence population? What is the correlation between individual factors and aggregates of these risk factors with various complications?

Can additional risk factors be identified?

Which symptoms or signs do patients report as significant problems of the urinary tract that influence quality of life? How well do patients´ reports correlate with objective findings?

What is the outcome of interventions already carried out in this population?

How can we improve the global follow-up and treatment of urinary tract complications after SCI?

3 RESEARCH AIMS

Overall aims:

- to evaluate the types and prevalence of secondary complications of the urinary tract in a regional prevalence population of persons with chronic post-traumatic SCI including all neurological levels and severity of injury

- to evaluate patient-reported dysfunctions of the urinary tract and the correlations with objective findings of complications

- to improve follow-up for NLUTD after SCI by making the programme inclusive, patient friendly, easy to use, and at the same time accurate for neuro-urological evaluation

Aims for paper I

- To assess urinary tract function and complications in a regional prevalence group of patients with traumatic spinal cord injury (SCI), and to estimate risk factors for recurring complications.

Aims for paper II

- To examine symptomatic urinary tract infections (UTI) in the regional prevalence group, to assess risk factors for recurring symptomatic infections and to identify a high-risk subpopulation for frequently recurring and severe UTI´s.

Aims for paper III

- To examine the outcome of urodynamic studies in the regional prevalence group, to explore relationships between urodynamic parameters and renal complications and other SCI-related dysfunctions, to assess the role of urodynamics in SCI follow-up.

Aims for paper IV

- To examine the number and types of urological surgical interventions carried out in the regional prevalence population through the post-traumatic period, to evaluate objective as well as patient-reported outcomes and implications for the future role of urological surgery in this patient group.

4 MATERIALS AND METHODS

4.1 Study design

This thesis is built on a cross-sectional study of urinary tract function, complications, and interventions in the near-total regional prevalence population of patients with a chronic traumatic SCI. A comprehensive database was constructed including objective and patient-reported data. An inventory of the basic characteristics of the study population was reported in Paper I.

Several areas for further investigation were identified. The following studies were informed by the database and supplemented with additional cross-sectional and retrospective surveys from clinical file records.

Paper II utilizes database information on urinary tract infections supplemented with a scrutiny of patient file records, prescription records of antibiotics and microbiology laboratory reports during the preceding year.

Paper III includes database information on urodynamic studies carried out in connection with the cross-sectional study visit, complemented with a renewed analysis of all urodynamic tracings to include novel metrics, and a retrospective survey of patient file records on previous urodynamic observations and bladder management (time span 1- 25 years).

Paper IV employs database information on the history of urological surgery after the SCI and patient-reported outcomes of reconstructive surgery, satisfaction with current bladder management and complications during the preceding year, as well as objective data on renal function. These data were supplemented with a retrospective review of patient file records of urologic interventions from the time of SCI until 2010 (time span 1-50 years), complications and re-operations, follow-up, and patient-reported and objective outcomes during the previous years.

4.2 Study population

Participants in the cross-sectional study were men and women aged

18 years or older with a post-traumatic SCI for at least 1 year. All individuals were living in the greater Stockholm area and registered at the Spinalis clinic, which oversees follow-up for the regional SCI population. Patients were offered participation in the study as they consecutively attended annual check-up visits. 412 patients consented to participate, constituting 91% of those who attended the yearly check-up.

Fifteen patients declined participation and 26 were excluded. Reasons for exclusion were old age and multiple other illnesses (n=10), language difficulties (n=1), non-traumatic SCI and no residual symptoms (n=15).

The groups of included vs not included patients were similar in distribution of age, neurological level of injury and severity of SCI.

Papers I-II include the entire study population of 412 patients. In paper II additional focus was placed on the subset of 183 patients who reported ≥ 1 episode of UTI during the preceding year.

Paper III includes a subset from the entire study population, namely 211 patients who had undergone a urodynamic study as part of the follow-up. Urodynamic studies which were completed within two years of the check-up visit were included, provided bladder management had not changed.

Paper IV includes a subset from the entire study population, namely 137 patients who had undergone urological surgical interventions at any time during the period from the event of traumatic SCI until 2009.

Table 1. Total study population, urodynamics group and surgery group.

	Paper I-II	**Paper III**	**Paper IV**
	Total study population n=412	**Urodynamics group**, n=211	**Surgery group, n=137**
Male/ female, n (%)	320 (78%)/ 92 (22%)	164(78%)/47 (22%)	108(79%)/ 29(21%)
Age, (years) mean, (SD), /range/	49.1 (14.7) /18-88/	44.9 (13.6) /18-78)	49.5,48 (14.5)/20-83/
SCI duration, (years) mean, (SD), /range/	16.4 (11.8) /1-51/	14.9 (11.8) /1-49/	18.5,15 (12.3)/1-52/
Severity of spinal cord injury, n (%)			
C1-C4, A-C	37 (9)	14 (7)	32 (23.5)
C5-C8, A-C	83 (20)	49 (23)	44 (32)
T1-S3, A-C	149 (36)	96 (45)	44 (32)
AIS D at any level	143 (35)	52 (25)	17 (12.5)
	412 100)	**211 (100)**	**137 (100)**

Footnotes:
SCI = spinal cord injury

American Spinal Injury Association (ASIA) Impairment Scale (AIS) grades:
A Complete. No motor or sensory function is preserved in the sacral segments S4-S5.
B Incomplete. Sensory function preserved but not motor function is preserved below the neurological level and includes the sacral segments S4-S5.
C Incomplete. Motor function is preserved below the neurological level, and more than half of key muscles below the neurological level have a muscle grade less than 3.
D Incomplete. Motor function is preserved below the neurological level and at least half of key muscles below the neurological level have a muscle grade of 3 or more.

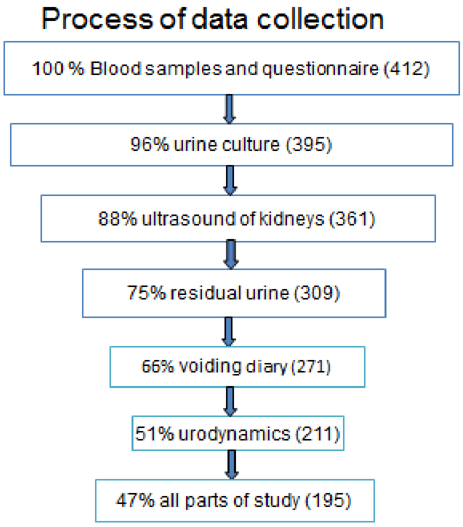
4.3 Data collection

In the cross-sectional study two programmes for follow-up of chronic SCI were applied: a national Swedish programme for follow-up of medical SCI complications (93) and a regional programme for neurogenic bladder dysfunction (89), complemented with a study-specific questionnaire regarding urinary tract function and complications during the preceding year (supplement 1). Objective measurements and patient-reported data were collected as shown in Table 2. A study-specific database was created in Microsoft Office Access 2003 (Microsoft Corporation,1 Microsoft Way, Redmond, WA 98052, USA).

Table 2. Data collection. Modified from papers I-II

Information on past illnesses, concurrent medical conditions, current medication, bowel function, pain, spasticity, history of pressure ulcers, circulatory complications related to spinal cord injury	Individual structured interviews, medical file reviews
Complications of the urinary tract during the preceding year, prophylactic measures to avoid urinary tract infection, bladder management	Study-specific questionnaire completed by patient, medical file reviews
Blood chemistry	S-creatinine and S-cystatin-C. Blood samples taken at check-up visit.
Residual urine	Measured by ultrasound or catheter immediately after patient-preferred method of voiding.
Urine culture	Collected at check-up visit. Notes made on current symptoms.
48-hour voiding diary	Completed by patient at home, sent back in pre-stamped envelope.
Physical and neuro-urological examination	Complete physical examination done by neuro-urology specialist.
Examination of neurological level of injury and severity of lesion	Performed by neurologist according to international standards for neurological classification of spinal cord injury.
Ultrasound of urinary tracts	Performed by radiologist.
Urodynamic testing	Performed by urotherapist/ nurse specialist according to Good Urodynamic Practice. Evaluation of graphs by specialists in neuro-urology.

Figure 4. Process of data collection. This figure is included in paper I.



In paper II the database was supplemented with additional information from patient file records, prescription records of antibiotics and microbiology laboratory reports during the preceding year: all urine cultures and resistance testing, all prescriptions of antibiotic courses with type of antibiotic and dosage, matching of patient-reported symptoms of UTI with urine culture and antibiotic prescription.

In paper III the data base was complemented with an analysis of all urodynamic tracings where the following measurements were collected: maximum detrusor pressure during the filling phase, detrusor pressure at maximal filling volume, maximal cystometric bladder capacity, length of detrusor contractions during the filling phase, bladder wall compliance, the ice-water cooling test (positive or negative), maximum detrusor pressure during voiding, maximum urethral pressure, maximum urethral closure pressure at internal sphincter, maximum urethral closure pressure at external sphincter. Urodynamic observations were registered: neurogenic detrusor overactivity, underactive detrusor, acontractile detrusor or normal detrusor. A retrospective survey of patient file records was performed, and the following data collected: primary urodynamic study after SCI – time of investigation and urodynamic observation, types of bladder management from SCI until the time of the cross-sectional study.

In paper IV the data base was supplemented with a retrospective review of patient file records and the following data registered: types, dates and number of urologic surgical interventions, complications, re-operations, times and duration of follow-up at departments of urology or at the Spinalis clinic, renal function by S-creatinine and/ or cystatin-C and cystatin-C related GFR, any other renal function testing, renal ultrasound or other radiology, patient-reported outcomes in the number of UTIs, incontinence, and any other surgery-related complication.

4.4 Data analysis and statistical methods

In paper I-III data were analysed using SPSS for Windows 25 software (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp). Descriptive statistics were calculated. Regression analysis was used to estimate risk factors for renal impairment in paper I and risk profiles for more than three UTI´s during the preceding year in paper II. Non-normally distributed data were evaluated by descriptive statistics only in papers I-II.

In paper III descriptive and comparative statistics were calculated. The independent samples *t*-test was used for the comparison of groups with normally distributed variables, which applied to urodynamic parameters in relation to groups with or without signs of renal complications or other SCI-specific dysfunctions in the total urodynamic population (n=211). The Mann–Whitney *U* test was used for non-normally distributed variables, which applied to groups of injury duration 11-20 years (n= 37), 21-30 years (n=25), and 31-49 years (n=17). *p*-values <0.05 were considered statistically significant. Logistic regression analysis was used to estimate urodynamic parameters as risk factors for renal and other SCI-related complications in groups of injury duration 1–10, 11–20, 21–30, and 31–49 years, respectively.

In paper IV data were analysed using SPSS for Windows 28 software (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Descriptive statistics were calculated. Logistic regression was used to determine risk profiles for incidence of urological surgery.

4.5 Ethical considerations

The present work was conducted in conformation with the Declaration of Helsinki which specifies principles for all medical research involving human subjects (94). Ethical approval was obtained from the Regional Human Ethics Committee at the Karolinska Institute, Stockholm, reference number 2007/35-31/3. Verbal and written information was given about all parts of the study. Participants could withdraw at any time if they so wished without any consequences for further medical follow-up or treatment.

Informed consent was obtained from participants before study activities commenced.

The study was based on existing national and regional follow-up programmes. All tests were normally used in clinical routine, except the collection of a urine culture from patients with no current symptoms of a urinary tract infection.

A careful analysis was conducted of potential risks and benefits to participants. The study-specific questionnaire and structured interview included questions about urine voiding patterns and infection-related symptoms which might be experienced as intimate and intrusive. The annual check-up visit was more time-consuming when all parts of the study were included. It was estimated that any discomfort and inconvenience would be outweighed by the fact that the interview and careful tests could enable improvement of bladder management and reduction of current or future risks of complications.

Results from the cross-sectional study have been presented as scientific articles in peer-reviewed journals and in this thesis. The findings will be utilized in the continuous improvement of the NLUTD follow-up programme for all patients at Spinalis.

5 RESULTS

Paper I. Basic characteristics and problem inventory

The basic characteristics of the regional prevalence population were summarized.

Objective data

102 patients (25%) displayed at least one sign of *renal complications* in laboratory results and/ or renal ultrasound. These patients had cervical or high thoracic neurological levels of SCI and AIS grades A-B. The mean SCI duration was 19.7 years.

Logistic regression verified the main risk profile for renal complications as cervical lesions with AIS grades A-B. There was no difference in risk profile between bladder management subgroups or the presence/ volume of residual urine.

Urodynamic observations were neurogenic detrusor overactivity (NDO) in 150 patients, neurogenic underactive or acontractile bladder in 43 patients and a normal detrusor reaction during the filling phase in 18 patients. These findings were approximately consistent with the distribution of neurological levels and severity of SCI. However, one fourth of patients with a thoracic neurological level of SCI unexpectedly displayed underactive/ acontractile bladder. These patients had a mean SCI duration of 20.3 years.

Patient-reported data

Bladder management:

Clean intermittent catheterisation (CIC)	38%
Normal voiding	29%
Indwelling suprapubic catheter	11%
Bladder reflex triggering	8%
Indwelling urehtral catheter	4%
Continent urinary diversion	4%
Incontinent urinary diversion	2%
Other (abdominal pressure, external pressure, sacral anterior root stimulation)	4%

Among patients who used normal voiding 88% had an AIS D and 8% an AIS C lesion.

Forty-seven % reported at least one episode of *complications* during the preceding year. UTI was experienced by 44%, including those reporting febrile UTIs requiring treatment in hospital. Epididymitis, orchitis or prostatitis was reported by 3% and bladder stones, renal stones, haematuria, or urogenital pain by 8%.

Fifteen % reported > 3 UTI´s during the preceding year. Five % reported a febrile UTI that had been treated in hospital.

Patients with an AIS D lesion reported fewer UTIs and no febrile UTIs requiring hospital treatment. The proportion of other urinary tract complications was half that of patients with an C5-C8 AIS A-C classification of SCI. The prevalence of ABU was half that of patients with cervical-thoracic neurological levels of injury. However, 21% of AIS D patients demonstrated signs of renal complications. These patients had a mean SCI duration of 15.5 years. Residual urine and bacteriuria were common among those who practiced normal voiding, but symptomatic UTIs were few.

Table 3. SCI characteristics, objective, and patient-reported data from papers I-II.

SCI characteristics	**Signs of renal complications, n (%)**	**≥1 UTI during preceding year, n (%)**	**Number of UTIs mean/median**	**Other urinary tract complications n (%)**	**ABU n (%)**
C1-C4, A-C, n=37	10 (27)	22 (59)	2/2	4 (11)	33(89)
C5-C8, A-C, n=83	21 (25)	53 (64)	2.4/2	16 (19)	47 (57)
T1-S3, A-C, n=149	41 (28)	77 (52)	1.9/1	11 (7.5)	84 (56)
AIS D at any level, n=143	30 (21)	31(22)	0.6/0	12 (8.5)	43 (30)
412	102 (25)	183 (44)	1.6/0	43 (10.5)	207 (50)

SCI = spinal cord injury
UTI = urinary tract infection
ABU = asymptomatic bacteriuria

Paper II. Urinary tract infections in a regional prevalence group: Frequency, symptoms, and treatment strategies

This paper focussed on UTI as the most prevalent patient-reported complication.

Objective data

The number of positive/ negative *urine cultures* were 56%/ 44%. 207 positive urine cultures were classified as asymptomatic bacteriuria (ABU) and 13 as a current UTI.

E coli was the most frequently diagnosed agent in ABU and in current UTI´s, found in about 40% of ABU and in 6/13 symptomatic infections. A mixed bacterial flora was found in approximately 30% and klebsiella, enterococci, pseudomonas, and other species in proportions of 1-8%.

The highest prevalence of *residual volume* > 100 mL was found among patients who practice normal micturition or bladder reflex triggering (17% and 67%, respectively). Users of CIC or indwelling catheter had the lowest rates (6% and 0%, respectively). There was no co-variation between the presence or volume of residual urine and the number of UTI´s, or the number of antibiotic prescriptions for UTI.

Patient-reported data

Number of UTIs:

Forty-four % reported ≥1 UTI during the preceding year. Of those patients, two-thirds reported 1-3 infections and 3 was the most prevalent number. The male/female distribution was 78% / 22%, equal to the gender proportions in the total study group.

A total of 661 symptomatic UTI´s were reported, with a median/ mean number of 3/3.6 UTI´s in the group that had infections. According to medical files, 690 antibiotic courses were prescribed due to urinary symptoms and 450 actual prescriptions were verified.

Patients who reported >3 UTI´s (n=63, 15.5%) were mostly found in the CIC group (n=40) and suprapubic group (n=13) and were characterized by a cervical (n= 30) or thoracic (n= 20) neurological level injury with AIS grades A-C. Regression analysis verified the main risk profiles as cervical lesions with AIS grades A-C. There was no risk difference with age or gender. SCI-related dysfunctions such as spasticity, neurogenic pain, autonomic dysreflexia, and pressure ulcers were frequent in this group, whereas other specific complications of the urinary tract were not more common than in the entire study group. The mean SCI duration was 13.4 years.

Twenty-one patients reported treatment in hospital due to a febrile UTI. Among them 11 patients had other SCI-related dysfunctions such as spasticity, neurogenic pain, autonomic dysreflexia, and pressure ulcers. Five patients in this group had other complications of the urinary tract, such as bladder stones, orchitis and prostatitis. Thirteen patients overlapped with the group who had >3 UTI’s. The mean SCI duration was 26 years.

Cardinal *signs and symptoms of UTI* were reported by patients who had ≥1 UTI during the preceding year as

Foul smell and cloudiness of urine	88%
General feeling of malaise/ illness	62%
Rise in body temperature ≤ 38 degrees Celsius	61%
Rise in body temperature > 38 degrees Celsius and shivering	52%
Increased spasticity	48%

In the total study population use of *antibiotics or antiseptics to prevent UTI* was reported by 28%, vitamins and health foods by 38%. There was no difference in the number of UTI´s between those who practiced these preventive measures and those who did not.

Bladder management: In the total study population patients who practiced normal voiding had a low number of UTIs, comparable to that of the general population. Those who voided by CIC or suprapubic catheter reported the highest mean number of UTIs (2.5/ year) followed by patients who practiced abdominal pressure/Valsalva (2.2), had an indwelling urethral catheter or an incontinent urinary diversion (1.6).

Risk profiles for more frequent and/ or more severe UTIs were cervical-thoracic neurological levels of lesion and AIS A-C, SCI-duration >10 years, a urodynamic observation of NDO, and catheter-assisted voiding. SCI-related autonomic dysfunctions were common, but there was no co-variation with other complications of the urinary tract

There was no risk difference with age, gender, or the presence of residual volume.

Paper III. Urodynamic characteristics in a regional prevalence group of persons with spinal cord injury and indications for improved follow-up

The role of urodynamic studies for characterization and follow-up of NLUTD after SCI was explored.

Among the 412 patients in the cross-sectional study, 211 had a urodynamic study as part of the follow-up. NDO was found in 150, underactive/acontractile detrusor in 44, and normal detrusor function in 17 patients.

Urodynamic parameters which have traditionally been considered risk factors for long-term renal impairment were frequent:

Maximum detrusor pressure >40 cm H2O during filling	66%
Maximum detrusor pressure >25 cm H2O during filling	80%
Detrusor overactivity leak point pressure >40 cm H2O	92%
Maximum detrusor pressure during voiding >55 cm H2O (voluntary voiding)	41%
Reduced compliance of the bladder wall	12%
Cystometric bladder capacity <250 mL	30%

The highest detrusor pressure was obtained among persons who used normal voiding, bladder reflex stimulation or sacral anterior root stimulation.

Among patients with a current underactive/acontractile or normal detrusor 36% had a primary NDO consistent with a cervical/thoracic neurological level of injury and AIS grades A-C. These patients had a median SCI duration of 28 years. Initial bladder management was bladder reflex triggering or combinations of bladder reflex triggering, Valsalva manoeuvres and normal voiding for a median of 15 years.

Among patients with NDO and an SCI duration of 11-20 years there was a statistically significant relationship between *the duration of detrusor overactivity* during the filling phase (DO ratio) and signs of renal complications. 61% of all patients with NDO had a DO ratio of more than 33%.

Logistic regression verified the DO ratio as a risk factor for renal complications (odds ratio, OR 1.3). There was *no risk difference with other urodynamic parameters.*

Patients with/ without on-going bladder relaxant medication at the time of the examination had a mean maximum detrusor pressure during filling of 26/60 cm H2O ($p<0.001$), but a mean DO ratio of 40%/43% ($p=0.455$).

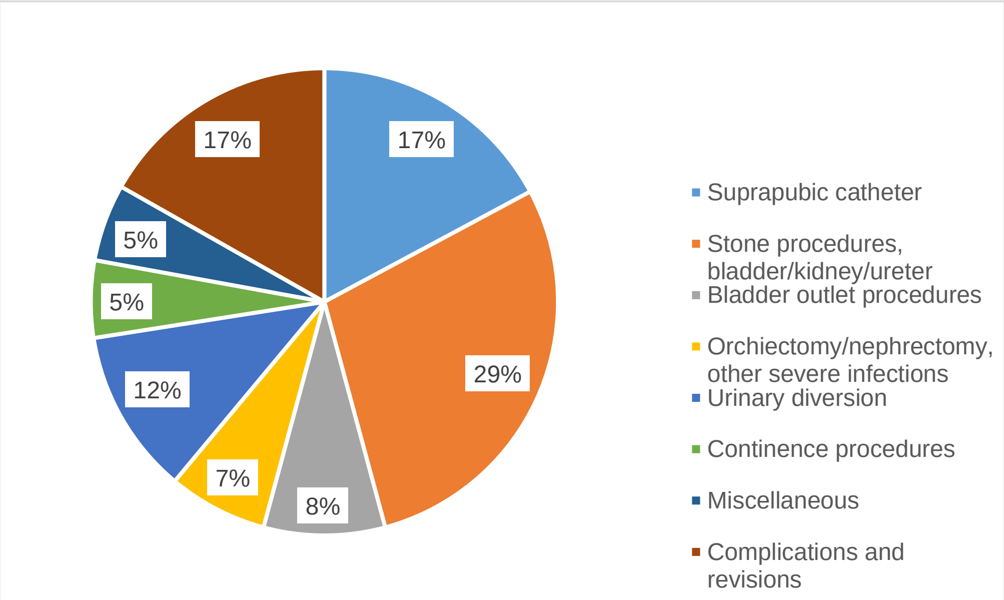
PAPER IV – Changing patterns of urological surgery in a regional prevalence group through 50 years. Outcomes and implications for the future.

The history and outcomes of urological surgical treatment in the study population was surveyed.

Among 412 patients in the cross-sectional study, 137 had undergone 262 urological surgical interventions during the period 1960-2009.

The gender ratio for all surgical procedures was 81% men/ 19% women. For urinary diversions and continence procedures with implants the ratio was 57%/ 43% women.

Figure 5. Types of urological surgery and relative proportions (%)



Imperative surgery was performed due to symptomatic urinary stones, severe infections and to ensure efficient voiding by suprapubic catheter. These interventions constituted 53% of all urological operations and included transurethral cystolithotripsy, open or endoluminal extraction of renal/ureter stones, nephrectomy, orchiectomy, and insertion of a suprapubic catheter.

Reconstructive surgery was undertaken at a median of 7-10 years after SCI. Indications were facilitation of complete voiding, reduction of incontinence, reduction of the number and severity of UTIs, decrease of spasticity and autonomic dysreflexia, to gain increased independence in activities of daily life. Reconstructive procedures were sphincterotomy, urinary diversion, and continence procedures with implants.

Primary surgery was performed at a median of 3 years after SCI with 50% occurring within two years, almost all of these were imperative procedures.

The latest surgical procedure was carried out at a median of 7 years post SCI with a wide range of 0-50 years.

Surgery for urinary stones constituted 29% of all procedures.

One-fourth of the patients had undergone ≥3 procedures (47% of all urological surgery), notably urinary diversion and ensuing complications, implants and revisions, repeated stone interventions or repeated bladder outlet procedures. Among these patients 59% had developed signs of renal complications after a median follow-up of 18 years. SCI characteristics of these patients were cervical-thoracic neurological levels of SCI and AIS A-C.

The *relative risk (RR) of urological surgery* was:

- in the total study population (n=412)	0.50
- among patients with SCI at neurological level C1-T12 and AIS A-C (n=269)	0.87
- among patients with an AIS D lesion (n=143)	0.13

There was no difference with age at the time of the SCI.

Imperative surgery was performed almost exclusively in patients with cervical and high thoracic neurological level of lesion and AIS A-B. Patients with AIS C and D lesions had a higher relative representation of reconstructive surgery with revisions.

Follow-up after urological surgery in this study was a mean 10-19 years for the various types of surgery. Re-operations/revisions had occurred:

- after urinary diversion in 43% with a mean of 2.3 procedures each
- after continence procedures with implants in 4/9 patients with 1.5 procedures each
- after sphincterotomy in 4/7 patients with 1.5 procedures each

Signs of renal complications were noted among 60% who had a urinary diversion, 18% of patients who had bladder outlet surgery, and 44% of those who had undergone stone surgery.

Patient-reported outcomes included a UTI frequency of ≥3 per year among 25% of patients after continence procedures, 33% after urinary diversions and 44% of those who had ≥1 stone procedures. Daily incontinence was reported by 13% who had urinary diversions and 0% after continence procedures. Independence and ease of voiding were reported by 80% after reconstructive procedures.

SUMMARY OF RESULTS FROM PAPERS I-IV

In a regional prevalence population of 412 patients with a chronic traumatic SCI the following results were noted:

Risk profiles for *renal complications* were cervical-thoracic neurological level of SCI and AIS grades A-B.

Regarding urodynamic parameters there was a statistically significant relationship between the duration of detrusor overactivity during the filling phase (DO ratio) and signs of renal complications. Logistic regression verified the DO ratio as a risk factor for renal complications (odds ratio, OR 1.3), whereas there was no risk difference with other urodynamic parameters.

Risk profiles for *more frequent and/ or more severe UTIs* were cervical-thoracic neurological levels of lesion and AIS A-C, SCI-duration >10 years, and catheter-assisted voiding. A urodynamic observation of NDO was a further risk factor: 85% of patients who reported >3 UTIs had NDO, and 93% of those who reported a febrile UTI requiring hospitalization had NDO.

There was no risk difference with age, gender, or the presence of residual volume. Among patients who reported more frequent or more severe UTIs autonomic dysfunctions were common, but there was no co-variation with other complications of the urinary tract.

The *relative risk (RR) of urological surgery* in the total study population (n=412) was 0.5, among patients with a cervical-thoracic neurological level of lesion and AIS grades A-C 0.87 (n=269) and among patients with an AIS D lesion 0.13 (n=143). The odds ratio (OR) was 6.75 for any type of urological surgery among patients with a cervical-thoracic level of lesion and AIS grades A-C versus an AIS D lesion. There was no difference with age at the time of the SCI.

Imperative surgery was performed almost exclusively in patients with cervical and high thoracic neurological level of lesion and AIS grades A-B. Patients who had undergone *≥3 urological procedures* had cervical-thoracic neurological levels of SCI and AIS A-C.

Patients with an AIS D lesion reported a lower frequency of UTIs and no febrile UTIs requiring hospital treatment. The proportion of other urinary tract complications was half that of patients with a C5-C8 AIS A-C classification of SCI. The prevalence of ABU was half that of patients with cervical-thoracic neurological levels of injury. However, AIS D patients demonstrated signs of renal complications in 21%. SCI duration among these patients was a mean/median of 15.5/13 years. Residual urine and bacteriuria were common among those who practiced normal voiding, but symptomatic UTIs were few. Patients with AIS C and D lesions had no imperative urological surgery but a higher relative representation of reconstructive surgery with revisions.

6 DISCUSSION

The Stockholm Spinal Cord Uro Study is a cross-sectional survey based on a comprehensive inventory of objective data from medical examinations and patient-reported data which were collected within the framework of annual check-up visits at a regional outpatient centre, the Spinalis clinic. A large proportion of the regional population with chronic traumatic SCI attended the visit. Approximately 75% of the regional prevalence group were included in the study, which can therefore be considered representative of an urban SCI-population in Sweden. Patients with all neurological levels and severity of SCI were included.

The inventory was complemented with thorough investigations of retrospective data from urodynamic tracings, patient files and surgical records adding further information and weight to the data base and inventory.

A majority in the regional population was found relatively healthy in terms of objective laboratory and radiological findings regarding the urinary tracts, and just over half of all patients reported ‘no complications’ during the preceding year. Internationally, these are favourable results and most probably reflect the fact that this regional population is found in a high-income country, in an urban area with easy access to a dedicated/specialised SCI clinic and to medical care in general.

Objective data displayed that 25 % of the study patients had signs of renal complications, with 15% showing pathological levels of creatinine, cystatin-C, and cystatin-C related GFR. In comparison, chronic kidney disease has been estimated among 6% of persons accessing primary care in the Stockholm area as determined by creatinine estimated GFR (95).

A cross-sectional study in the United States revealed chronic kidney disease among more than 1 in 3 of 9000 patients with traumatic and non-traumatic SCI across Veterans Administration facilities in the country (96). A report from Denmark stated that in a population of 116 persons the cumulative risk of moderate or severe renal impairment was 58% and 29% respectively after 45 years SCI duration (81). Risk factors were dilatation of the upper urinary tracts and renal/ureter stones requiring surgery. Others have reported loss of bladder compliance, repeated bouts of pyelonephritis, chronic indwelling catheterization (97), older age and longer duration of injury, hypertension, and chronic decubitus ulcers (98) as risk factors.

Data in this study indicate several background factors for a potential successive and ‘silent’ development of renal complications even in a privileged population with access to specialized follow-up, including present and previous urodynamic characteristics. Some types of bladder management were shown to imply an increased risk, for example urinary diversion and long-term results of sphincterotomy with bladder reflex triggering. Indwelling suprapubic catheters may cause a risk situation because of chronic inflammation (98). Febrile UTIs, aging with an SCI and co-morbidities are further risk indicators as well as any imperative or elective surgical trauma. Thus, follow-up programmes should be offered to all patients after SCI and continued long-term. Prevention of renal deterioration after SCI remains a major responsibility for all care institutions involved in follow-up. Identified urodynamic risk factors must be treated. Bladder management should be routinely follow-up, monitored and changed when necessary. Co-morbidities must be closely observed and treated appropriately.

Patient-reported data clarified that UTIs were by far the most frequent complication and had affected nearly half of the study population during the preceding year with 15 % reporting >3 UTIs and 5 % having febrile UTIs requiring in-hospital treatment. Other complications of the urinary tracts were reported at low frequencies. Cross-sectional interview-based studies in Australia, Canada, and Switzerland (49, 91,92) displayed a higher rate of patient-reported UTIs during the previous year of 58-59 %, and an occurrence of kidney/bladder stone in 3% (91), which was similar to our results. However, in these surveys there were fewer patients with an AIS D lesion which may explain the higher prevalence of UTI.

In this cross-sectional study risk profiles were identified for renal complications, UTIs, and the need for imperative surgery. In general, risk indicators were consistent with results from other researchers regarding the neurological level and severity of SCI, the urodynamic observation of NDO, and the duration of detrusor overactivity during bladder filling (50,66,84). In contrast to some previous classical analyses (21,28) there were no significant relationships between other urodynamic parameters and signs of renal complications. Consequently, there is room for development in the measurement and understanding of urodynamic parameters and the application of those results into clinical interventions.

Additional risk factors for more frequent and more severe UTIs were catheter-assisted voiding and an SCI duration of >10 years. In addition, the severity of injury as classified by AIS grade A–B had a greater impact than neurological level of injury. There was no risk difference with age, gender, the presence of residual volume, or other complications of the urinary tract in our population.

Risk profiles for the incidence of imperative and reconstructive urological surgery raises special concerns as some of these characteristics indicate the same subset of patients that are already at greater risks for renal impairment, autonomic dysfunctions and recurring UTIs. The addition of surgical trauma may cause aggravation of autonomic symptoms and a further strain on renal function. Surgical treatment is therefore best carried out in specialised units where all staff have sufficient experience in SCI care. Reconstructive procedures should be carefully planned in collaboration with rehabilitation professionals and subject to diligent follow-up. Surgery is one part of the global treatment of NLUTD after SCI, along with pharmaceutical therapy, life-style issues, and technical aids.

The evolution into more minimally invasive procedures has improved outcomes and reduced complication rates, as illustrated by our data over several decades. Further progress in this regard will no doubt be of benefit to the patients with SCI and other neurological conditions.

In this regional prevalence population 143 patients (35%) had an AIS D lesion. This is a larger proportion than in other recent cross-sectional studies (49,91,92) and reflects the fact that all regional patients had access to annual check-ups at the Spinalis clinic and all attendees were invited to participate in the study. Among the included AIS D patients one-fifth had signs of renal complications. In several cases they were patients with a history of untreated NDO over more than fifteen years. Patient-reported data indicated relatively few experienced complications and traditionally this subset of patients has not been at the focus of attention in

SCI follow-up. However, given the urodynamic risk factors for long-term renal dysfunction and possible unfavourable interaction with aging processes of the urinary tracts more attention and individualized information should be offered to these patients.

Many cross-sectional studies are based on interviews, either personal or internet based. This thesis attempts to further our understanding through the combination of objective and patient-reported data, signs, and symptoms and correlations between them. Signs and symptoms were often unspecific, as exemplified by the most reported symptoms of UTI, and unfortunately did not correlate well with objective findings. This situation has been previously described by other authors (99). There is a risk that autonomic dysfunctions are misunderstood, that unspecific antibiotic treatment is administered, and other diagnoses are delayed. Some complications may develop in silence over the course of many years. In the context of an organized follow-up programme, it is possible to learn more about which symptoms and patient-reported signs should be cause for more immediate attention. Structured reports and symptom diaries from patients' daily life can be invited as integral parts of the follow-up.

A cross-sectional study has advantages and limitations. Some advantages in this survey were the use of a system for annual check-up visits which was already in place and provided easy access to potential participants. Interested patients could be offered inclusion without extra study visits and could avail of a more thorough assessment of their urological situation by application of the two follow-up programmes and the study-specific questionnaire. The detailed check-up made it possible to present individualized clinical recommendations and improvements to a larger extent than in a regular check-up visit. Limitations were selection bias regarding the inclusion of patients who chose to attend the annual visit but no access to non-attendees. Participants may have been those who were particularly interested in further urological advice, while some others deliberately wanted to avoid a urological work-up. Another limitation was that only approximately half of the patients completed all parts of the study. Considering these limitations, participation by approximately 75% of the regional prevalence population with a traumatic SCI still provided a good opportunity for an assessment of the urological situation in the regional population and identification of issues for further research.

This thesis contributes to a further understanding of the complexity of NLUTD after SCI and the risk factors for secondary complications. There are emerging clinical issues and research needs concerning the management of NLUTD in the context of aging with an SCI. A holistic view of co-morbidities and life-style issues along with the important neurological impairment is warranted. Prevention strategies for recurring UTIs, bladder stones, and renal deterioration are in continued need of update as the knowledge base expands. Urodynamic parameters can be additionally explored to depict the pathophysiology of the lower urinary tract more accurately. Urodynamic methods may be developed into less invasive and more patient-friendly procedures. Urological surgical procedures for this patient group should continue evolvement into minimally invasive methods whenever possible with continued focus on the prevention of autonomic dysfunctions in the peri-operative period. Structured follow-up programmes which are offered to all patients with NLUTD after SCI can help identify new research questions and drive expeditious transformation of new insights into clinical practice.

7 CONCLUSIONS

In a regional population of patients with chronic post-traumatic SCI the following observations were made:

- With the aid of a structured follow-up programme the majority had a stable and relatively healthy situation regarding urinary tracts and renal function. However, indicators of renal complications were present in one-fourth. UTI was the most common complication, experienced by nearly half of all patients during the preceding year.

- Risk profiles for renal complications and recurring UTIs were cervical-thoracic neurological level of SCI and AIS grades A-B and a duration of detrusor overactivity during bladder filling of more than one-third. Further risk factors for more frequent and more severe UTIs included AIS grade C, SCI-duration >10 years, catheter-assisted voiding, and a urodynamic observation of NDO.

- Risk profiles for imperative surgery during the first two years after SCI were cervical-high thoracic neurological level of lesion and AIS grades A-B. Patients who had three or more urological procedures had cervical-thoracic neurological levels of SCI and AIS A-C.

- Risk groups overlap in several characteristics. Prior to invasive urological procedures or surgery these patients need special attention. Any added hazard to renal function must be recognized and prevented. Risks of further complications beyond the current procedure must be recognized.

- Among patients with an AIS D lesion UTIs were less frequent but three-fifths had NDO, and one-fifth had signs of renal complications. There is a possibility that these persons do not receive adequate attention, particularly in aging with an SCI. The effect of NLUTD must be remembered in the context of other age-related alterations of urinary tract function.

- Structured follow-up programmes should be offered to patients with all neurological levels and severity of SCI. Cardiovascular and metabolic co-morbidities which may influence renal function should be considered.

- Future development and research are warranted in the areas of prevention of UTI and bladder stones, evaluation of urodynamic parameters, and minimally invasive methods in urological surgery of patients with SCI.

- Prospective studies of surgical treatment of neurogenic bladder dysfunction after SCI are needed including more extensive patient-reported outcomes.

8 FUTURE PERSPECTIVES

This thesis presents a basis for further research in several areas regarding the prevention of urinary tract complications, update of follow-up programmes, and prospective studies on interventions.

Prevention and appropriate treatment of UTIs need new strategies in the era of multi-resistant microbes and increasing knowledge about bacteriuria and biofilm formation. Prevention of bladder stones, effective minimally invasive dissolution or disintegration of stones may be developed, thus significantly reducing the need for surgery.

My own priority will be further development of follow-up programmes regarding the recommendations on bladder management, prevention of UTIs, and urodynamic parameters, thus continuing work on the underlying ideas for this thesis and hopefully applying some of the findings.

Programme structure can generally be improved to enable easier registration of important parameters. The results of follow-up should be more regularly evaluated to monitor the urological situation at group level in regional and national patient populations which may now be feasible with concentration of care to a restricted number of highly specialised centres in Sweden. Inclusion of relevant new research findings should be prioritized, shortening the distance from science to clinical application.

New forms of bladder relaxant therapy in NDO are essential to reduce the use of anticholinergics and other systemic medications in favour of targeting the bladder or micturition reflex directly.

Prospective studies on reconstructive surgery in NLUTD are required with more focus on patient-identified needs and patient-reported outcomes. Such studies may ideally be carried out as multicentre undertakings on a national or international basis.

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KAROLINSKA
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Supplement 1
Study-specific questionnaire

Spinalis clinic

The Spinalis clinic will perform an inventory of urinary tract problems in persons with traumatic spinal cord injury during the following year.

In connection with your yearly check-up at Spinalis, we would be grateful if you would like to answer some questions about any bladder or kidney problems you may have had during the past year, and any treatment you have received.

A voiding protocol is included. This is a simple and helpful instrument to document bladder function. **Date:** ___________________________

1. Did you have any urinary tract problems before the spinal cord injury?

- ☐ Yes
- ☐ No

2. Can you feel when your bladder is full or the need to pass urine?

- ☐ Yes
- ☐ No

3. How do you empty your bladder/ void urine?

- ☐ Normal voiding (like you did before the spinal cord injury)
- ☐ Tapping on the bladder or other type of reflex stimulation
- ☐ Straining with abdominal muscles
- ☐ Manual pressure over bladder area
- ☐ Self-catheterisation / clean intermittent catheterization/ CIC
- ☐ Indwelling urethral catheter
- ☐ Indwelling suprapubic catheter
- ☐ Continent urinary reservoir / Kock reservoir
- ☐ Urinary diversion with urostomy bag
- ☐ Other method or comments? Please specify! _______________________________________

4. For users of self-catheterisation/ CIC: what type of catheter do you use?

☐ Hydrophilic catheter and I pour water on it before use

☐ Hydrophilic catheter ready-to-use, water already added in the package

☐ Plastic catheter and I add lubricant gel before use

☐ Plastic catheter without addition of gel

☐ Plastic catheter with added gel and collecting bag in the package

☐ Catheter with a curved tip/ tiemann tip

5. Do you experience involuntary urinary leakage between times of bladder emptying/voids?

☐ Never

☐ Only when I have a urinary tract infection (UTI)

☐ Every week

☐ Every day

6. If you experience urinary leakage, how does this occur?

☐ Suddenly, with no warning at all

☐ Suddenly, with some warning just before

☐ At times of transfer (e g into or out of wheelchair) or physical exertion

7. Do you use a collecting appliance for urinary incontinence?

☐ Yes

- ☐ A small absorptive pad
- ☐ A medium-sized absorptive pad
- ☐ A large absorptive pad/ diaper
- ☐ A condom catheter

☐ No

8. Do you use any of these medications on a regular basis?

☐ Yes

- ☐ Ditropan/ oxybutynin tablets
- ☐ Detrusitol IR/ tolterodin IR tablets
- ☐ Detrusitol SR/ tolterodin SR tablets
- ☐ Vesicare/ solifenacin tablets
- ☐ Kentera/ oxybutynin cutaneous application
- ☐ Emselex/ darifenacin tablets
- ☐ Oxybutynin bladder instillation (solution instilled via catheter)

☐ No

9. Number of UTI´s during the past year, where you received treatment with a course of antibiotics

☐ None

☐ 1-3

☐ 4-6

☐ more than 6. Please specify how many: ____________________

10. What are your symptoms in case of a UTI?

	Usually	Sometimes	Never
☐ smelly urine	__	__	__
☐ cloudy urine	__	__	__
☐ increased urinary incontinence	__	__	__
☐ increased frequency and urgency to pass urine	__	__	__
☐ burning sensation when voiding	__	__	__
☐ increased spasticity	__	__	__
☐ sweating	__	__	__
☐ pain in bladder area	__	__	__
☐ pain when voiding	__	__	__
☐ general feeling of illness	__	__	__

☐ increased temperature/ fever/ 37.0-38.5 degrees Celsius __ __ __

☐ increased temperature/ fever/ more than 38.5 degrees Celsius __ __ __

☐ shivering __ __ __

☐ other __ __ __

Please specify____

11. Who do you primarily contact when you suspect a UTI?

☐ Primary care facility/ general practitioner

☐ Spinalis clinic

☐ other care facility. Please specify ____

12. Do you have a urine culture test taken when you suspect a UTI?

☐ never

☐ usually

☐ always

13. Did you have UTI´s during the past year, which were treated with antibiotics without a prior urine culture? If so, how many?

☐ 1-2

☐ 3-6

☐ more than 6. Specify how many ____________________________________

☐ No, I always had a urine culture taken

14. Reasons why you did <u>not</u> have a urine culture taken

☐ the doctor did not think it was necessary

☐ I had antibiotics at home and started treatment on my own initiative

☐ I was too sick/ my symptoms were too bad/ to have a urine culture taken and delivered to a care facility

☐ I recognized the symptoms and did not think it was necessary

15. Have you been hospitalized during the past year for treatment of a UTI?

☐ Yes How many times? ______________ What hospital? ________________________

☐ No

16. Do you take any regular medication to prevent UTI?

☐ Yes

- ☐ Hiprex/ methenaminehippurate
- ☐ Antibiotic Name and dose of antibiotic_________________________________ Started when ________________________
- ☐ Other medication

☐ No

17. Do you use any other measures to prevent UTI?

☐ Yes

- ☐ Vitamin-C tablets
- ☐ Fresh squeezed lemon
- ☐ Cranberry juice
- ☐ Cranberry capsules
- ☐ Rinsing of bladder with chlorhexidine (via intermittent catheter)
- ☐ Rinsing of bladder with saline (via intermittent catheter)
- ☐ Other Please specify ___________________________________

☐ No

18. Have you ever been recommended rinsing of the bladder as a treatment of an ongoing UTI?

☐ Yes

☐ No

19. Have you had any other complications from the urinary tract during the past year?

☐ Kidney stone

☐ Bladder stone

☐ Inflammation or infection of the prostate/ Prostatitis

☐ Infection of the epididymis or testicle/ Epididymitis, orchitis

☐ Neurogenic pain in the bladder and genital area

☐ Other   Please specify____

20. What care facilities have you been in contact with during the past year for examination or treatment of urinary tract problems?

☐ primary care/ general practitioner   Name of practice_____________________________

☐ private doctor   Name of doctor or practice_____________________

☐ Spinalis clinic

☐ hospital   Name of hospital and department ______________